UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): May 19, 2023

2seventy bio, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**001-40791**	**86-3658454**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

60 Binney Street,	
Cambridge, MA	**02142**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (339) 499-9300

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instructions A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.0001 per share	TSVT	The NASDAQ Stock Market LLC

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company x

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. o

Item 7.01 Regulation FD

On May 19, 2023, 2seventy bio, Inc. (the "Company") will host a Virtual R&D Deep Dive at 10:00 a.m. ET. A copy of the presentation slide deck that will be presented is being furnished as Exhibit 99.1 to this report on Form 8-K. A recording of the Virtual R&D Deep Dive presentation may be accessed for thirty (30) days following the Virtual R&D Deep Dive presentation by visiting the Investors Relations section of the Company's website at https://ir.2seventybio.com.

The information in this Item 7.01 and Exhibit 99.1 attached hereto is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section. It may only be incorporated by reference in another filing under the Exchange Act or the Securities Act of 1933, as amended, if such subsequent filing specifically references the information furnished pursuant to Item 7.01 and Exhibit 99.1 of this Current Report on Form 8-K.

Item 8.01 Other Events.

On May 19, 2023, the Company issued a press release announcing its late-breaking interim data from its going Phase 1 trial in collaboration with Seattle Children's Therapeutics, PLAT-08, for SC-DARIC33, an investigational CD33-targeting CAR T in pediatric and young adult patients with relapsed or refractory acute myeloid leukemia that will be presented at this year's American Society of Gene & Cell Therapy (ASGCT) Annual Meeting in Los Angeles, California. A copy of the press release is filed herewith as Exhibit 99.2 to this Current Report on Form 8-K and incorporated herein by reference.

Item 9.01 Financial Statements and Exhibits

(d) Exhibits

Exhibit No.	Description
99.1	Presentation given by 2seventy bio, Inc. on May 19, 2023.
99.2	Press release issued by 2seventy bio, Inc. on May 19, 2023.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document and incorporated as Exhibit 101)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Dated: May 19, 2023

2seventy bio, Inc.

By: /s/ Chip Baird

Chip Baird
Chief Financial Officer
(Principal Financial and Accounting Officer)

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

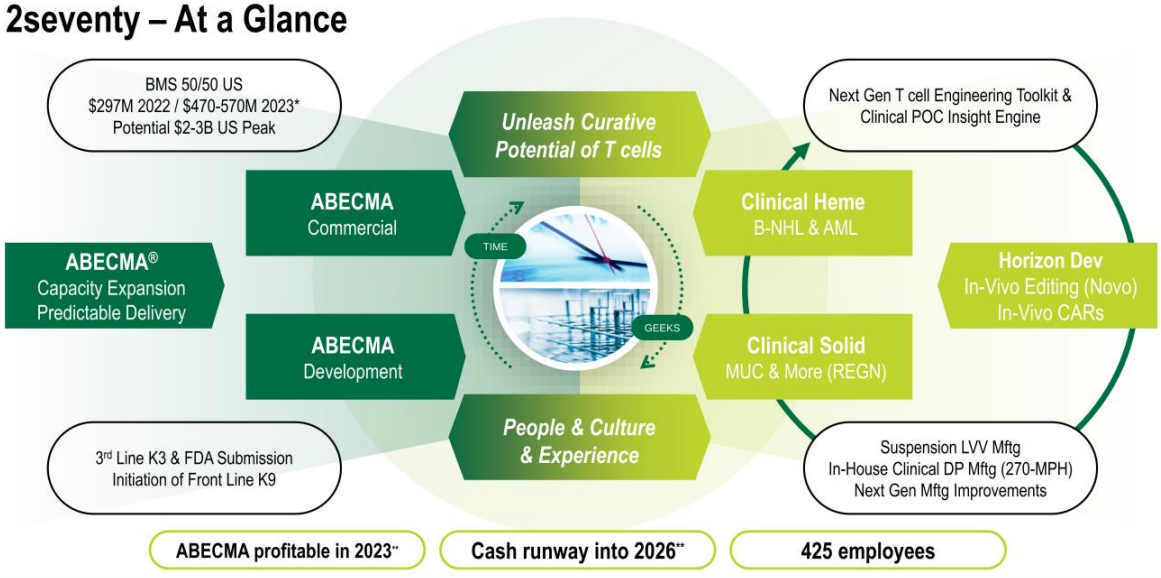
Nick Leschly, chief kairos officer

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.

it's about time

2seventy – At a Glance



*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

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

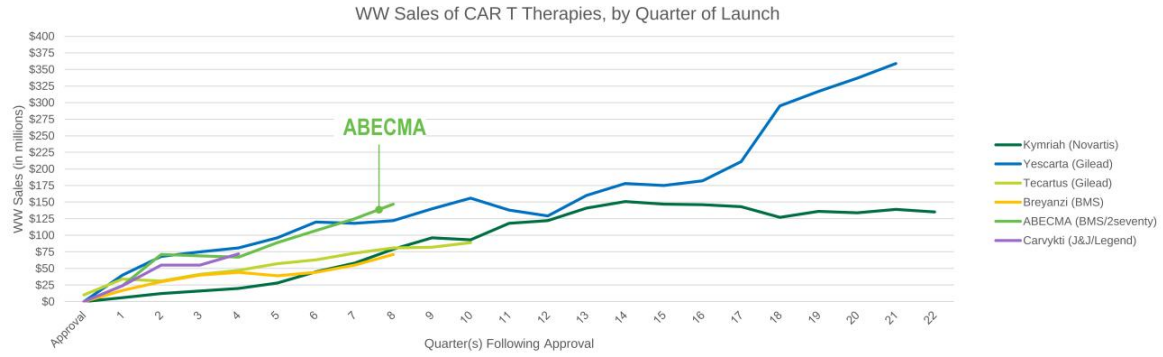
Chip Baird, chief financial officer

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

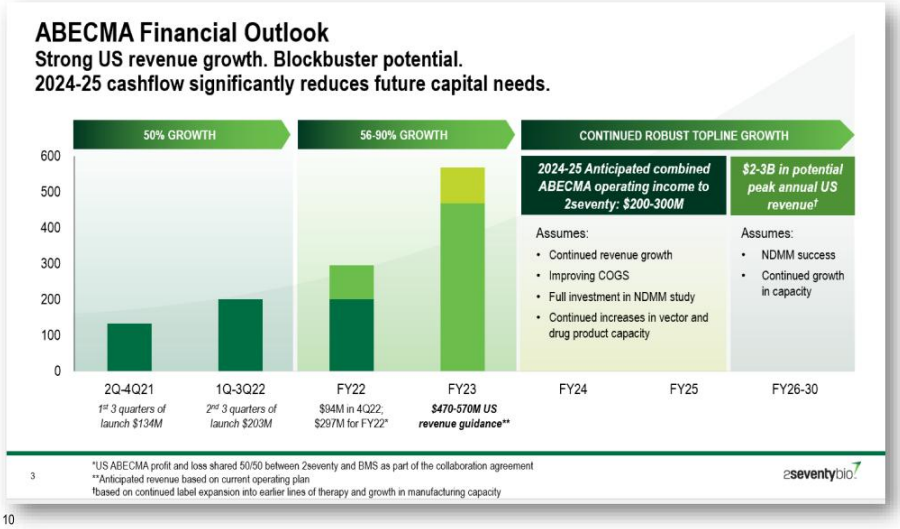


Average Annual Growth Rate	Year 2	Year 3	Year 4	Year 5
	94%	49%	29%	33%

Class CAGR for years 3-5: 37%

Source: Company filings

Strong start to 2023 for ABECMA



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****

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

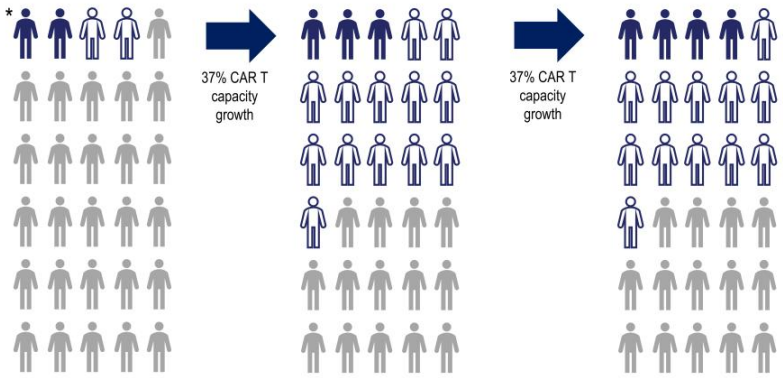
Select ABECMA Launch Metrics

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

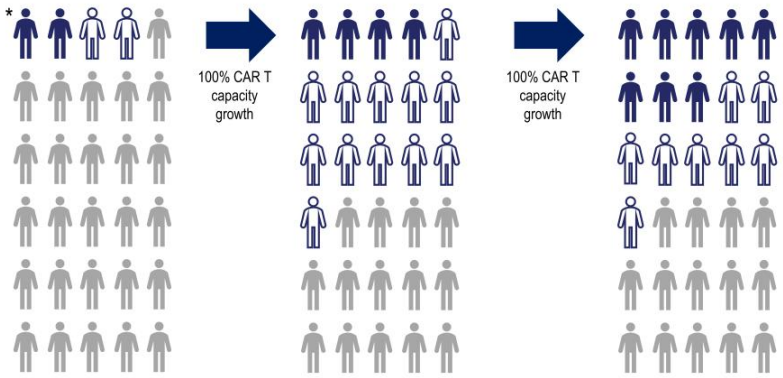
= RRMM patients treated with CAR T

= 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



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- 2024 & 2025 patients treated based on 100% annual growth from 2023 levels
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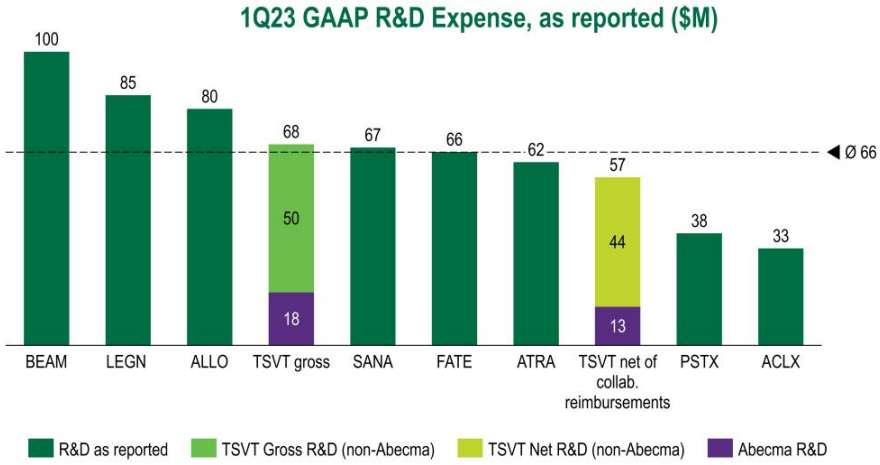
= RRMM patients treated with CAR T

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

= not eligible for CAR T

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

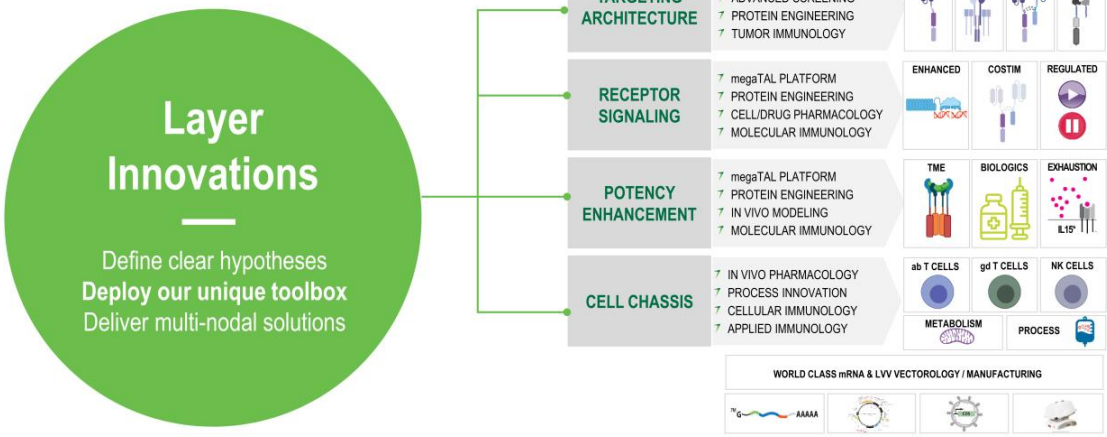
2seventy bio's R&D philosophy

Accelerate with Industry Leading Partnerships

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

Our Innovation Ecosystem

~10 years in the making



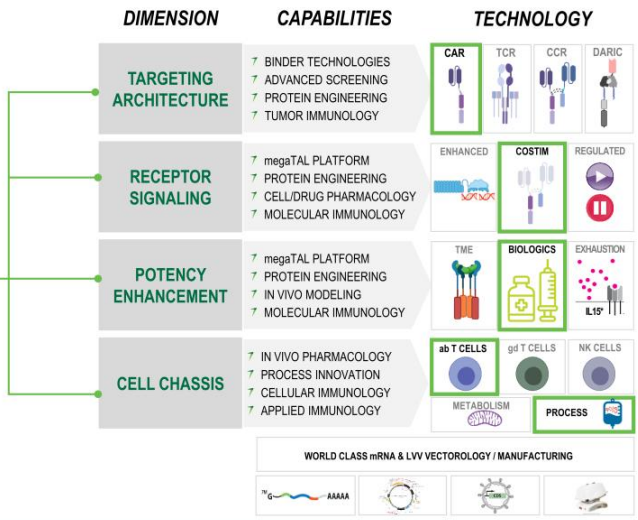
Our Innovation Ecosystem

~10 years in the making

Solid Tumor Example: MUC16

Layer Innovations

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



Our Innovation Ecosystem

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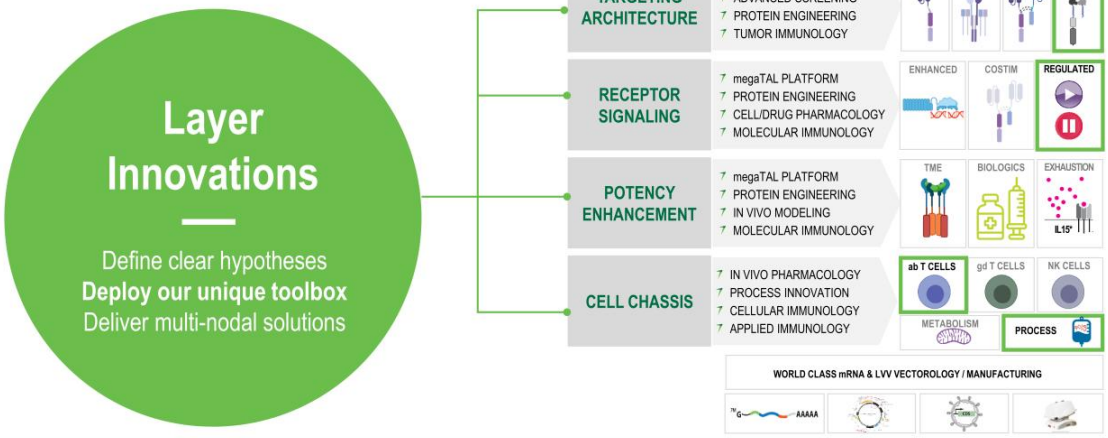
Example: SC-DARIC33



Our Innovation Ecosystem

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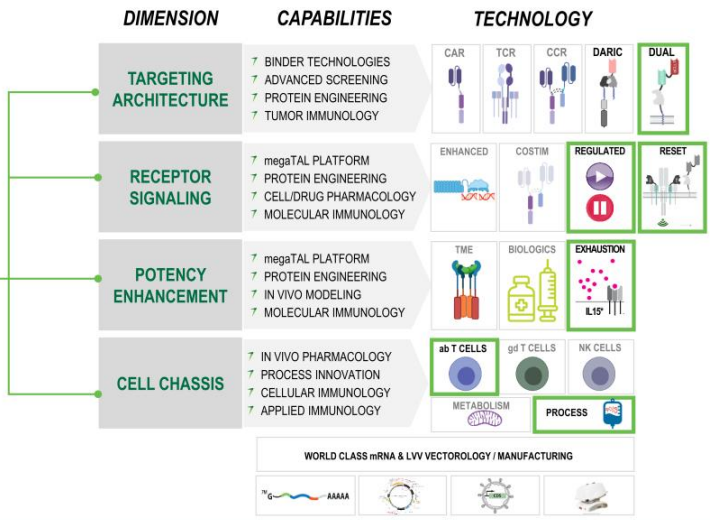
Example: NG-AML – 27T32

Layer Innovations

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



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.		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

2seventybio

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

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2seventybio

Programs featured today

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Collaboration program
TSVT-owned program

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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

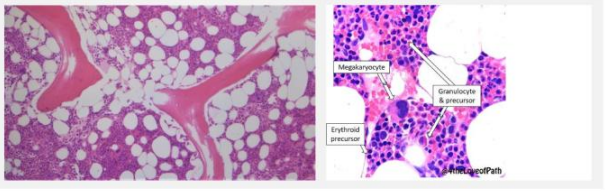
- First direct *in vivo* application of the megaTAL technology
- Key proof of concept data and pre-clinical milestones achieved
- Supports additional applications of our mRNA and megaTAL technology

* *Presentations given at* ASGCT 26TH ANNUAL MEETING

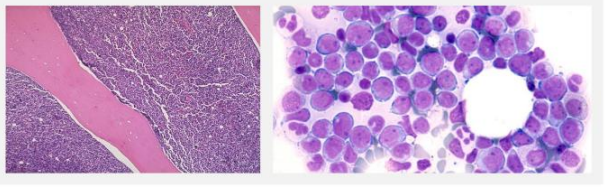
AML Clinical and Preclinical Developments

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

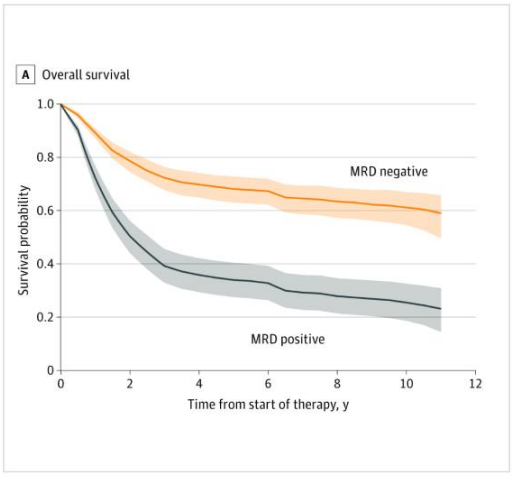
Acute Myeloid Leukemia is a devastating disease in desperate need of new therapeutic approaches



A normal bone marrow making WBC, RBC and platelets



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



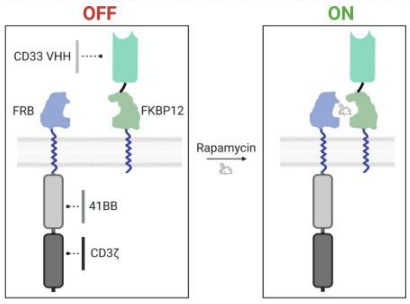
Challenges in developing T-cell therapies for AML and 2seventy's solutions

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

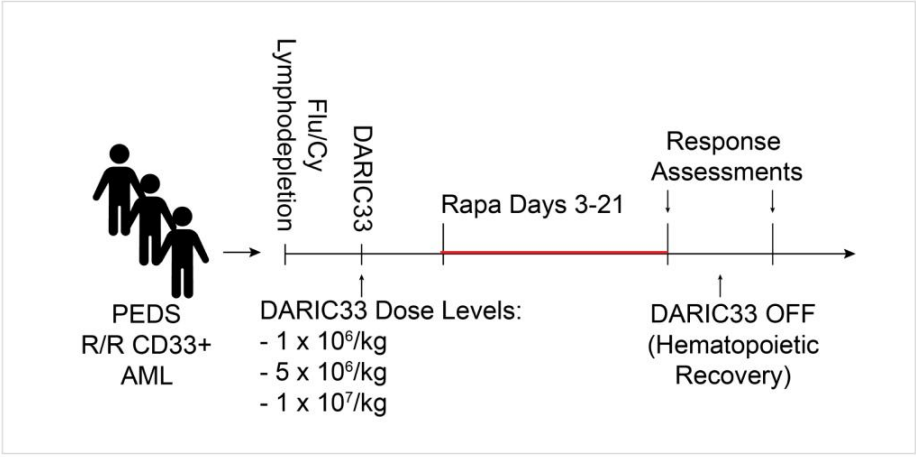
- Next-generation Regulatable CAR
- Separate antigen binding and signaling subunits contain drug-dependent dimerization domains
- Dimerizing drug (Rapamycin) required for antigen responses



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

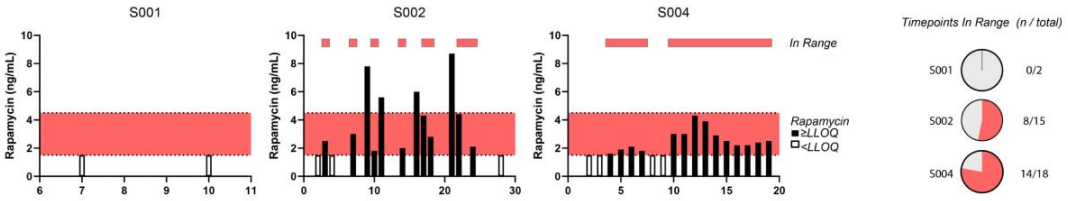
What are we looking for in the early days of this trial

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.

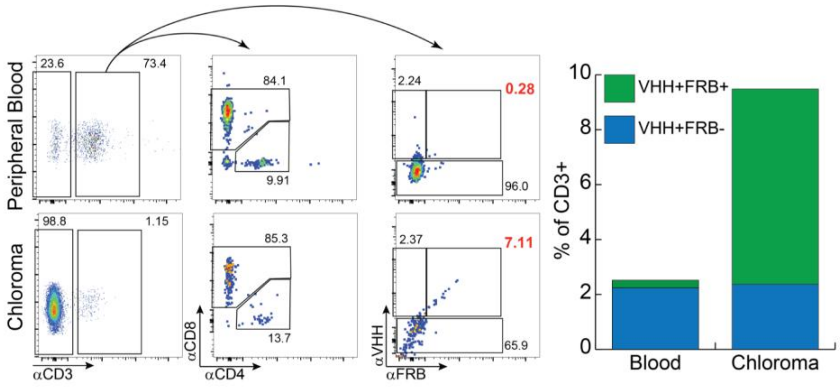


Improvement in Rapamycin targeting

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.

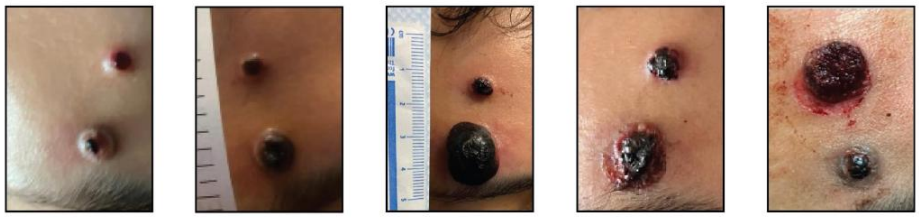


2seventybio

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

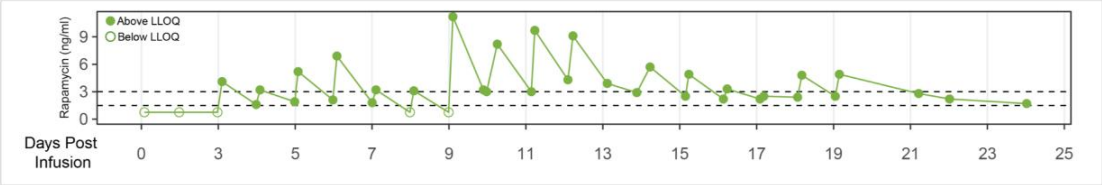


Day 3 | Day 4 | Day 8 | Day 13 | Day 22

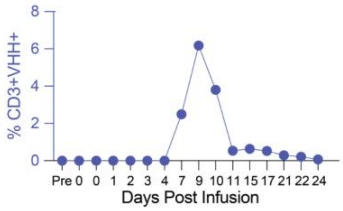
Progressive hemorrhagic necrosis of the chloromas

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

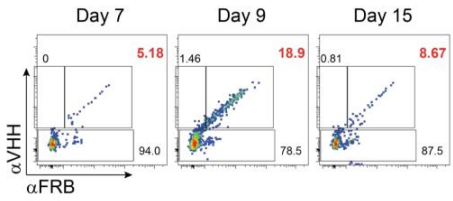
Patient S004



Percentage of total lymphocytes that are DARIC cells



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



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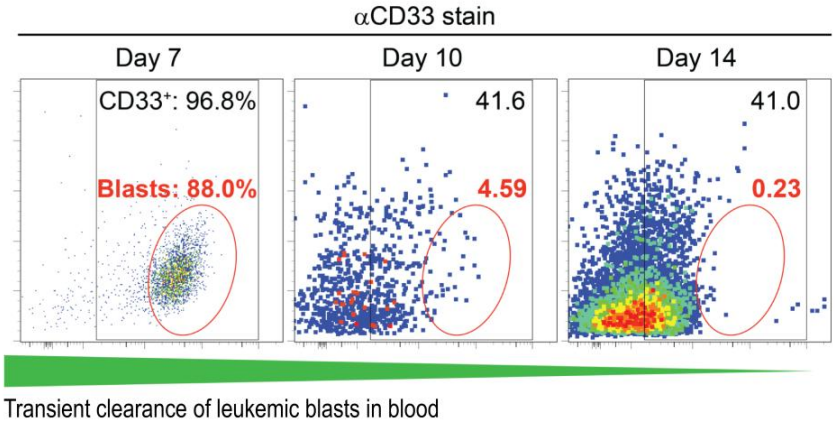
3 Do the DARIC cells engage antigen and mediate target cell cytotoxicity?

Patient S004



Transient clearance of leukemic blasts in blood

Summary of initial PLAT-08 correlative data

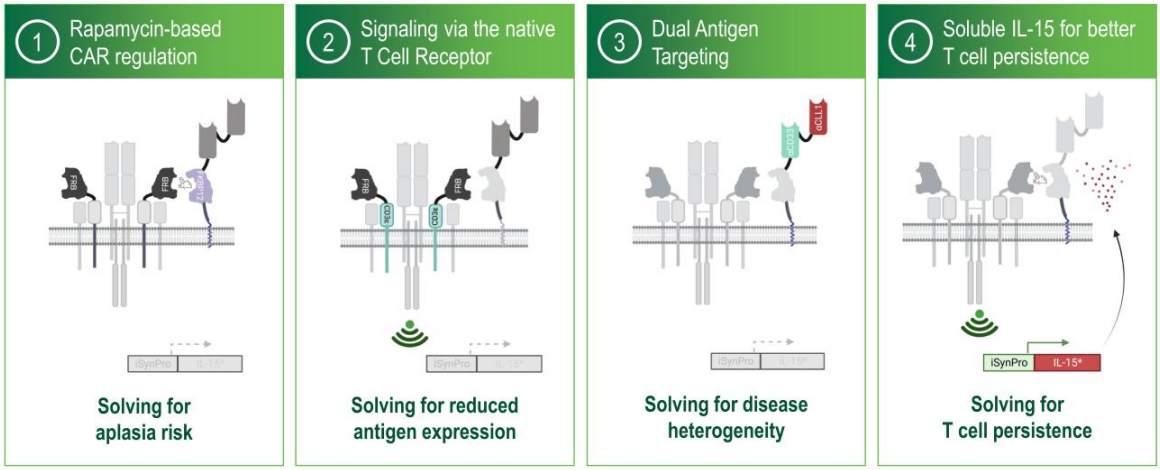
First three patients / Dose Level 1

- *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



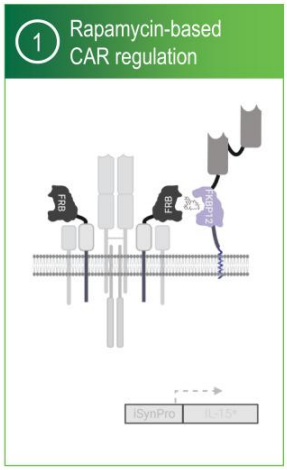
Solving for aplasia risk

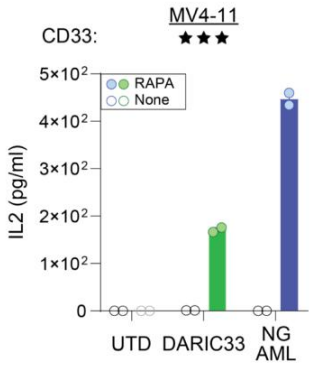
Solving for reduced antigen expression

Solving for disease heterogeneity

Solving for T cell persistence

The NG-AML CAR is tightly controlled by rapamycin dosing





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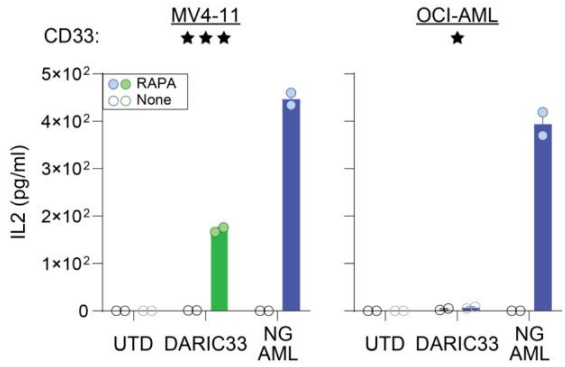
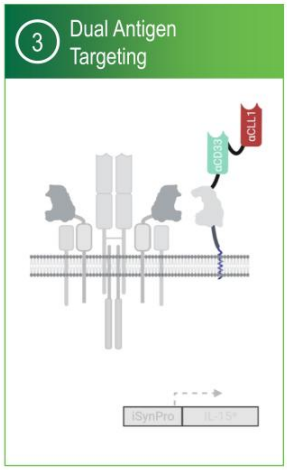
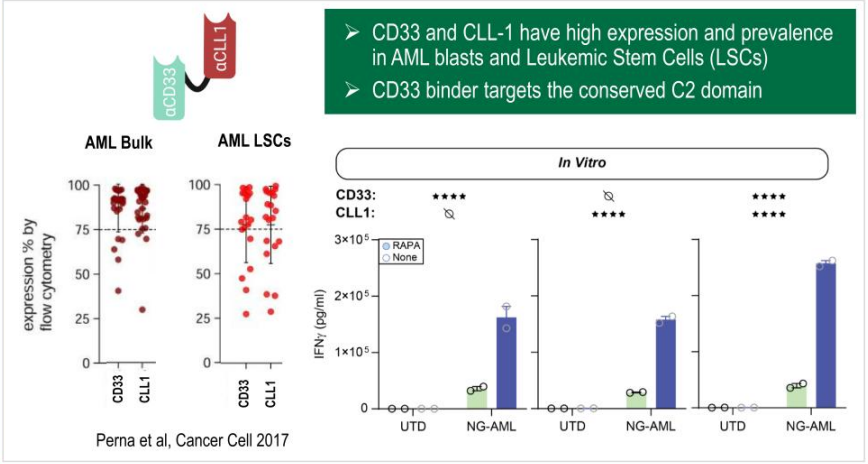
The NG-AML CAR uses the RESET architecture for higher antigen sensitivity



The **R**apamycin-**E**nabled, **S**witchable **E**ndogenous **T**CR **(RESET)** architecture demonstrates **enhanced sensitivity** to low target density limiting low antigen escape

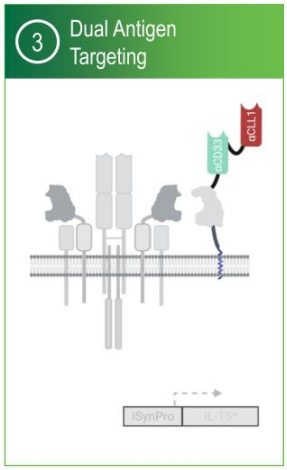
The NG-AML CAR recognizes CD33 and CLL-1 to address AML heterogeneity





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

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



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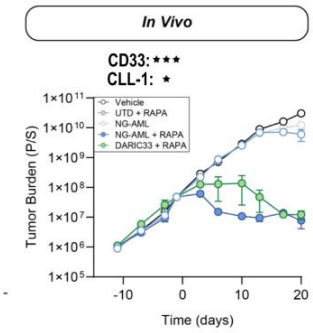

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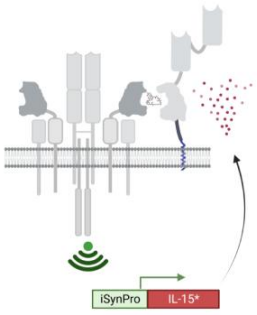
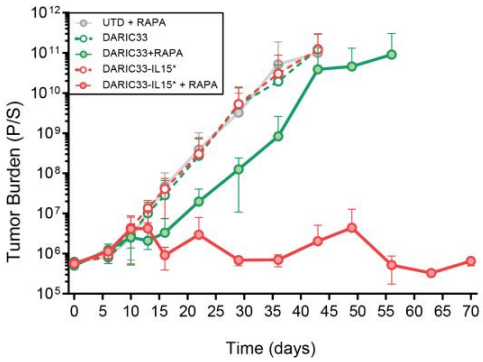
The NG-AML CAR incorporates IL-15, resulting in more potent T cells

4 Soluble IL-15 for better T cell persistence

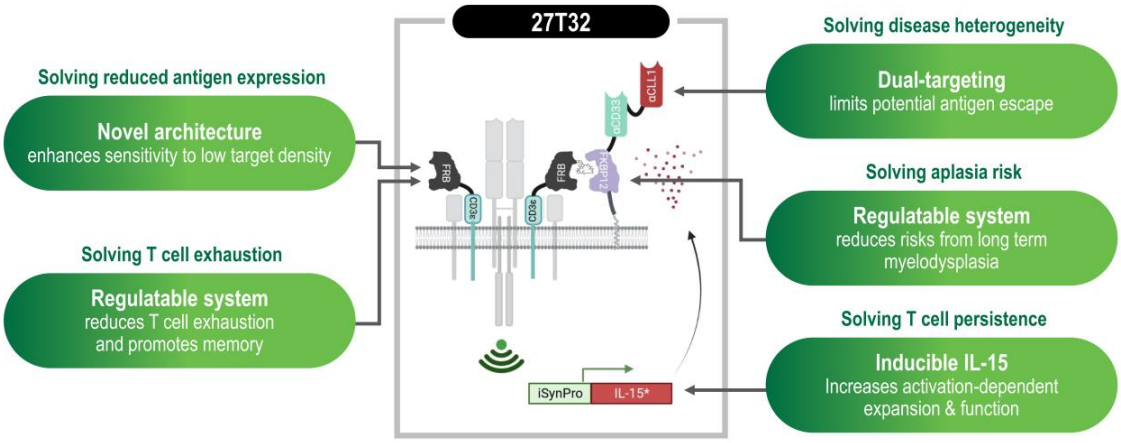


IL-15 activity is regulated by a T cell activation-dependent synthetic promoter



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

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



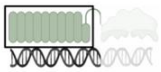
Ex Vivo and *In Vivo* Gene Editing Applications

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

megaTAL Platform: Engineering activity and specificity

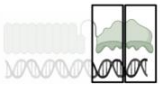
Gene Editing Architecture

TAL Array Anchor



10-12 bp TAL target recognition

Meganuclease Binding



22 bp MN target recognition

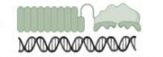
Meganuclease Cleavage

Creates a 4 bp, 3' overhang DSB

megaTAL attributes

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

2.5 kb

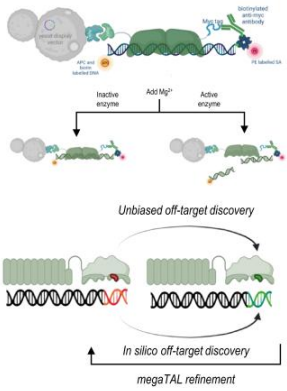


10-12 bp TAL target recognition

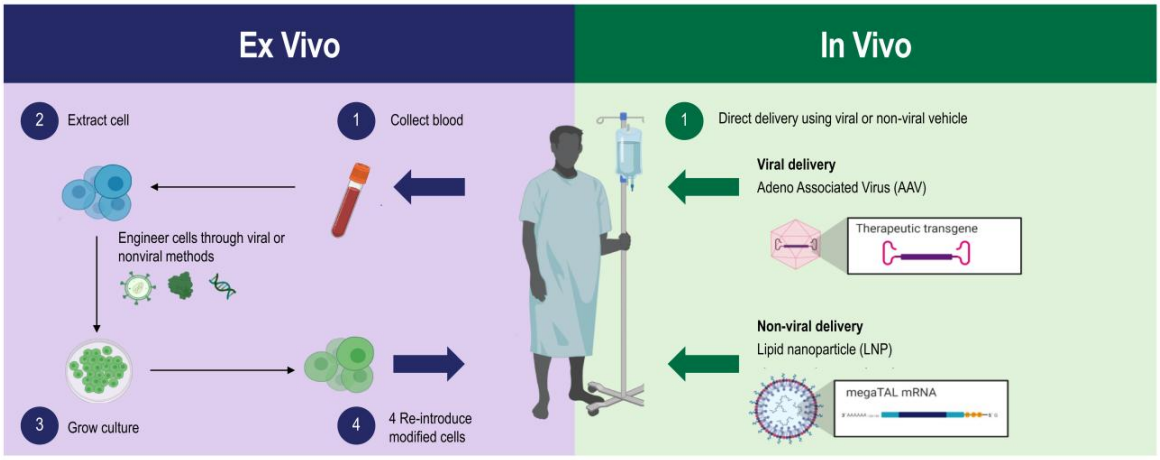
Each megaTAL is a fully orthogonal reagent

Single, monomeric component drives target recognition and cleavage

Protein Engineering for Activity and Specificity



Gene Editing
Ex Vivo vs In Vivo



Gene Editing
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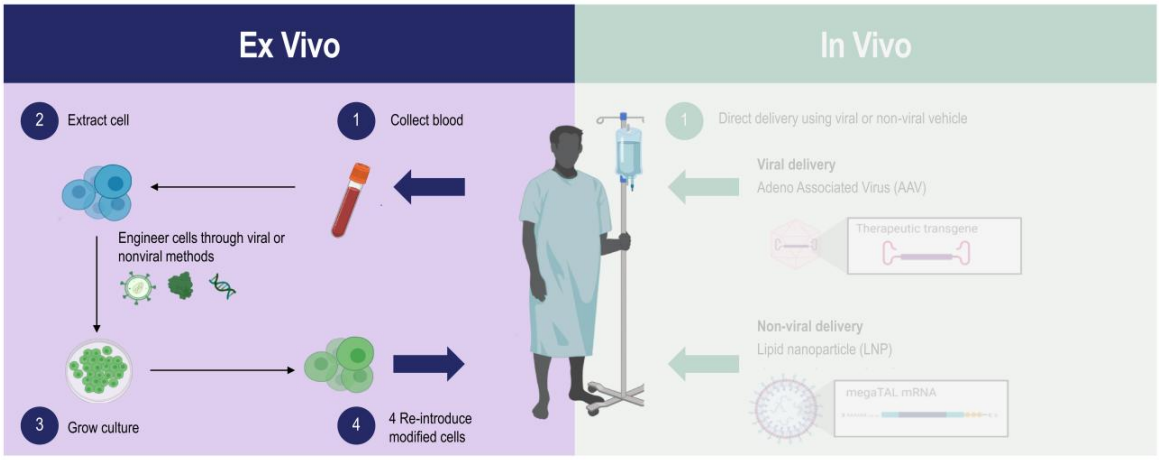


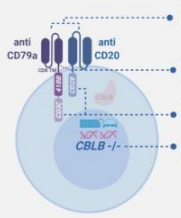
2seventybio

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

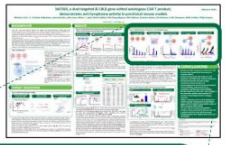
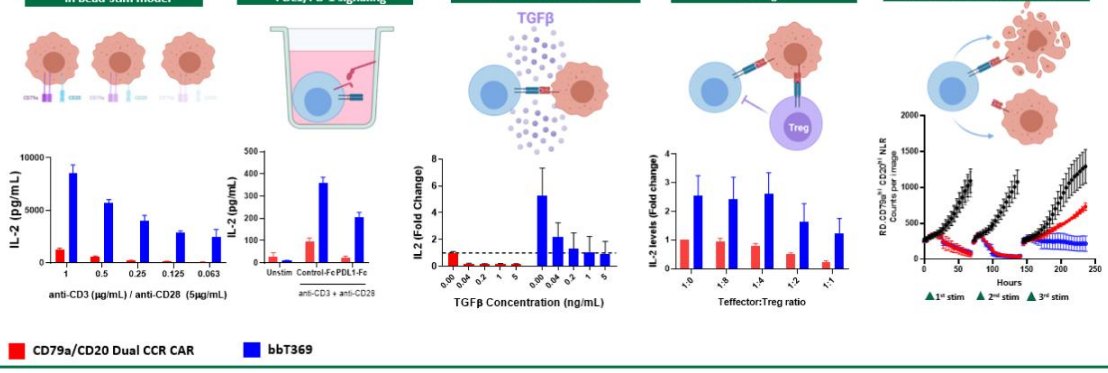


Figure 5: CBLB Edit Enhances Activity Across *in vitro* Challenging Assays



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

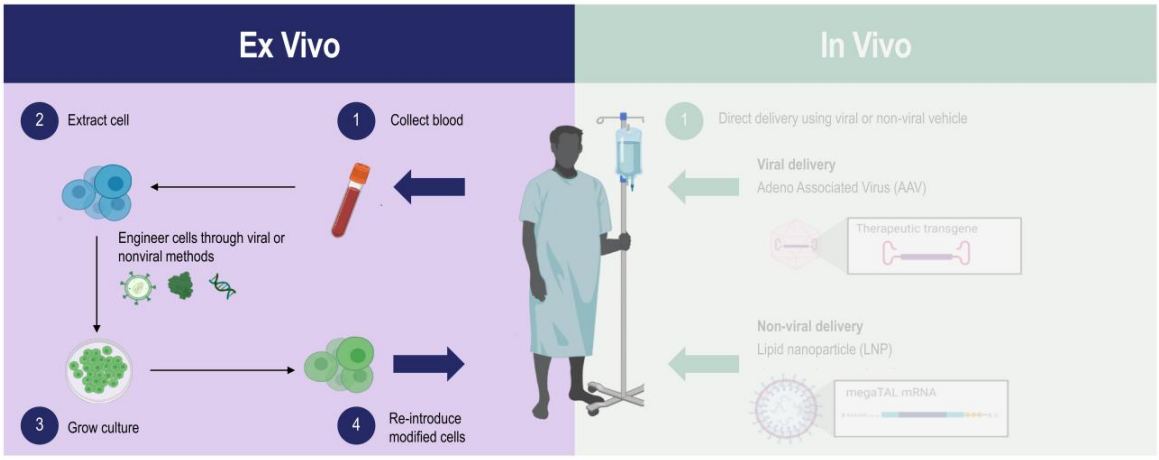
- Is the safety and tolerability of bbT369 in line with prior CAR Ts?
- Does bbT369 show anti-B cell activity in R/R B-NHL patients?
- Does bbT369 show deep and durable responses?
- Does the dual-targeting CAR architecture limit antigen escape?
- Do CBLB edited T cells expand and persist?

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



Gene Editing
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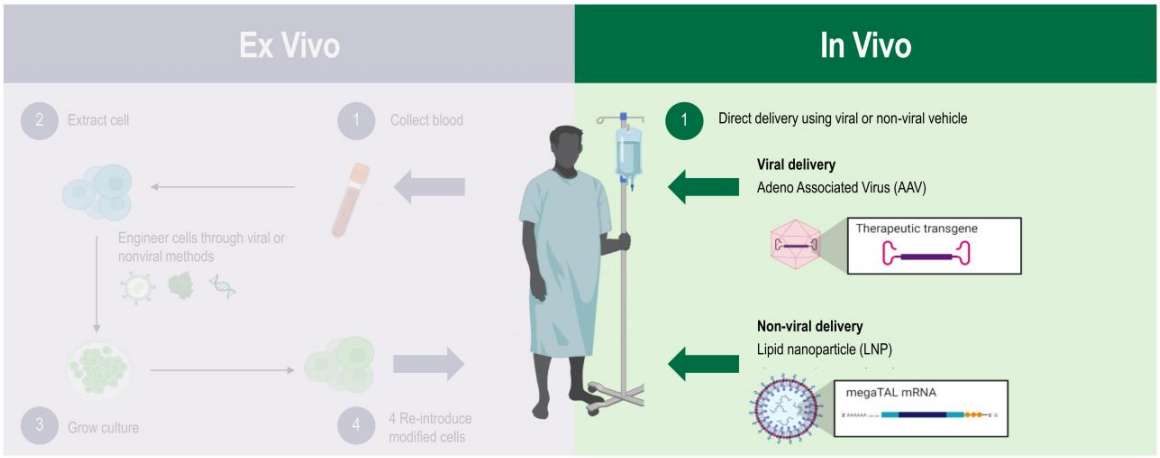


2seventybio

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

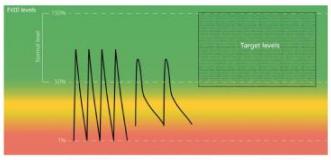
Bispecific antibodies can be used to replace FVIII function and prophylactically prevent bleeds, but is not suitable for traumatic and surgical bleed management

Addresses gaps in SOC and AAV Only Hem A approaches

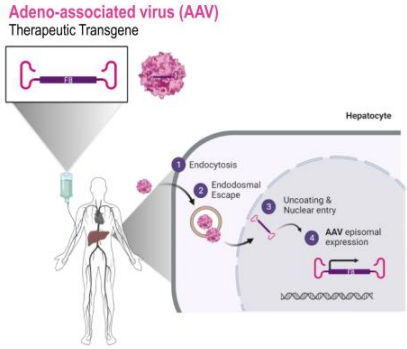
DURABLE expression without activity Troughs

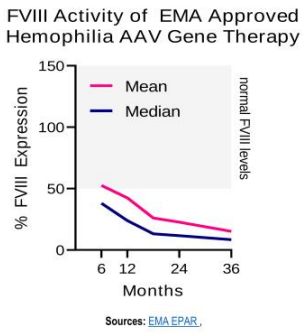
ERT SoC leaves gaps in protection that GTx tries to address

- 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

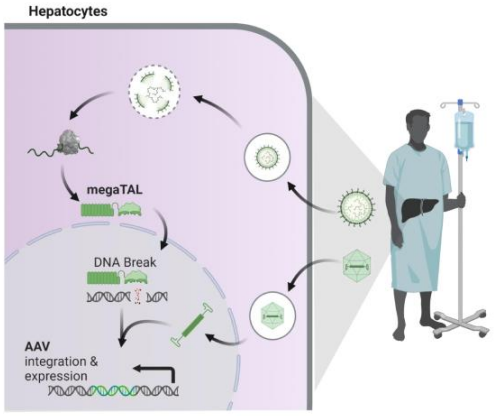




Sources: EMA EPAR ,

In Vivo Gene Therapy for Hemophilia A

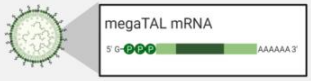
Product concept



In Vivo Gene Therapy

Direct delivery using viral or non-viral vehicle

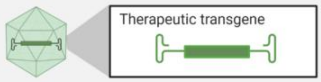
Non-viral delivery
Lipid nanoparticle (LNP)



Development Responsibilities

2seventybio in partnership with GENEVANT

Viral delivery
Adeno Associated Virus (AAV)



Potentially lifelong correction of FVIII deficiency

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

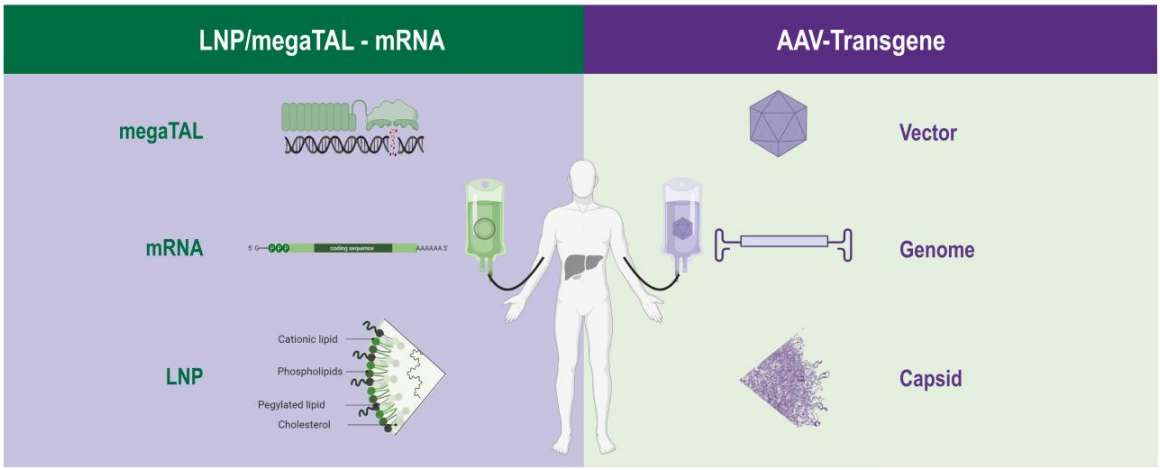
Partnership launched with Research Agreement to "make things happen fast"!

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

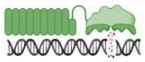
Research Agreement → Collaboration Agreement

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

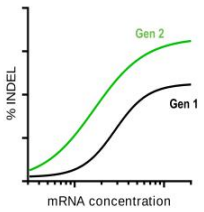
Scientific Considerations



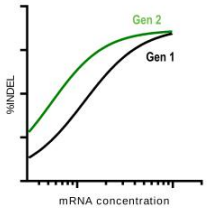
Exploring Product Component Designs



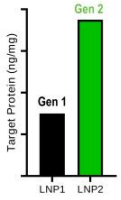
megaTAL Enzyme



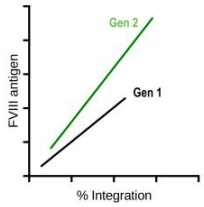
mRNA



LNP Formulations

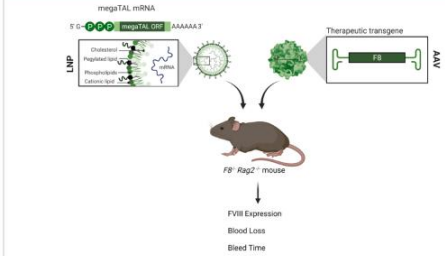


AAV - genome

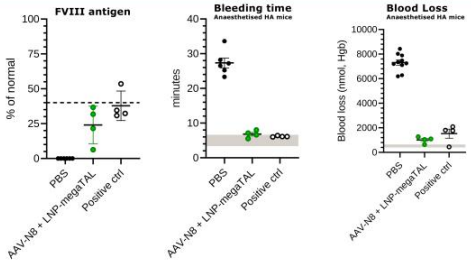


Mouse proof-of-concept
Bleed normalization

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

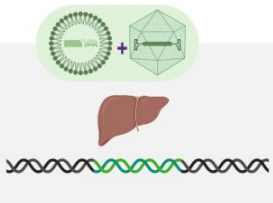
May 1, 2023 11:00 AM EDT

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

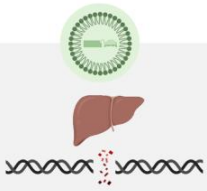
"Novo Nordisk is proud to work in such close and creative collaboration with the team at 2seventy. We are thrilled this program has achieved the strong proof of concept data, triggering this important milestone event."

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

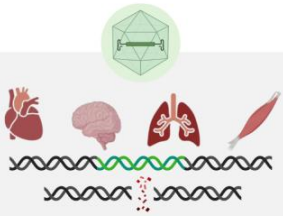
In vivo gene editing approaches
potential platform expansion



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

2seventy bio's R&D philosophy

Accelerate with Industry Leading Partnerships

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

Q&A

2seventy bio Presents Late-Breaking Results for SC-DARIC33, an Investigational CD33-Targeting CAR T in Pediatric and Young Adults with Relapsed or Refractory Acute Myeloid Leukemia

Results of preliminary correlative analysis from the PLAT-08 study show rapamycin-regulated in vivo expansion and activation of SC-DARIC33 T cells as well as concurrent anti-CD33 activity

Enhanced anti-acute myeloid leukemia (AML) potency was obtained with the combination of regulated IL-15 production combined with rapamycin-controlled DARIC33 activation – a potential next generation approach

SC-DARIC33 is a potentially first-in-class CD33-targeting, regulatable CAR T therapy in development with Seattle Children's Therapeutics

CAMBRIDGE, Mass.— (BUSINESS WIRE)—May 19, 2023—2seventy bio, Inc. (Nasdaq: TSVT), a leading immuno-oncology cell therapy company, today announced late-breaking results from the ongoing Phase 1 PLAT-08 trial, in collaboration with Seattle Children's Therapeutics, evaluating SC-DARIC33 in relapsed or refractory pediatric and young adult AML patients, as well as an oral presentation evaluating regulated IL-15 production combined with DARIC33 activation for anti-AML potency. The data were presented at this year's American Society of Gene & Cell Therapy (ASGCT) Annual Meeting in Los Angeles, California.

"The treatment of patients with relapsed and refractory AML represents a tremendous unmet medical need, particularly for pediatric and young adult patients. Progressing the promise of CAR T therapy, while mitigating potentially dose-limiting toxicity, has the potential to be a meaningful advance," said Steven Bernstein, M.D., chief medical officer, 2seventy bio. "Together with Seattle Children's Therapeutics, we are pleased to share results that demonstrate three key steps toward clinically meaningful outcomes: rapamycin dosing optimization, rapamycin-regulated in vivo expansion and activation of SC-DARIC33 T cells as well as concurrent anti-CD33 activity. These data reinforce the potential of SC-DARIC333 as a new T cell therapy approach in AML."

SC-DARIC33 is an investigational CD33-targeted chimeric antigen receptor (CAR) T cell therapy that utilizes 2seventy bio's proprietary Dimerizing Agent Regulated Immunoreceptor Complex (DARIC) T cell platform, a drug regulatable CAR T cell technology. SC-DARIC33 has been shown to be activated by low non-immunosuppressive concentrations of rapamycin in the blood and, when rapamycin is removed, DARIC returns to an inactive state. SC-DARIC33 tests the hypothesis that a pharmacologically regulated CAR can enable potent AML targeting while limiting toxicities associated with normal myeloid and myeloid progenitor cell targeting.

Eligible patients in the ongoing Phase 1 PLAT-08 trial are 30 years of age or younger in first early relapse (less than 6 months), first relapse refractory to reinduction, or ≥ second relapse.
Following lymphodepletion (LD) with fludarabine/cyclophosphamide, patients received SC-DARIC33 T cells followed by rapamycin to activate SC-DARIC33. Primary objectives include assessment of safety and toxicity of SC-DARIC33, as well as the feasibility of manufacturing. Secondary objectives include assessment of efficacy, as well as engraftment, expansion, persistence, and activation states of SC-DARIC33 T cells.

As of March 17, 2023, three participants had received cell product infusion at 1 x 10^6 SC-DARIC33 T cells /kg (dose level 1) following LD chemotherapy. Infusions were generally well tolerated without occurrence of dose-limiting toxicities.

Preclinical studies predicted that DARIC33 dimerization, activation and expansion would occur at rapamycin trough levels in the range of ~1.5-3 ng/ml, well below the trough levels associated with immune suppression. Such levels were not achieved in the initial patient; however, after adjusting rapamycin monitoring and dosing algorithm, these levels were attained in the next two patients. As anticipated, attainment of such levels was associated with DARIC33 dimerization, activation, engagement of antigen and elicitation of CD33 expressing leukemic cell cytotoxicity. Of the two patients who achieved target rapamycin trough levels, the first one had extramedullary leukemia, and in this patient, we were able to infiltrate, activate and expand DARIC33 cells within an extramedullary leukemic infiltrate in the skin, resulting in hemorrhagic necrosis of this infiltrate. In the second patient, we saw DARIC33 expansion in the peripheral blood, peaking nine days after DARIC33 infusion, where 6.1% of the total lymphocytes were DARIC33 cells. The expansion of DARIC33 was associated with a significant transient reduction in the CD33 leukemic burden in the blood. Taken together, we believe this indicates at this very low cell dose that we can dose rapamycin to target levels resulting in the activation and expansion of DARICC33 cells which can then traffic to, engage, and kill leukemia cells.

In a separate oral presentation, researchers evaluated whether regulated IL-15 production combined with drug-controlled DARIC33 activation could enhance anti-AML potency without driving uncontrolled T cell growth or severe toxicity in the preclinical setting. Genetic modules were designed in which a novel synthetic promoter (iSynPro or iSP) transiently drove transcription of a modified IL-15 variant that further restricts IL-15 signaling to cells expressing IL-15Ra. The DARIC33 and iSP-IL-15 DARIC33 CAR T cells had similar expansion and phenotype characteristics during initial manufacturing and T cell activation with tumor cells resulted in rapamycin-dependent secretion of IL-15 in vitro and robust T cell expansion. When IL-15 was omitted from the culture media, iSP-IL-15 DARIC33 demonstrated enhanced expansion following tumor exposure but normal contraction kinetics, suggesting that iSP transcription may enhance T cell function through tightly regulated IL-15 production without promoting unrestrained T cell growth. Further, when AML tumor bearing mice were treated with DARIC33 with or without iSP-IL-15, we observed that both controlled tumor growth, but only iSP-IL-15 DARIC33 CAR T cells controlled tumor growth at a limiting cell dose.

These results demonstrate that Seattle Children's proprietary iSynPro-regulated expression combined with rapamycin-controlled DARIC33 activation has the potential to enhance T cell function while preventing unrestrained T cell outgrowth.

About PLAT-08

PLAT-08, the Phase 1 study of SC-DARIC33 in relapsed/refractory pediatric AML, led by Seattle Children's Therapeutics, couples 2seventy bio's DARIC T cell platform with Seattle Children's world-class bench-to-bedside expertise in oncology cell therapies. This study is a first-in-human investigation of the DARIC T cell platform and is now open for enrollment at Seattle Children's.

PLAT-08 is enrolling pediatric and young adult patients with relapsed or refractory CD33+ leukemia with and without prior history of allogeneic hematopoietic cell transplantation, to examine the safety and feasibility of administering an autologous T cell product that has been genetically modified to express a Dimerizing Agent Regulated Immunoreceptor Complex (DARIC).

For more information visit: clinicaltrials.gov using identifier NCT05105152.

About SC-DARIC33

2seventy bio is collaborating with Seattle Children's Therapeutics to rapidly accelerate development of potential new therapies for patients with acute myeloid leukemia (AML). This research collaboration is investigating potential solutions to two challenges in treating AML: disease heterogeneity and toxicity due to shared expression of targets between tumor and normal tissue.

SC-DARIC33 is an investigational, pharmacologically controlled CD33-targeted autologous T cell product that utilizes 2seventy bio's proprietary Dimerizing Agent Regulated Immunoreceptor Complex (DARIC) T cell platform, a regulatable CAR T cell technology. DARIC T cells are intended to be switched from "OFF" to "ON" in the presence of rapamycin, such that while in the "ON" state the T cell is poised to be activated upon encounter with its target antigen.

SC-DARIC33 is not approved for any indication in any geography.

About 2seventy bio

Our name, 2seventy bio, reflects why we do what we do - TIME. Cancer rips time away, and our goal is to work at the maximum speed of translating human thought into action – 270 miles per hour – to give the people we serve more time. We are building the leading immuno-oncology cell therapy company, focused on discovering and developing new therapies that truly disrupt the cancer treatment landscape.

With a deep understanding of the human body's immune response to tumor cells and how to translate cell therapies into practice, we're applying this knowledge to deliver next generation cellular therapies that focus on a broad range of hematologic malignancies, including the first FDA-approved CAR T cell therapy for multiple myeloma, as well as solid tumors. Our research and development is focused on delivering therapies that are designed with the goal to "think" smarter and faster than the disease. Importantly, we remain focused on accomplishing these goals by staying genuine and authentic to our "why" and keeping our people and culture top of mind every day.

For more information, visit www.2seventybio.com.

Follow 2seventy bio on social media: Twitter and LinkedIn.

Cautionary Note Regarding Forward-Looking Statements of 2seventy bio

This release contains "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 results of ongoing and planned pre-clinical studies and clinical trials; statements about the safety, efficacy and perceived therapeutic benefits of our product candidates and the potential dosing and indications thereof, market opportunities and demand therefor; statements about the strategic plans for 2seventy bio and potential corporate development opportunities; and statements about our ability to execute our strategic priorities. Any forward-looking

statements in this press release 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 press release, including, without limitation; the risk that our plans with respect to the research, pre-clinical and clinical development and regulatory approval of our product candidates may not be successfully achieved on the planned timeline, or at all , and that the collaboration with Seattle Children's Therapeutics may not continue or be successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release 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. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, 2seventy bio undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

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2seventy bio

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