GENE EDITED CAR-T

Focusing on Effective Therapies

Cellectis, June 2018

Forward-looking Statements

THIS PRESENTATION CONTAINS “FORWARD-LOOKING” STATEMENTS THAT ARE BASED ON OUR MANAGEMENT’S CURRENT EXPECTATIONS AND ASSUMPTIONS AND ON INFORMATION CURRENTLY AVAILABLE TO MANAGEMENT.

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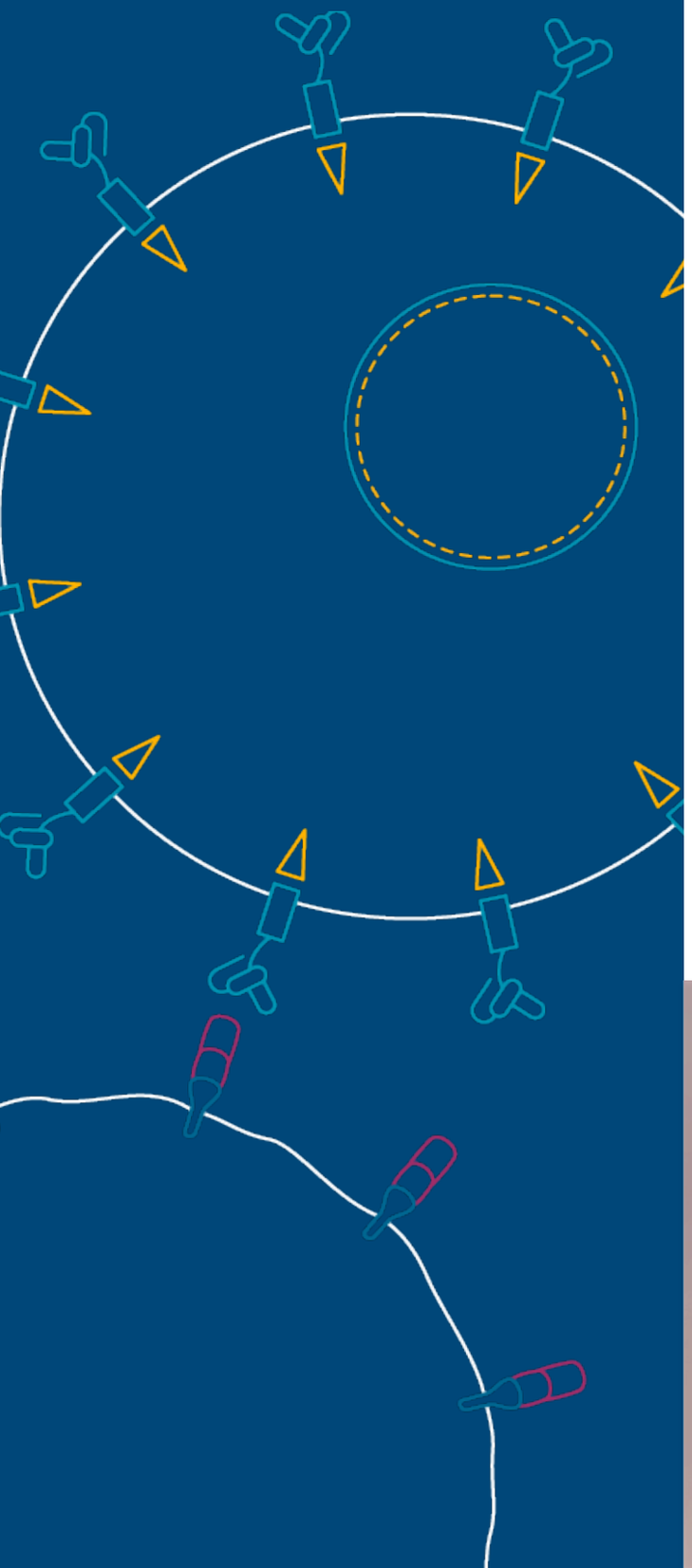
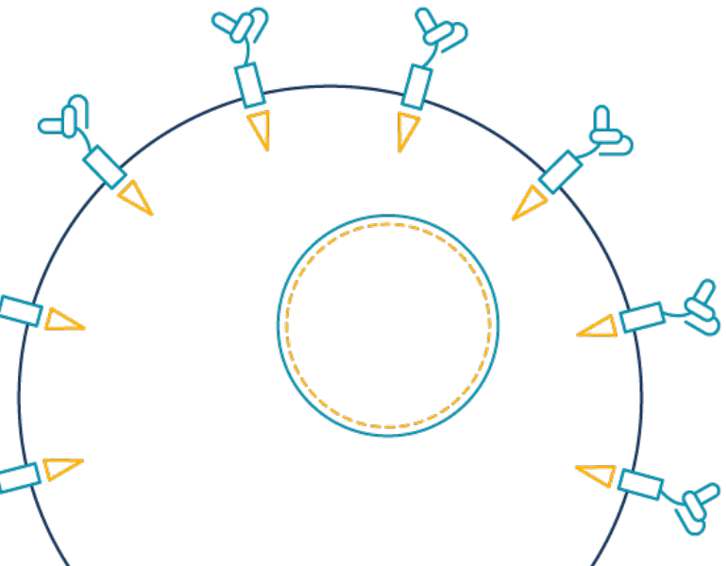


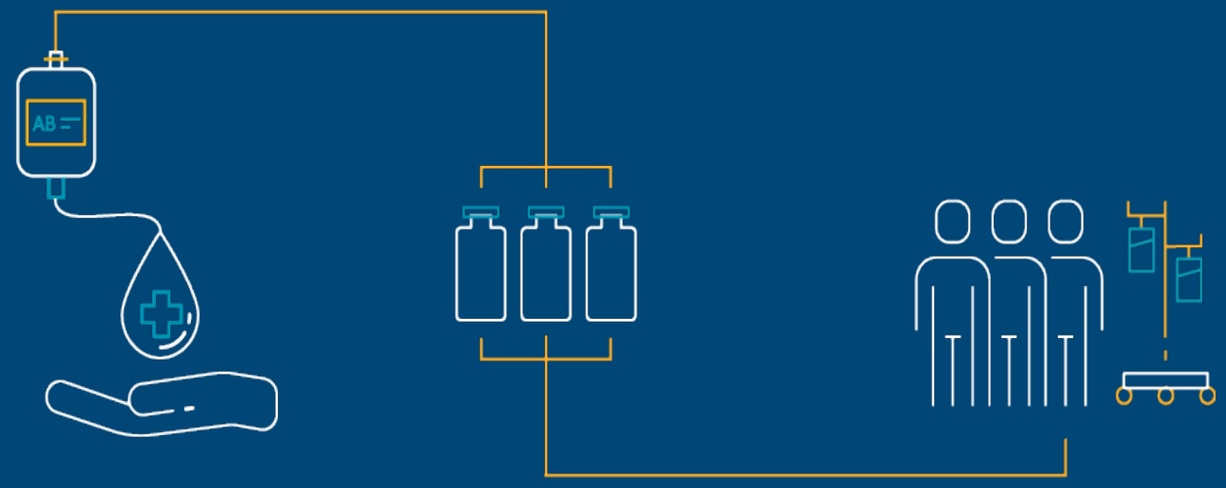
1. ALLOGENEIC CAR-T

The “Allogeneic” CAR-T Concept

- **Lessons of 2017:**

  I. CAR-Ts are here to stay
  II. 2 CAR-T BLAs approved by FDA
  III. Allogeneic concept validated
  IV. Sales benchmark for autologous CARTs



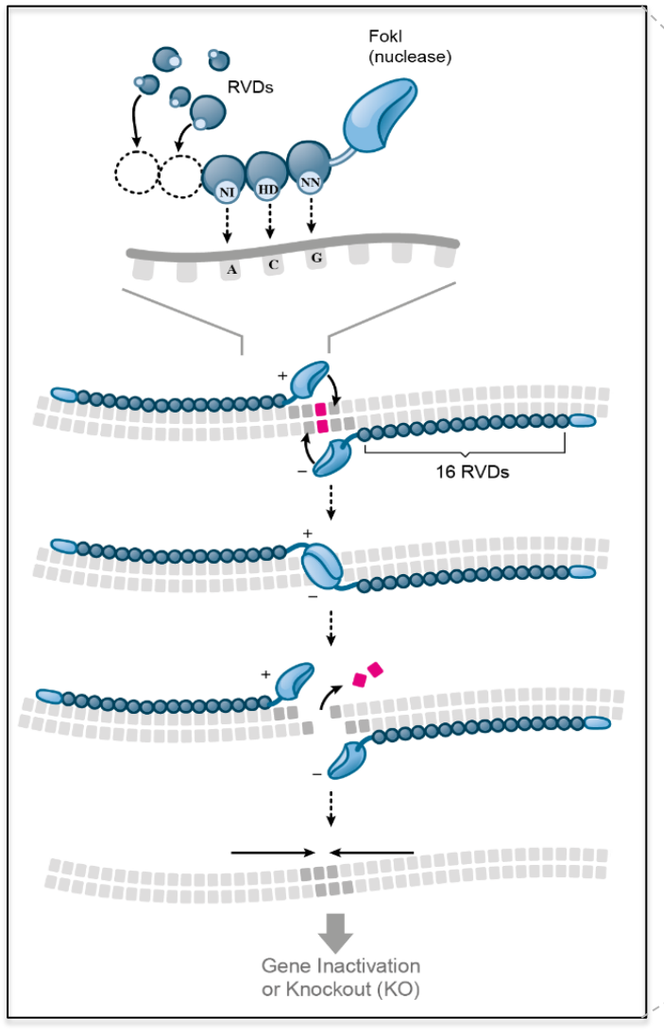


- **Allogeneic CAR-Ts: major uncertainties lifted**

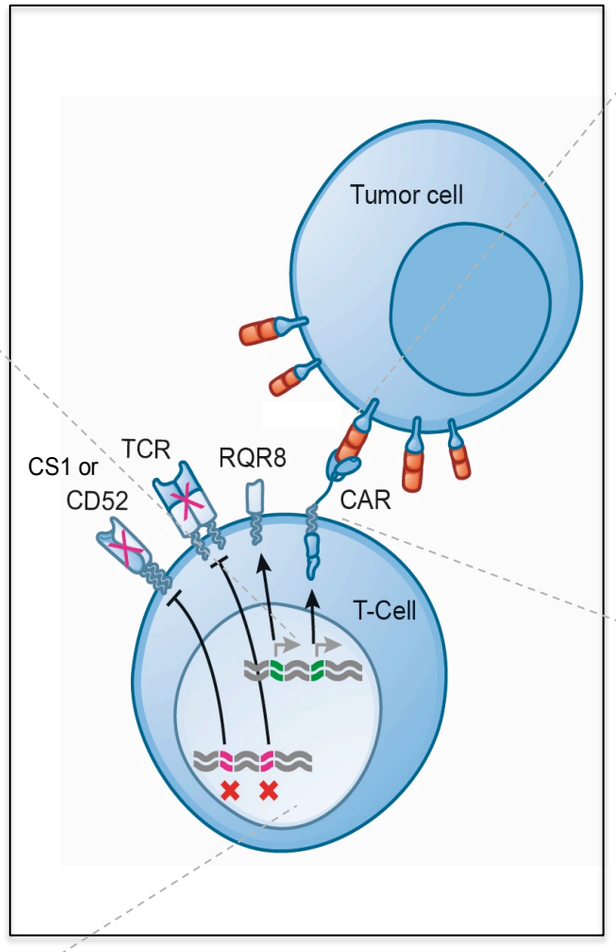
  ✓ **Industrialized manufacturing process**
  ✓ TALEN® gene editing in clinical trials in the US and EU
  ✓ **No significant GvHD**
  ✓ Allogeneic CAR-T **engraft and expand**

How it works

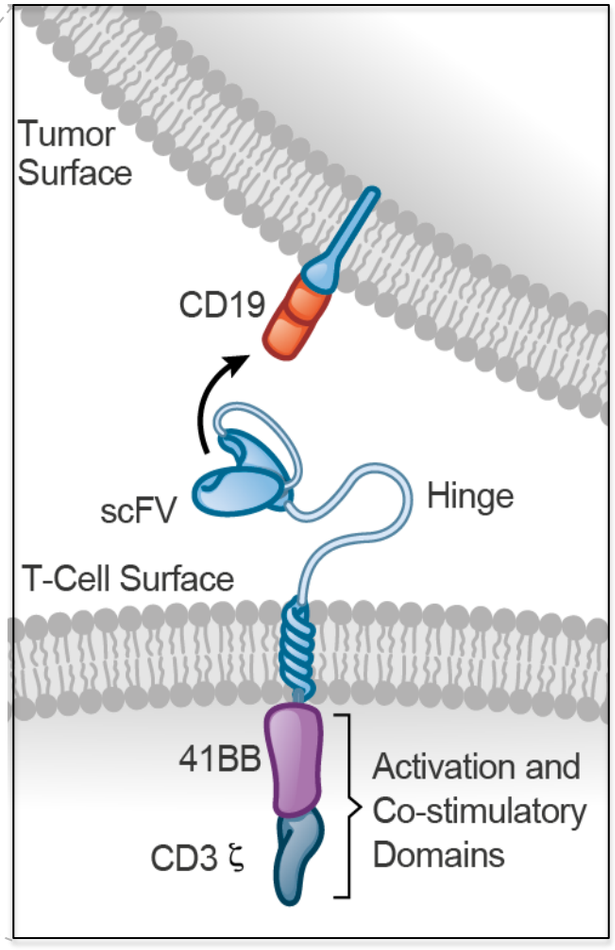
Allogeneic CAR T-Cells Through Gene Editing



Gene Editing
TALEN® Nuclease



Allogeneic
CAR T Cell



Chimeric Antigen Receptor
Tumor Recognition

The Benefits Of UCARTs

UCARTs = Cellectis' Allogeneic CAR T-Cells

Market access

- Ability to release large amounts of product in advance
- Easily available at hospitals
- Can address patient populations that are deficient in T-cells

Cost of treatment

- Possibility to lower the price range of CART therapies to other IO standard
- No additional cost linked to "segment of one" supply chain

Ability to re-dose

- Possibility to re-dose with same antigen targeting CARTs
- Possibility to combine different antigen targeting CARTs
- No issue of long term persistence and related side effects

A Strategic Alliance in Gene-Edited CAR-T

Leading the way in the allogeneic CAR-T arena

A team made of big pharma partners and leading biotechs strongly financed

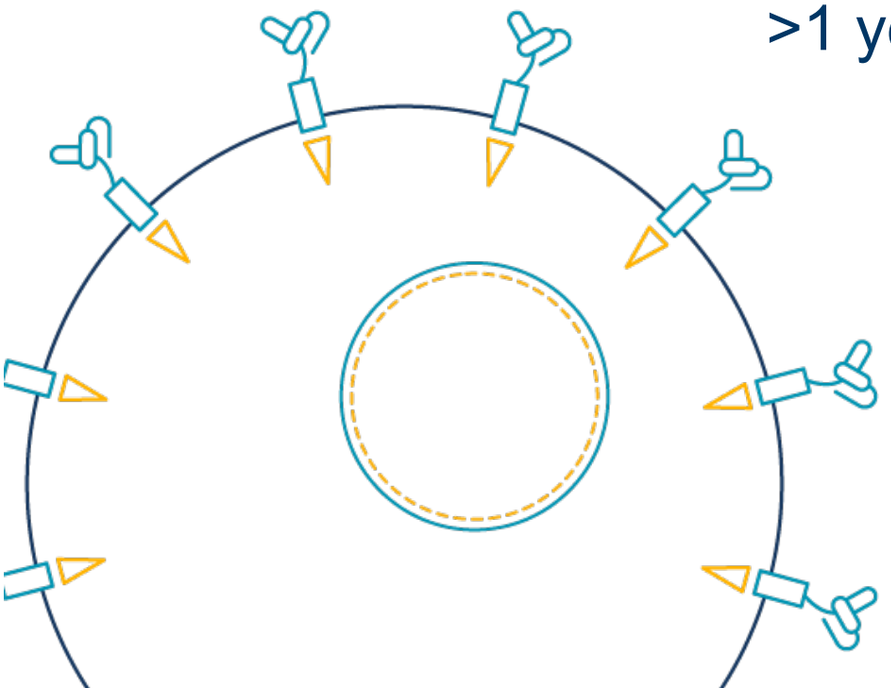
Pfizer

GILEAD

SERVIER

cellectis
EDITING LIFE

Allogene THERAPEUTICS
Kite's Former Leadership team



>1 year to clinic

- BCMA
- EGFRVII
- UCARTCS1

Phase 1 dose escalation in multi-centric trials

- UCART19
- UCART123
- UCART22

Expansion Phase in 2019

2. Leading the Gene Edited CAR-T Space

Rich Allogeneic CAR-T Pipeline

Addressing Unmet Medical Need With Proven Targets

Program	Indication	Preclinical	Manufacturing	IND Filing[1]	Phase I	Ph II	Ph III
UCART19[2] (Servier / Allogene)	ALL (PALL)						
	ALL (CALM)						
UCART123	AML						
	BPDCN						
UCART22	B-ALL						
UCARTCS1	MULTIPLE MYELOMA						

- **3 programs in clinic: UCART19, UCART123 & UCART22**
- **Manufacturing of UCARTCS1 ongoing**

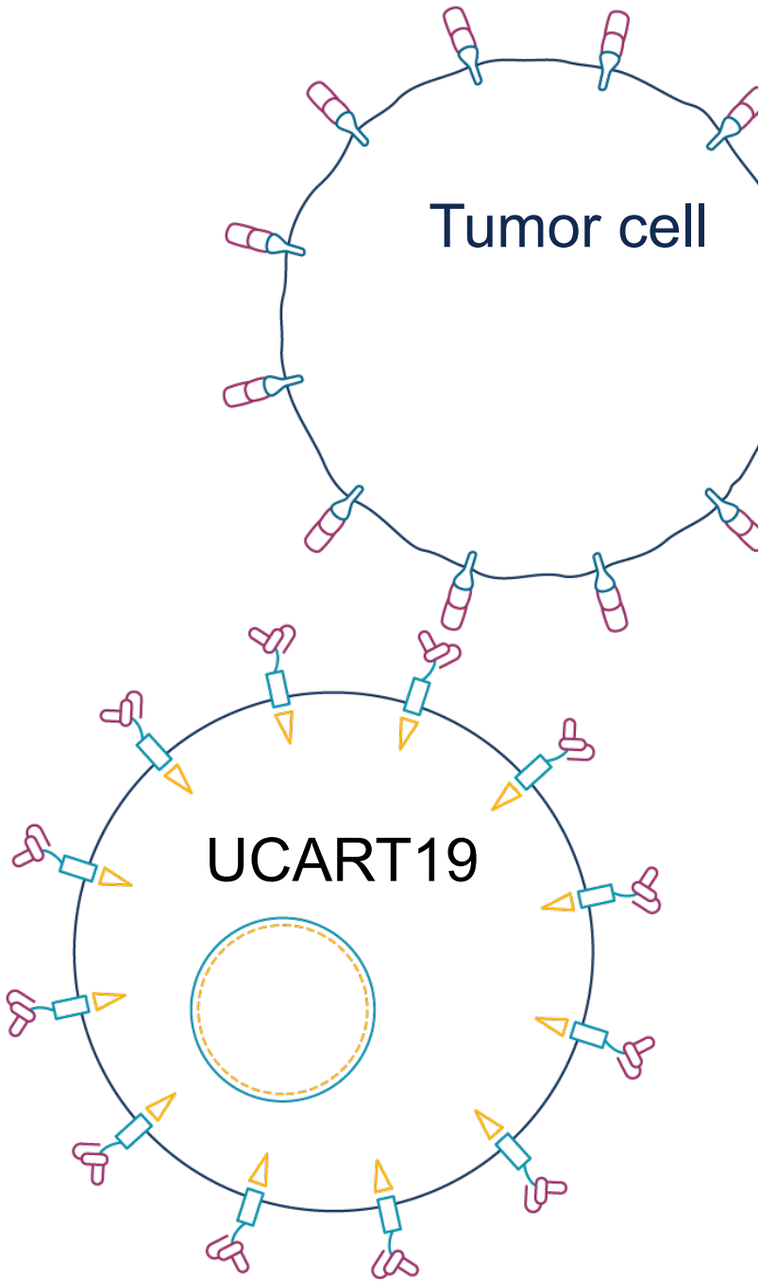
[1] *Or European equivalent.*

[2] *UCART19 is exclusively licensed to Servier and under a joint clinical development program between Servier and Allogene.*

UCART19[1]

Initial Proof Of Concept In ALL Patients

- 1st patient dosed in June 2015 (compassionate)
- Phase I trials started in June 2016 in EU, in 2017 in the US
- Multiple recruiting centers (EU and the US)
- 17 patients treated disclosed (9 adults and 8 pediatric)[2]



[1] *UCART19 is exclusively licensed to Servier and under a joint clinical development program between Servier and Allogene.*

[2] *Including compassionate.*

UCART19 Early Clinical Data

Interim Ph1 Dose Escalation In Pediatric & Adult ALL Patients

- Expansion of UCART19 and preliminary signs of efficacy in line with early autologous CAR-T Phase I results published in past years
- Proof of Concept of efficacy of redosing in one patient

	Lymphodepletion & Patient Age	Disease Status Before Treatment	Dose Level (CAR-T Cells/ kg)	Response	Adverse Event > Grade 3	Follow up
SERVIER & KCL (PALL) EBMT 2018	**FCA (5/6) or FC (1/6) 6 m to 18y**	**3/6 with >4 lines of treatment;**	**1.1 to 2.3x10^6**	**Flow MRD – in 5/6 and PCR MRD- in 3/6**	**CRS 17% (1/6)**	**2 patients still in remission > 10 months post-allo-SCT**
SERVIER & KCL (CALM) EBMT 2018	**FCA (8/9) or FC (1/9) ≥16y**	**5/9 with >4 lines of treatment; 7/9 with prior allo-SCT and in relapse; 2/9 with >85% BM blasts**	**1x10^5 to 1x10^6**	**67% (6/9) CR or CRi (5 MRD-)**	**CRS 11% (1/9) Prolonged cytopenia 33% (3/9)**	**2 patients still MRD- at 8 months post-allo-SCT**

MRD: Molecular Residual Disease
CRi: Complete Remission with Incomplete blood count recovery

UCART123 in AML and BPDCN

Product Attributes And Pre-clinical Data

Weill Cornell Medicine

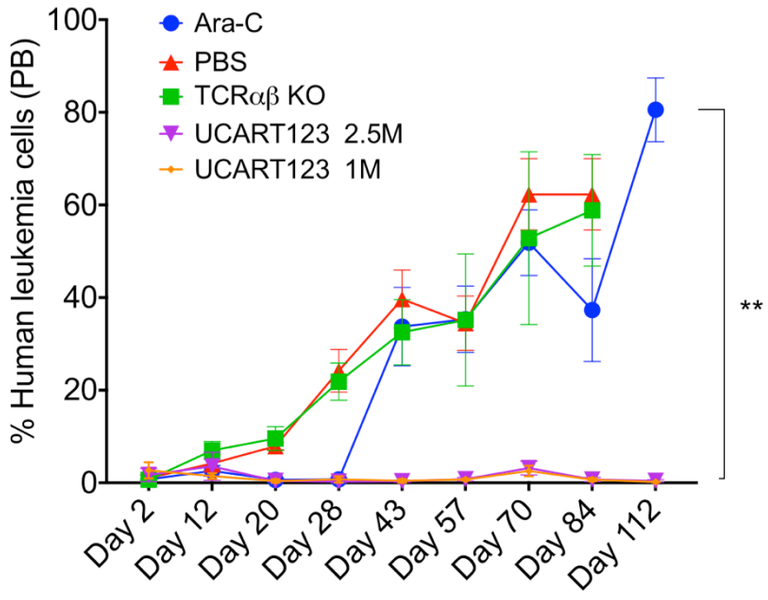
UCART123 attributes

- Anti-CD123 CAR expression to redirect T-cells to tumor antigens
- Suicide gene for safety
- TCR disruption to avoid GvHD

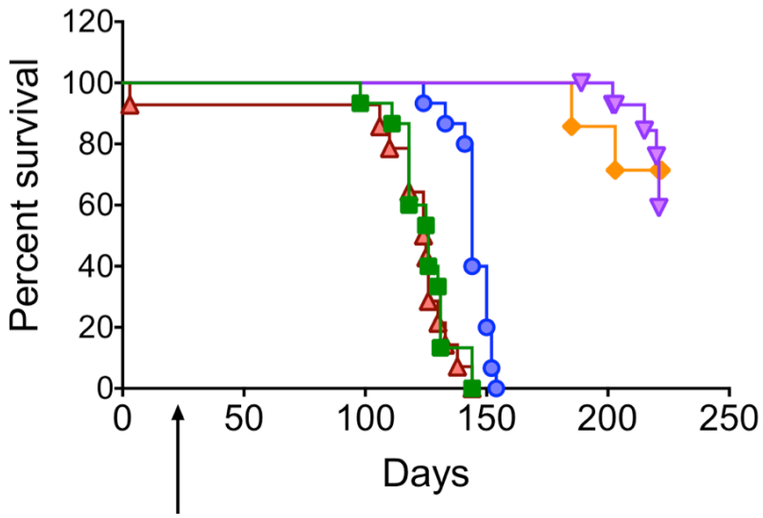
Encouraging pre-clinical efficacy data

- Significant improvement compared to Cytarabine standard-of-care (Ara-C)
- Encouraging results with CD123 target in autologous CAR-T approaches

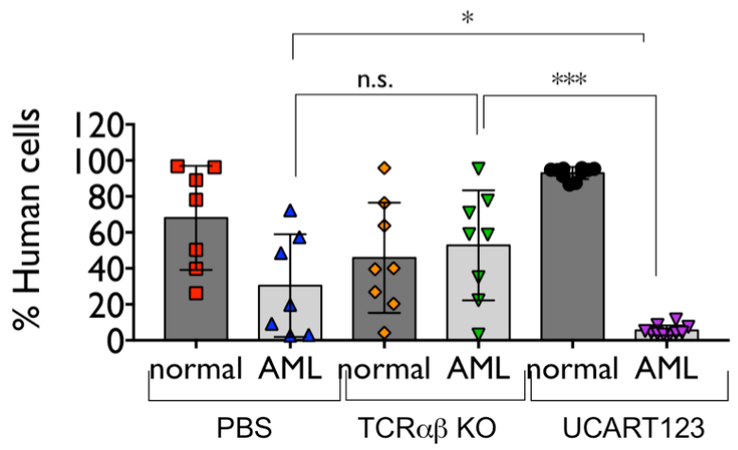
Peripheral Blood Evaluation



Overall Survival



Bone Marrow at Day 36



UCART123 Dosing Schedule

First wholly-controlled CAR-T in the clinic

- AML Phase 1 dose-escalation trial ongoing at Weill Cornell & MD Anderson Cancer Center
- First patient dosed in June 2017

Dose Escalation (mTPI) Phase (R/R AML)

DL3	$5.05x10^6$/kg
DL2	$6.25x10^5$/kg
DL1	$2.5x10^5$/kg
DL-1	$1.25x10^5$/kg

Total Dose Escalation N= 18 pts

Expansion Phase

RR AML
N=18-37

Untreated AML
ELN Adverse Genetic Group
N=46-107

Total Phase I Expansion
N=64-144

Clinical research coordinated by principal investigator Prof. Gail J. Roboz, MD, at Weill Cornell

UCART123 Protocol Amendment

Main changes to the revised protocol

- **Increase of dose levels:**

✓ DL1 increased from $6.25x10^4$ to $2.5x10^5$ UCART123 cells per kg. DL2 & DL3 now respectively at $6.25x10^5$ and $5.05x10^6$. DL-1 is now at $1.25x10^5$.

✓ The product's safety and tolerability profile allowed Cellectis to increase DLs with a capping at 80kg equivalent.

- **Treatment interval shortened** between patients from 42 days to 28 days between 1st and 2nd patient at each new dose level tested*, then to 14 days for subsequent patients.
- A **potential second UCART123 infusion** is implemented.
- The AML clinical study is now multicentric

*Except for patients with aplastic bone marrow at Day 28 for whom the DLT period will be extended to 42 days post UCART123 injection

UCART22

Product Attributes And Pre-clinical Data

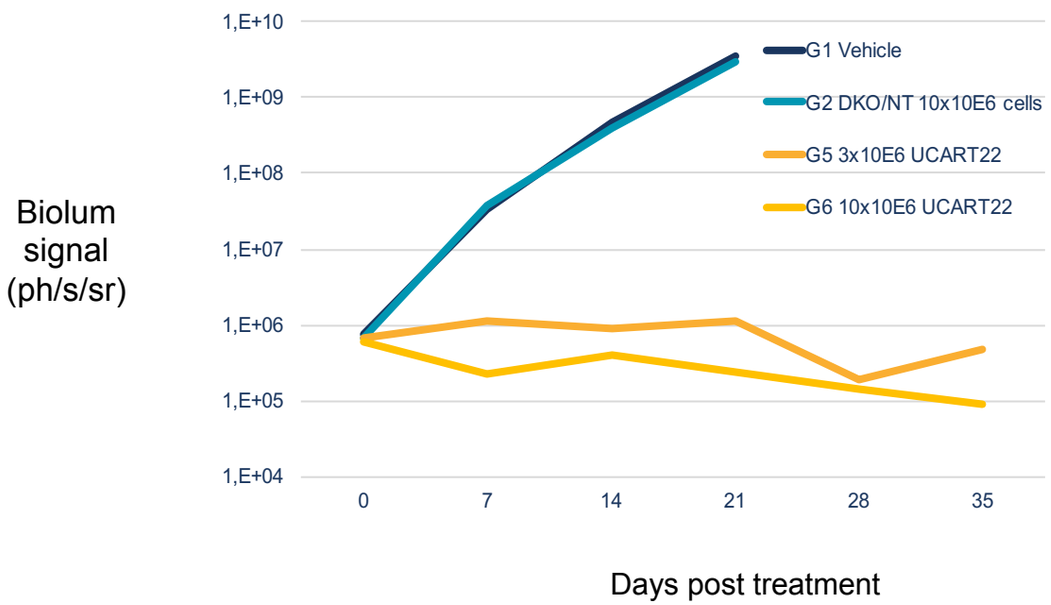
UCART 22 Rationale

- Both CD22 and CD19 are expressed on various B-cells
- CD22 expression frequently maintained in CD19-negative blasts1

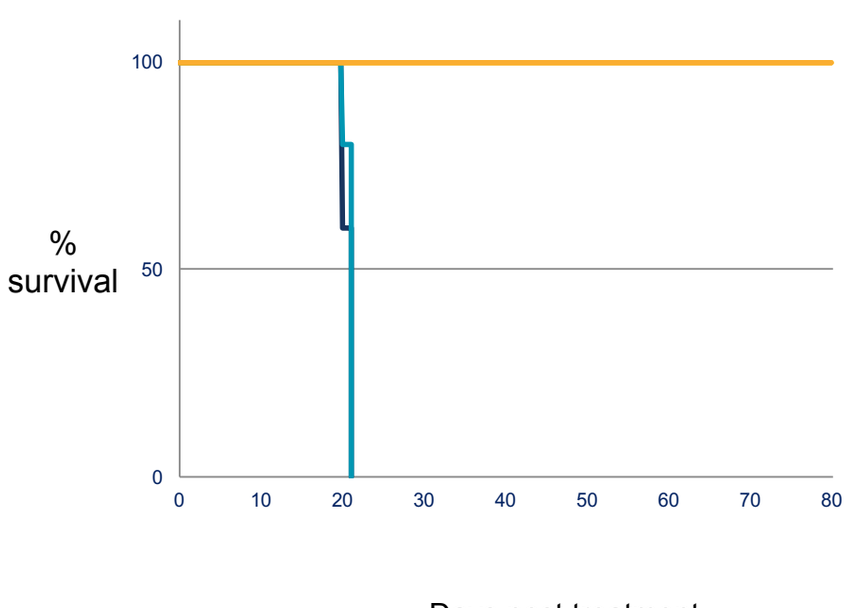
Strong anti-tumour activity

- UCART22 is highly efficient at eradicating tumors *in vivo*
- UCART22 cells result in increased mice survival

CD22+ Cell Line Show no Tumor Progression



Survival Curves



UCART22

Objective for patient enrolment

- Relapsed / refractory adult ALL patients first
- Potential to expand
- Enrolment open to CD19 treatment naïve patients
- Open also to anti-CD19 pre-treated relapsing patients
- Selection of strong CD22 expressing B-malignant cells (>2,000 CD22/cell)
- First dose cohort starting at $1x10^5$ UCART22 cells per kg
- Age limit is 65 years
- Transplant after UCART22 treatment not a requirement

UCARTCS1

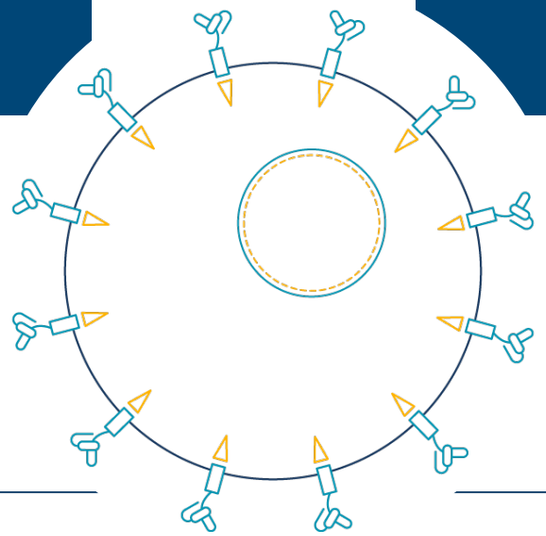
Targeting Multiple Myeloma

Unmet Medical Need

- > 30,000 patients / year in the US
- High relapse rate, median OS of 9 months

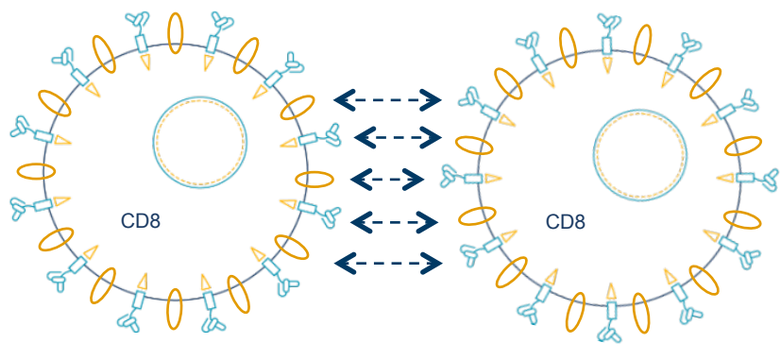
Target Antigen

- Well proven target with elotuzumab (BMS/ Abbvie) as PoC
- CS1 (SLAMF7) is highly expressed on MM cancer cells
- CS1 is expressed on CD8 T-cells



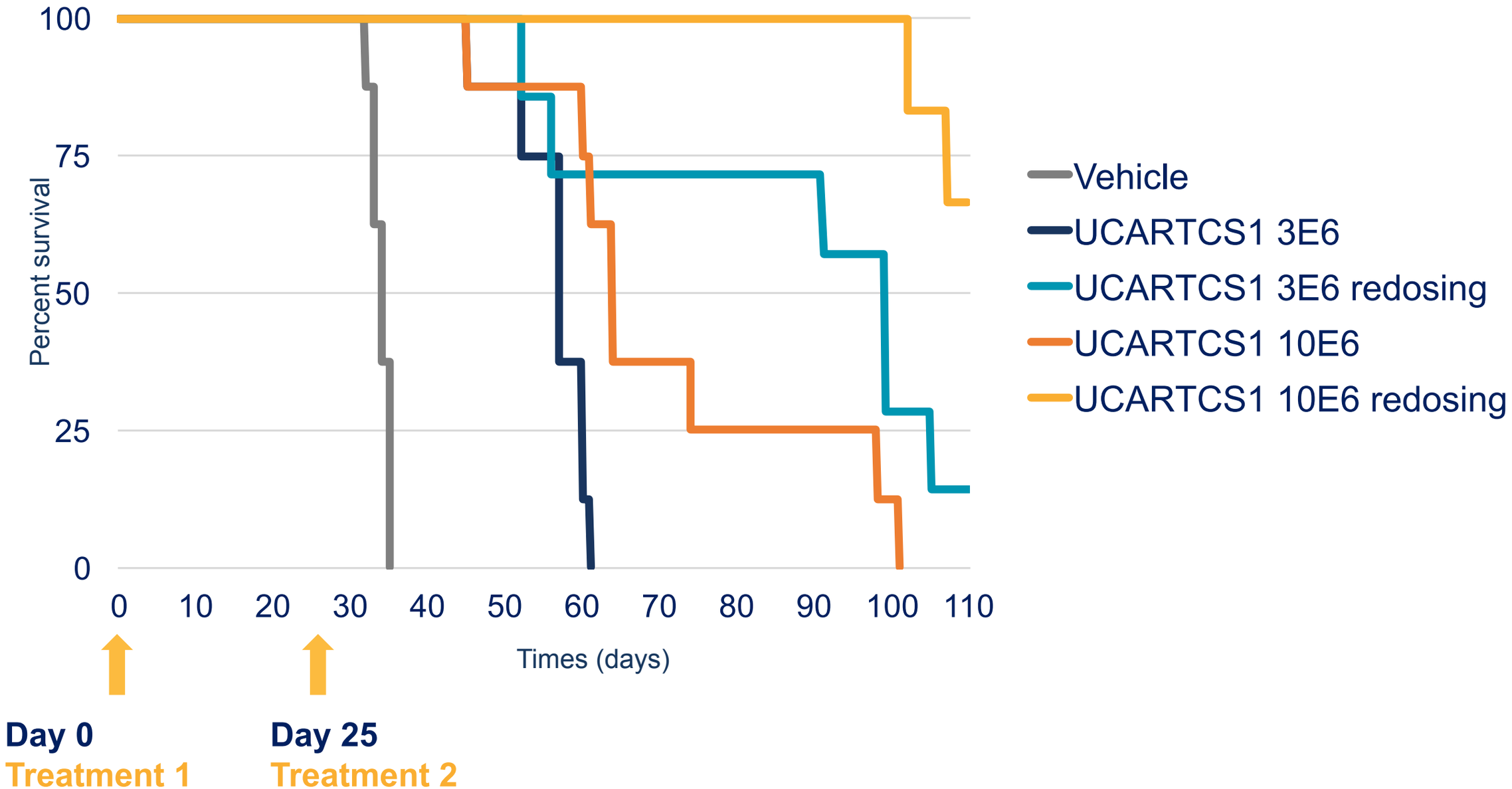
UCARTCS1 Attributes

- Pre-clinical data shows high efficacy of re-dosing strategies
- Suicide gene is included for safety
- TCR gene disruption using TALEN® to avoid GvHD
- CS1 gene is disabled by TALEN® to prevent CAR T-cell cross-reactivity (CS1 is naturally expressed on CD8+ T-cells)



UCARTCS1

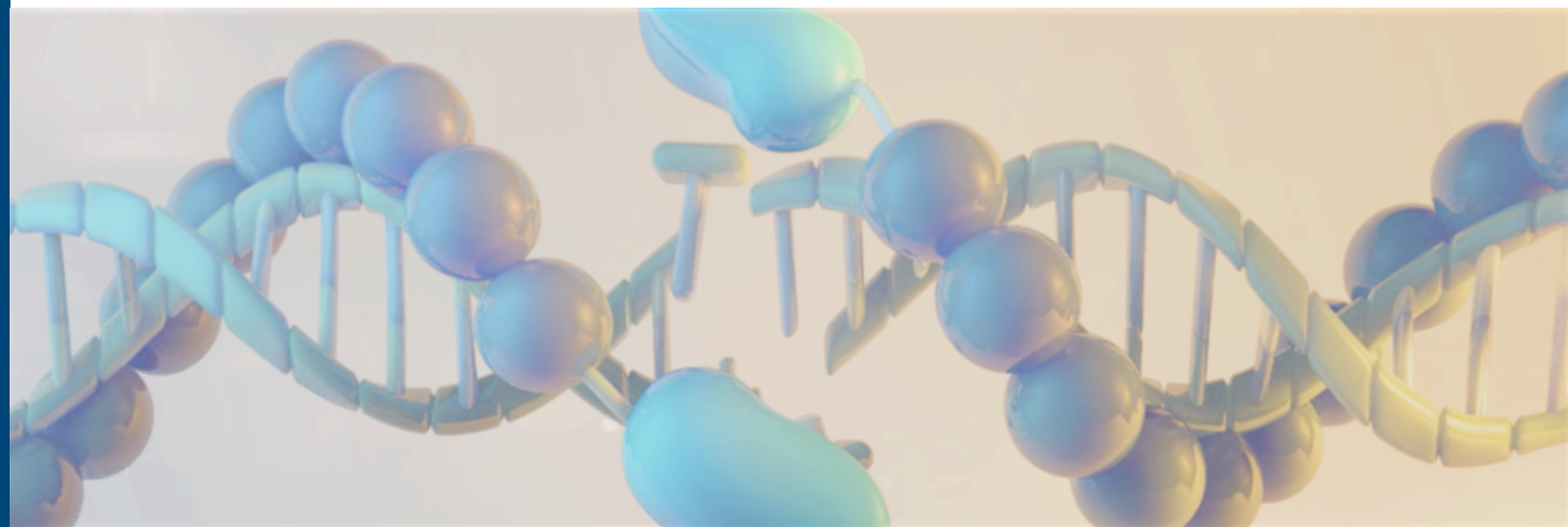
Anti-tumor activity: high performance with re-dosing



Day 0
Treatment 1

Day 25
Treatment 2

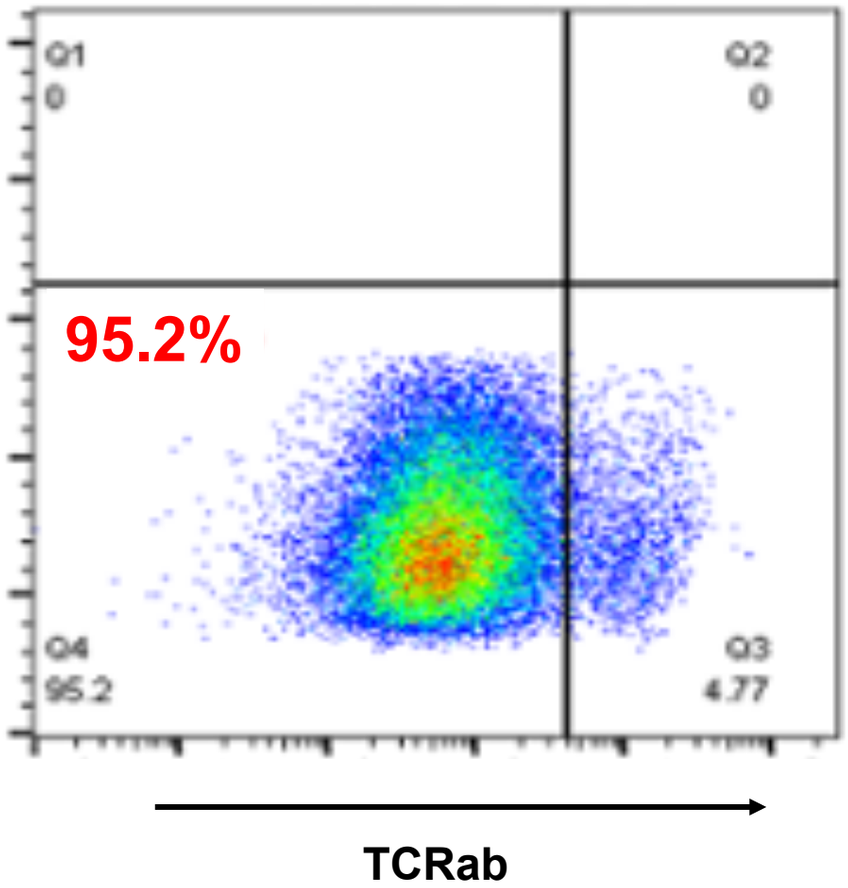
3. Gene-Editing Platform TALEN®



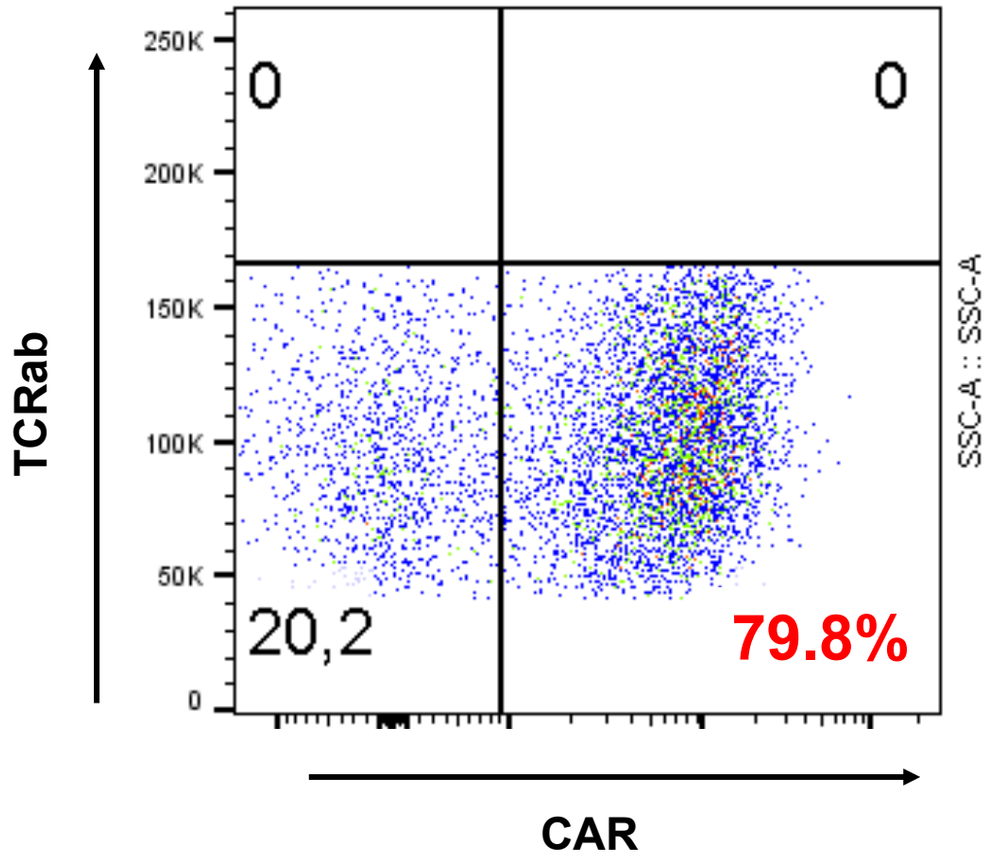
TALEN® High Yield Gene Editing

High Single Knock Out and Knock In Efficiencies

TRAC Knock Out



CAR Knock In at TRAC Locus



95.2% Single Knock-Out

~80% Single Knock-In

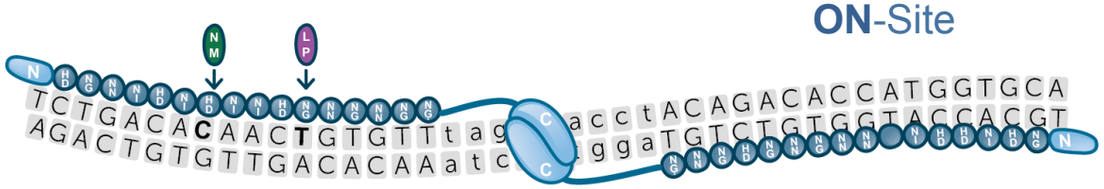
Control of TALEN® Off-Target Effect

Use of engineered RVDs to discriminate between ON and OFF-site

- Educated utilization of engineered RVDs to discriminate HBB loci preventing OFF-site cleavage

HBB

ON-Site



ON-site/OFF-site > 94 % identity

HBD

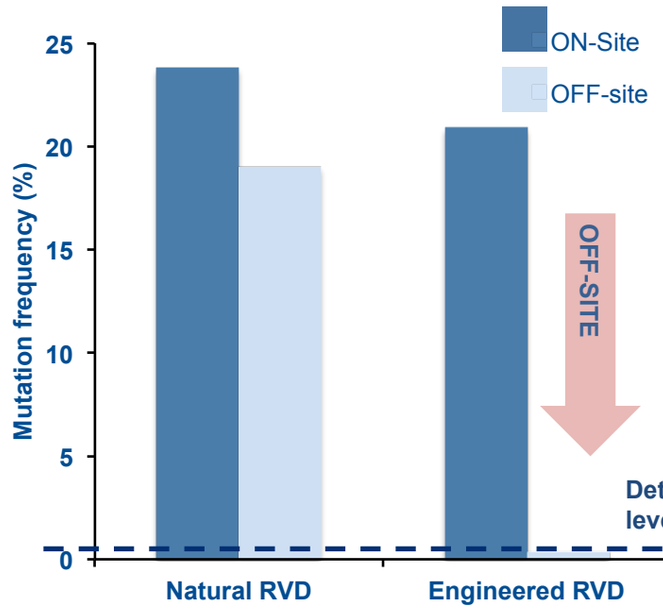
OFF-Site

PD1

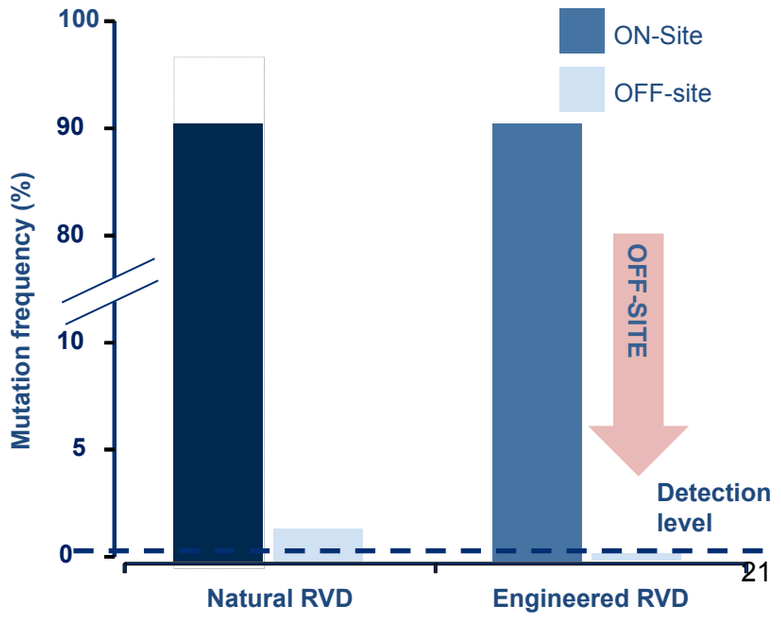
ON-Site

Chr17 q24.1

OFF-Site



Juillerat et al (scientific report 2015)



High Yield Multiplex Gene Editing

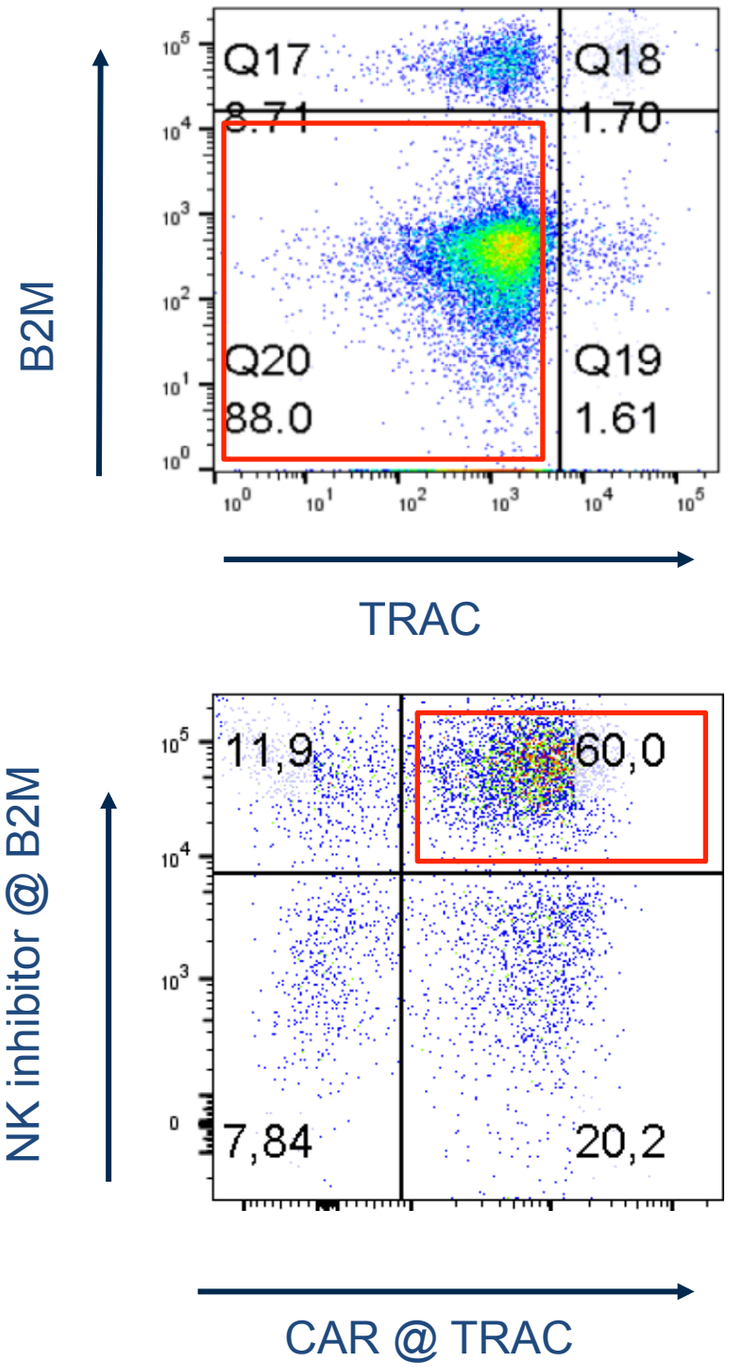
Combining Knock-Out and/or Knock-In in T-cells

Key Results

- **88% double targeted gene inactivation**
  TCR and B2M

- **60% double targeted gene insertion**
  CAR insertion at TCR
  NK inhibitor at B2M

TRAC TALEN® + CAR

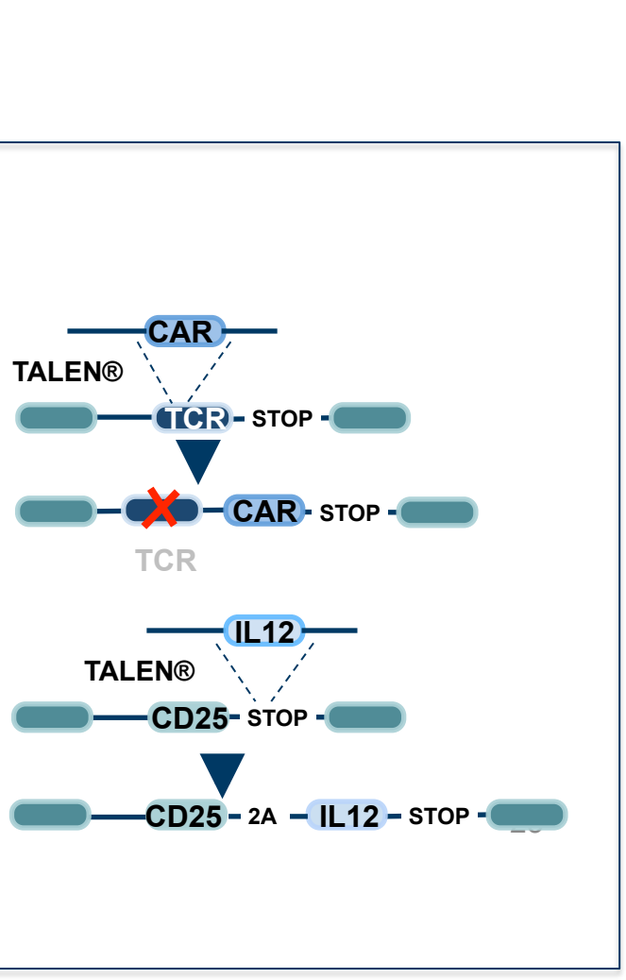


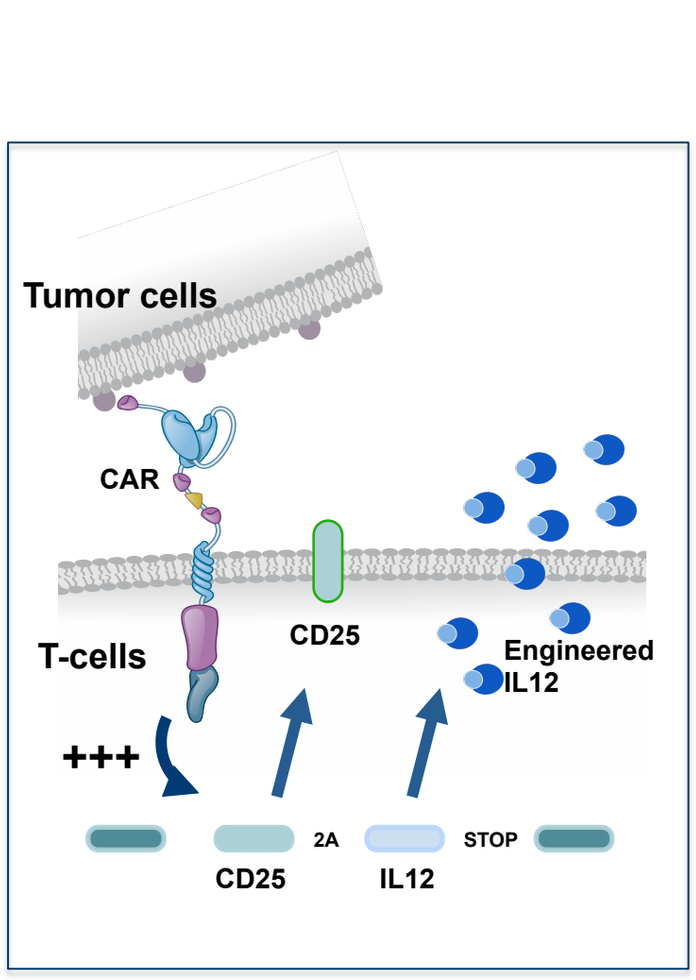
Next Gen. CARTs To Target Solid Tumors

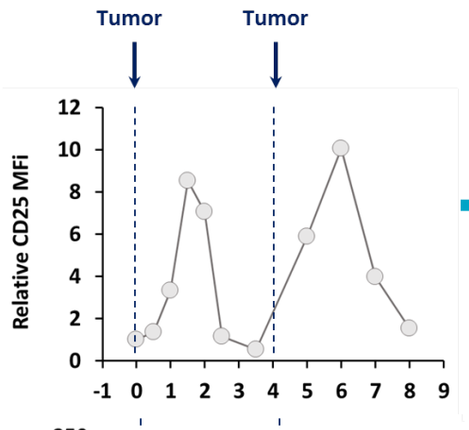
Synthetic Biology For High Performance UCARTs

Example of targeted integration at CD25 locus

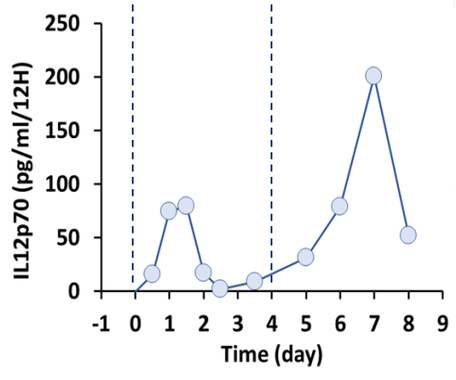
- IL12 contributes to anti tumor activity (Th1, NK, CD8)
- I.V. IL12 shows systemic adverse effects (BM, Liver, mucus membranes)
- Local On-Target IL12 secretion may avoid systemic toxicity



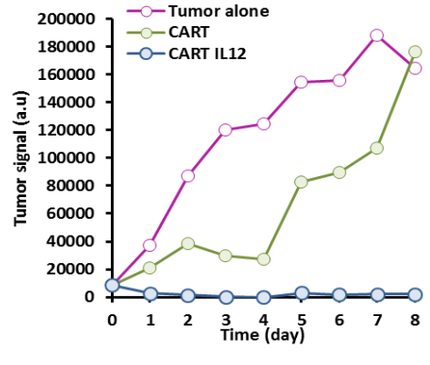




CD25 expression upon tumor engagement

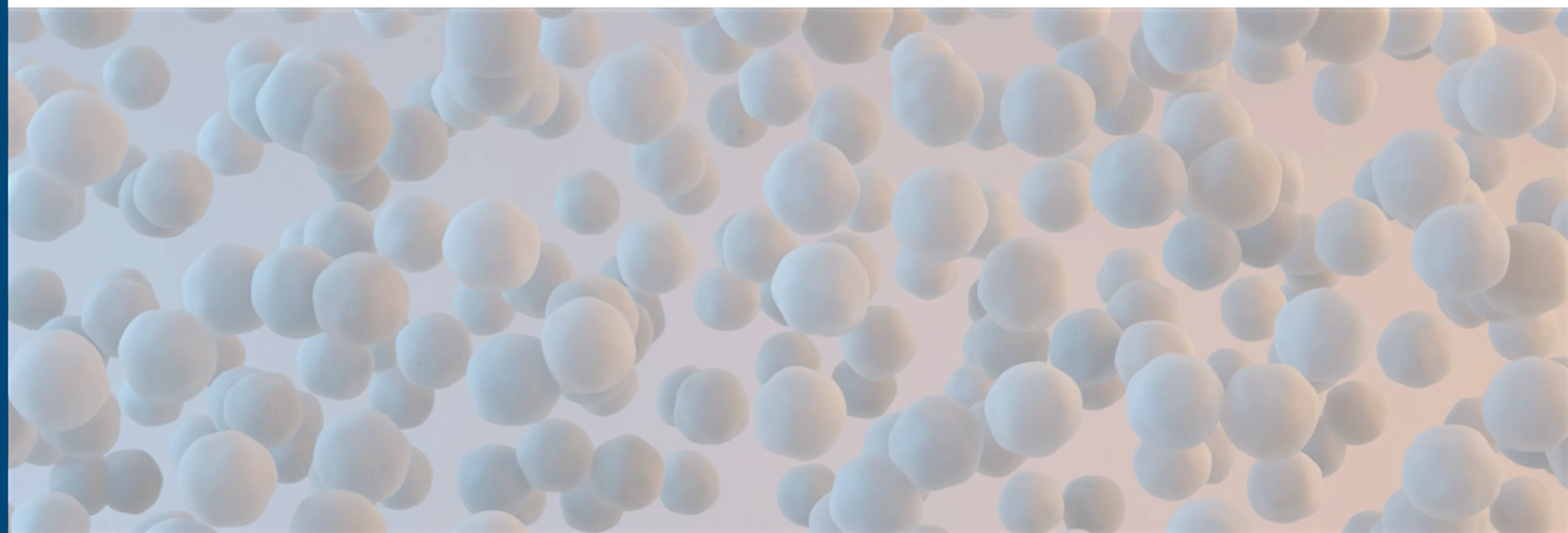


Engineered IL-12 follows CD25 expression pattern upon tumor engagement.



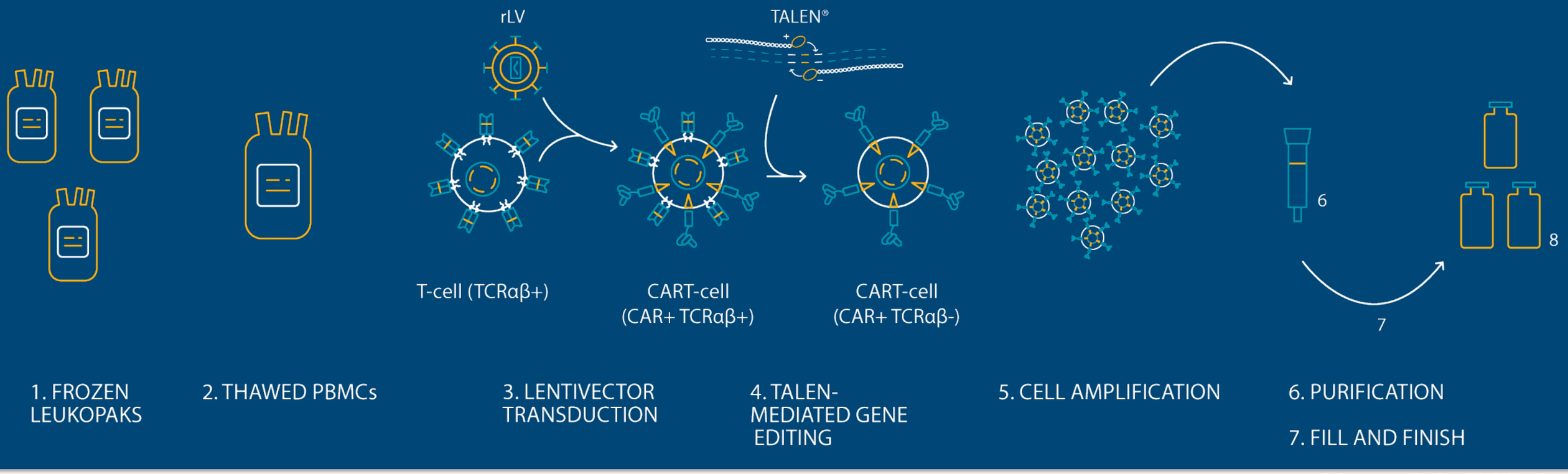
Tumor dependent expression of engineered IL-12 under the control of CD25 promoter significantly **improves tumor eradication.**

4. Acceleration of Manufacturing Capacity



Allogeneic CAR-T – GMP Manufacturing

An integrated system combining gene editing and CAR-T manufacturing



- Successful GMP manufacturing of UCART19, UCART123, UCART22
- GMP manufacturing of UCARTCS1 started
- Full QC system in place, cleared for clinical trials in the EU and by the FDA

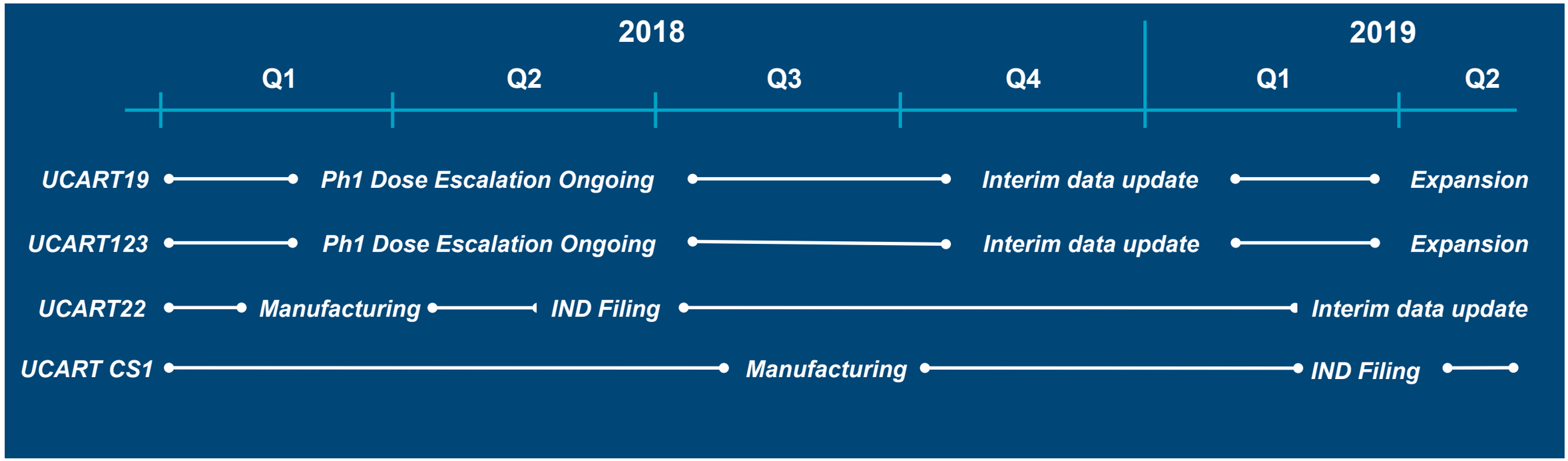
An Outstanding Experience in CAR-T

Acceleration of timelines through previous proof-of-concept studies

- **UCART19 in ALL patients**
  - Phase I dose escalation studies ongoing
  - Expected to enter multi-centric Phase II studies in 2019
- **UCART123 in AML and BPDCN patients**
  - Clinical hold lifted in November 2017
  - Phase I dose escalation resumed in December 2017
  - Protocol amendment for the AML study in May 2018
- **UCART22 in ALL patients**
  - IND approved in June 2018
  - Built on experience of UCART19
- **UCARTCS1 in Multiple Myeloma**
  - Manufacturing and pre-clinical testing ongoing

Expected Milestone Timeline

Strong progress expected over the next 18 months



- **UCART19 in ALL patients** Phase 1 clinical trials ongoing; interim data presented at ASH 2017
- **UCART123 in AML and BPDCN patients** Phase 1 clinical trials ongoing
- **UCART22** IND approved in June 2018
- **UCARTCS1** manufacturing ongoing
- **Cash Runway through 2021** providing funding through multiple data readouts

The Cellectis Group

cellectis

- NASDAQ: CLLS
- EURONEXT GROWTH: ALCLS
- c.$500M IN CASH (WITH CALYXT)
- IMMUNO-ONCOLOGY / CAR T
- THERAPEUTIC GENE EDITING
- GENE THERAPY

~70,6% ownership

calyxt

- NASDAQ: CLXT
- c. $100M IN CASH
- BASED IN MINNESOTA
- CONSUMER FOCUS
- HIGH VALUE ASSET

Gene editing is the link

THANK YOU

cellectis

EDITING LIFE

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