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the life science company

ENGINEERED CAR-T THERAPIES

A NEW PARADIGM IN ONCOLOGY

SEPTEMBER 2016

FORWARD LOOKING STATEMENTS

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Transforming CAR T Immunotherapy

CREATED

First off-the-shelf, gene-edited CAR T-Cells ever used in humans

First patient treated in phase 1 trial of UCART19 in B-ALL

ADVANCING

CAR T-Cells into pharmaceutical products

Cost effective, high yield, controllable cell properties, potential front-line therapy

TRANSLATING

Clinical success of autologous CARTs in off-the-shelf therapies

Next generation, commercially viable, universal treatment option

LEADING

Best in class gene-editing and electroporation platform

To-date unmatched gene editing efficiency and precision with TALEN®

SERVING

Worldwide patient population with unmet medical needs

Potentially increasing patient access and targetable tumor types

World Class Collaborations

for Cellectis

$80M upfront plus $35M in equity

$185M in milestones per product

$2.8B in aggregate total milestones

High single digit royalties on worldwide sales

Research, Product Development, Option, License and Commercialization Agreement with Servier on 5 targets, including UCART19

Early exercise of UCART19

$974M in aggregate total milestones

High single digit royalties on worldwide sales

Development of Cellectis' lead product candidate for AML, UCART123

Co-principal investigators are Dr. Gail Roboz, Director of the leukemia program and Professor of Medicine, and Dr. Monica Guzman, Assistant Professor of Pharmacology in Medicine

UCL / Great Ormond Street Hospital (GOSH)

Great Ormond Street Hospital (GOSH) / UCL delivered initial proof of concept for UCART19 with the in-human application of off-the-shelf allogeneic CAR T-Cells in two pediatric patients

Investigator Site for P1 clinical trial of UCART19 in pediatric patients sponsored by Servier

Development of UCARTCS1 for Multiple Myeloma, UCART22 for ALL, UCART38 in for T-Cell ALL and UCART123 for BPDCN

Alliance is led by Pr. Hagop Kantarjian, MD, Chair, Department of Leukemia, and Pr. Robert Orlowski, MD, PhD, Department Ad Interim Chair, Department of Lymphoma/Myeloma

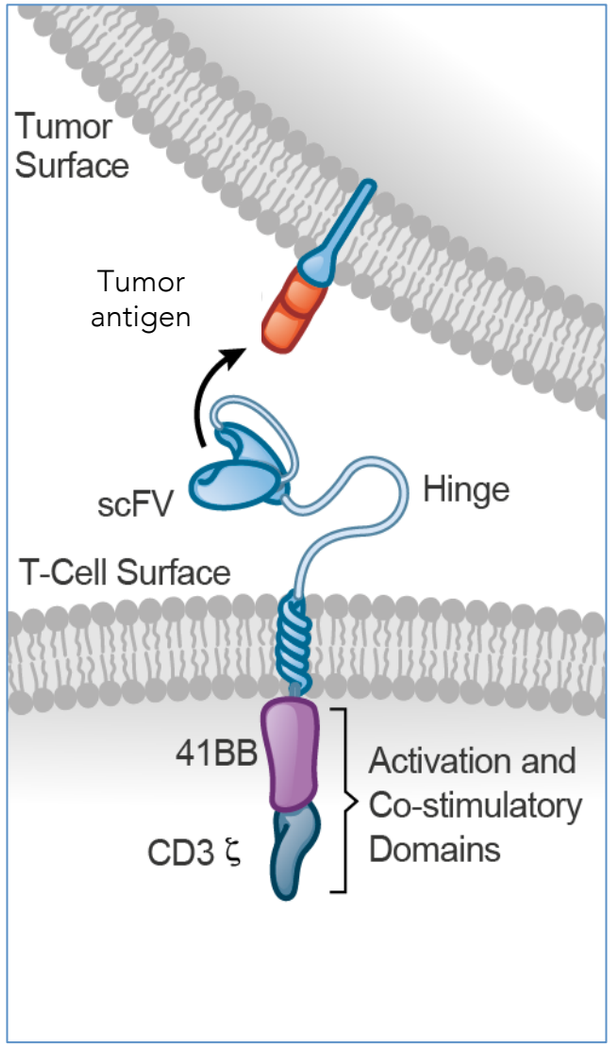
Kings College London

Investigator Site for P1 clinical trial of UCART19 in adult patients

Combining Our Technology Platforms

To enhance the power of the immune system against cancer

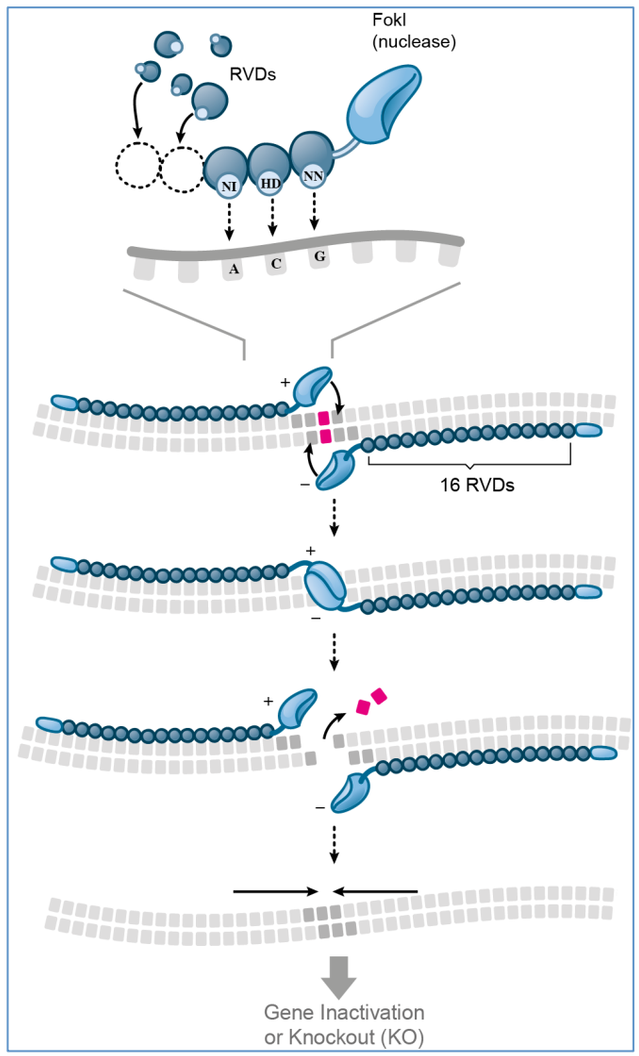
Chimeric Antigen Receptor



Enhancing

Tumor Recognition

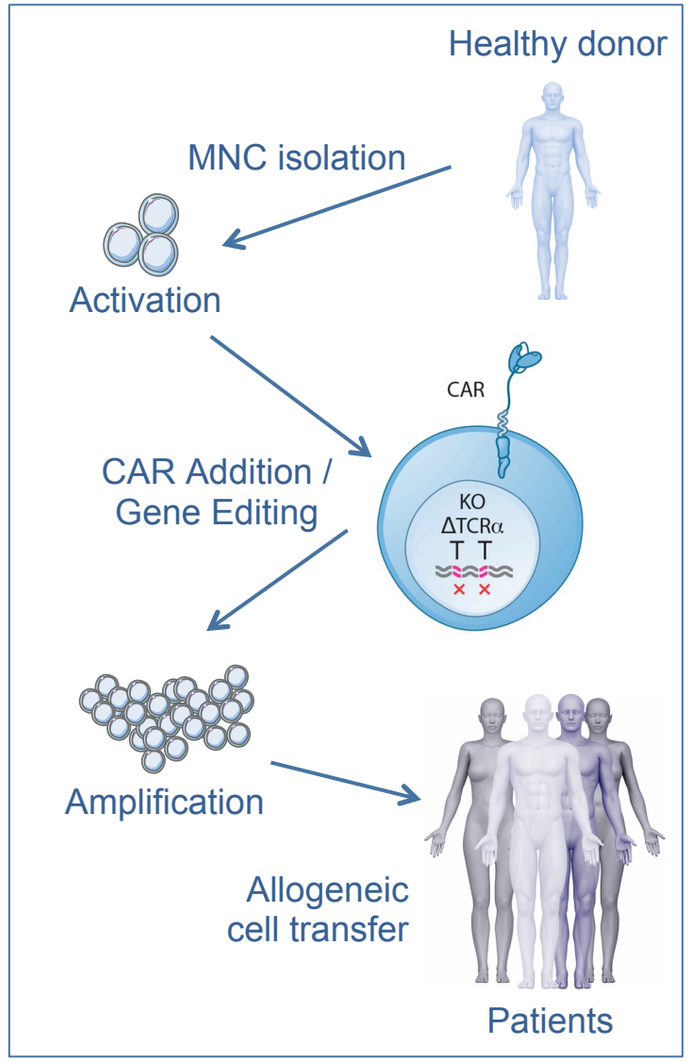
TALEN ® Gene Editing



Enhancing

T-Cell Properties

'Off-The-Shelf' CAR T-Cells



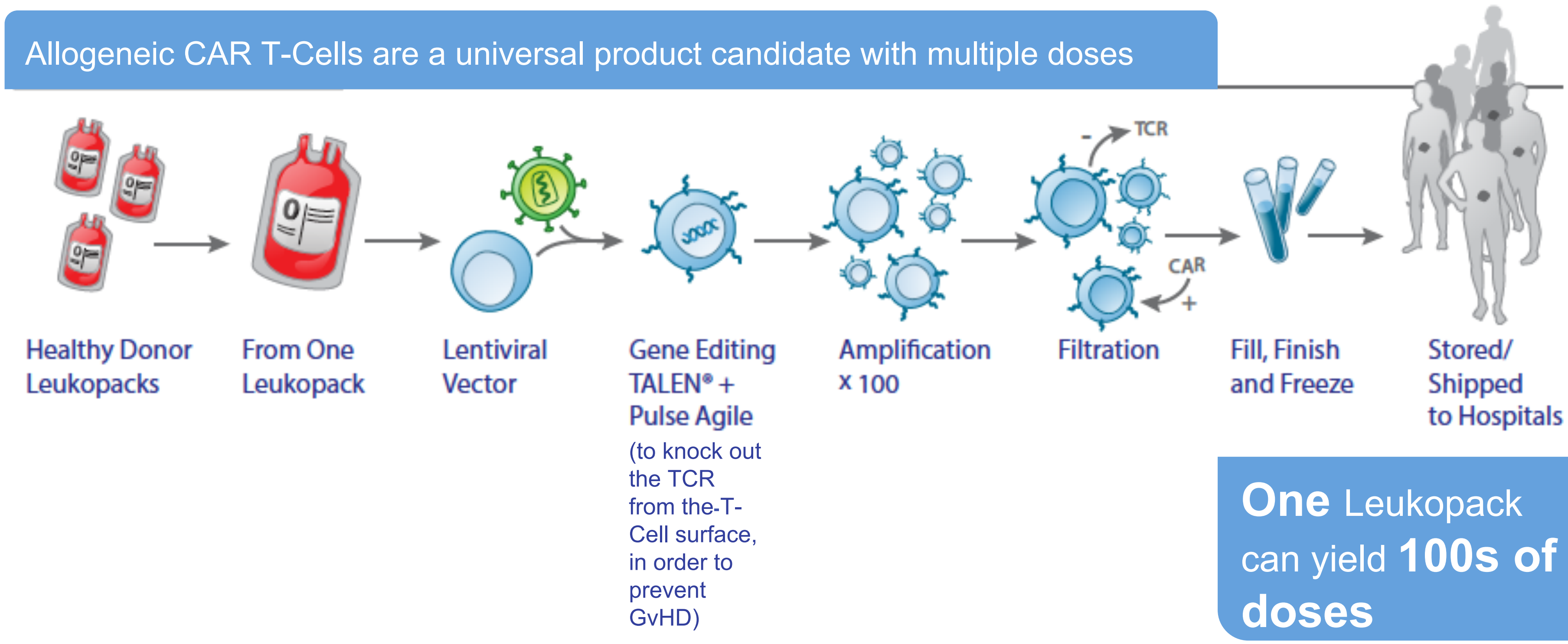
Expanding

Patient Access

Off-The-Shelf CAR T-Cells

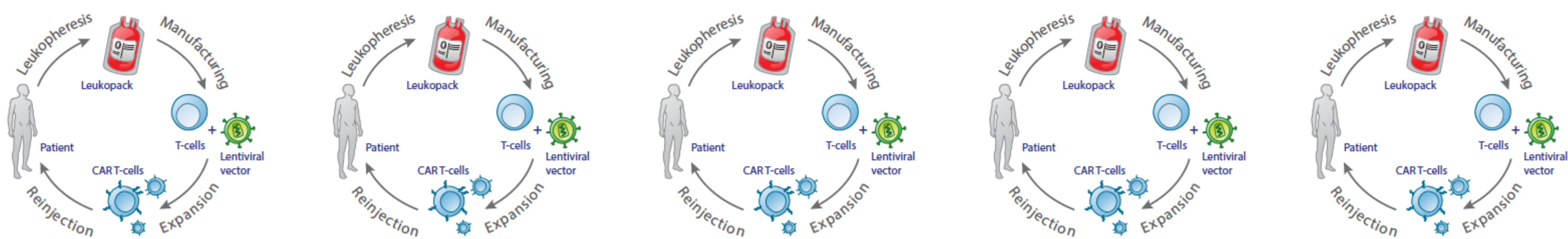
Allogeneic vs. Autologous CAR T-Cell Manufacturing

Allogeneic CAR T-Cells are a universal product candidate with multiple doses



One Leukopack can yield **100s of doses**

Autologous CAR T-Cells are a personalized therapeutic procedure



1 PROCEDURE BENEFITS 1 PATIENT

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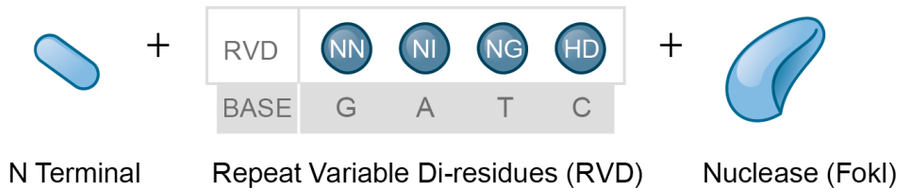
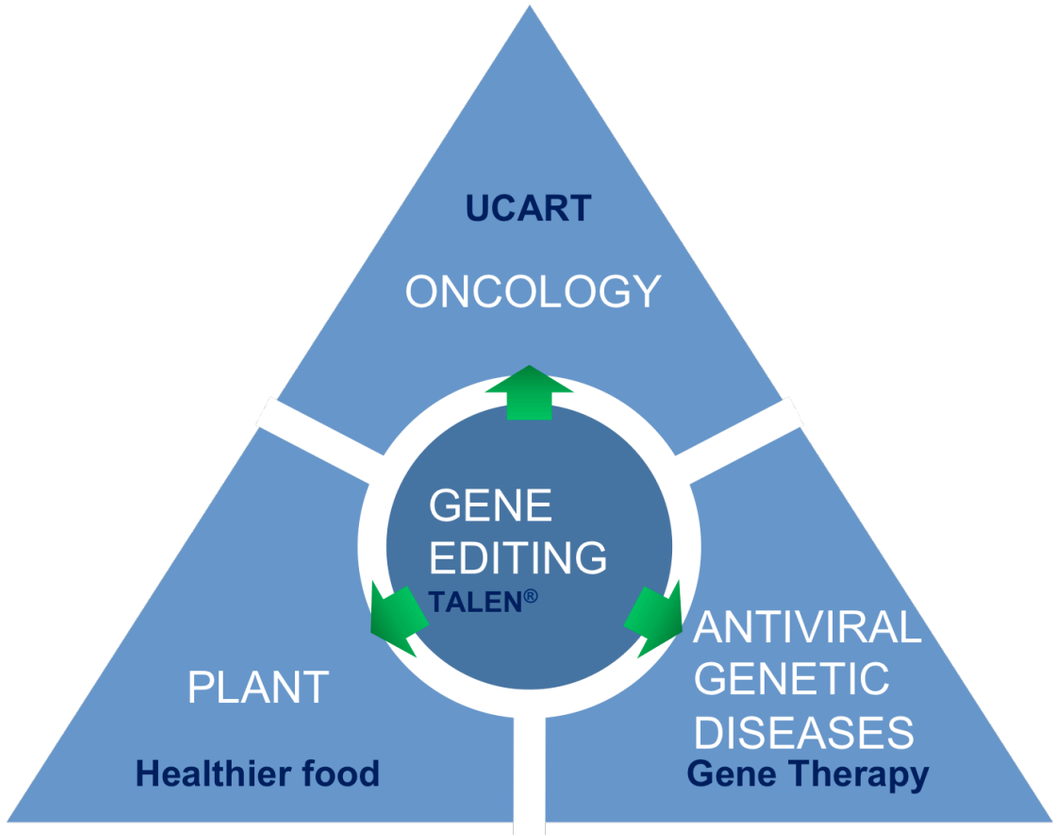
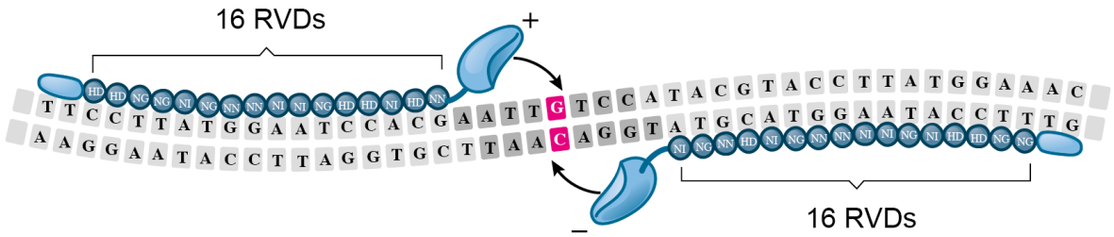
Unmatched Gene-Editing Platform

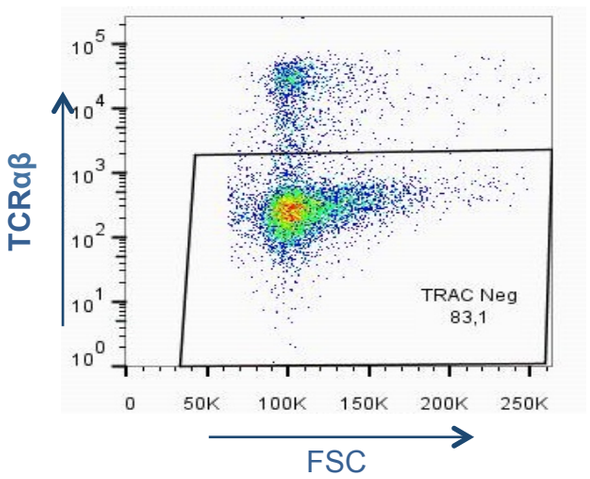
- TALEN® show **best-in-class** specificity, off-target profile and multiplexing capability
- Various potential applications in oncology, antiviral genetic diseases and plant development



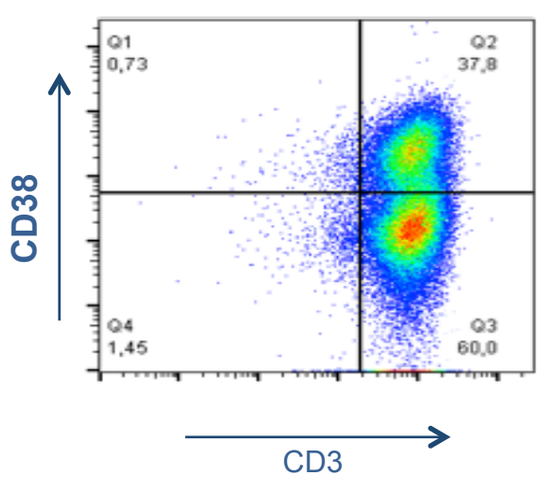




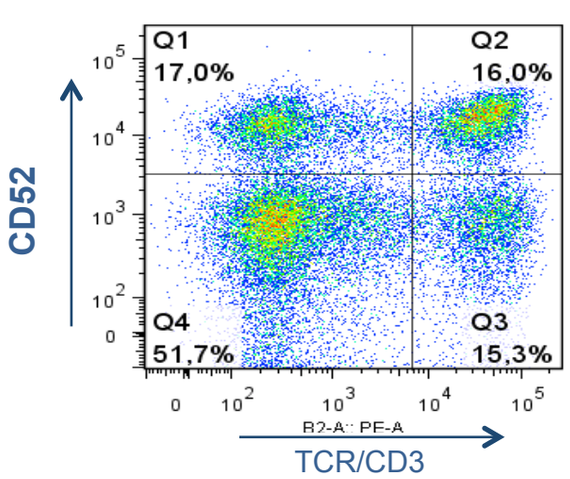
1 Allele KO: 83%



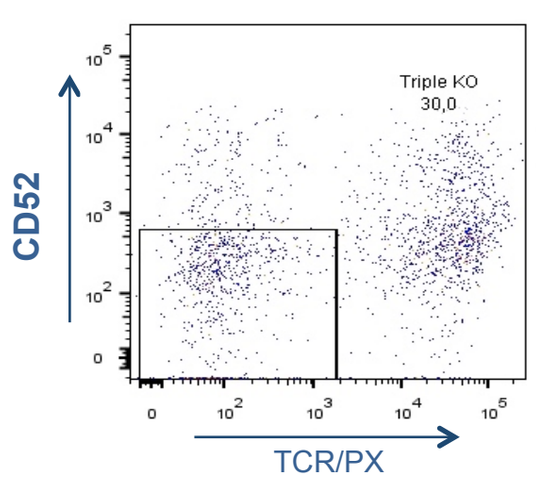
2 Alleles KO: 60%



3 Alleles KO: 51%



5 Alleles KO: 30%



Next Generation CAR Architecture

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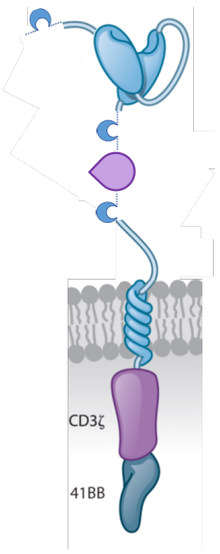
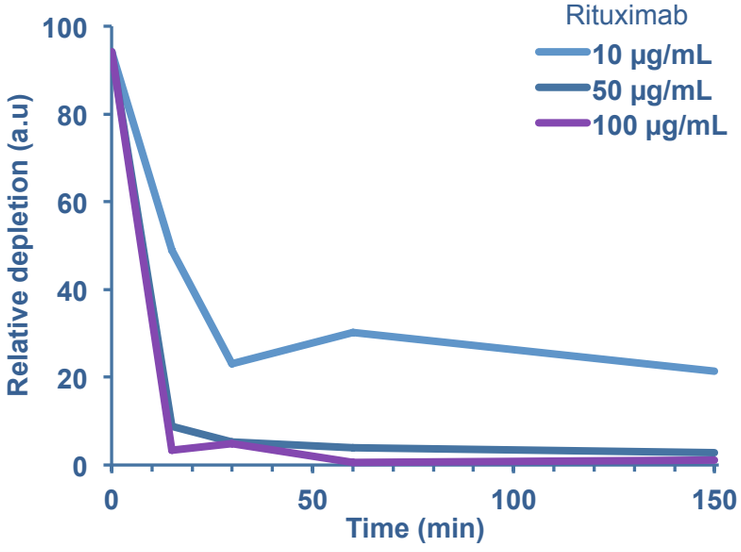
CAR Safety

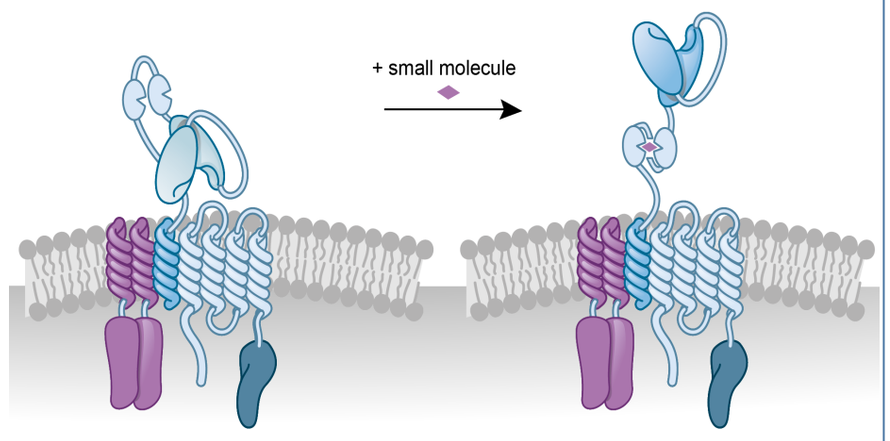
- Safety switch receptor directly on the CAR structure
- Fast and efficient depletion of safe CAR+ T-cells by Rituximab

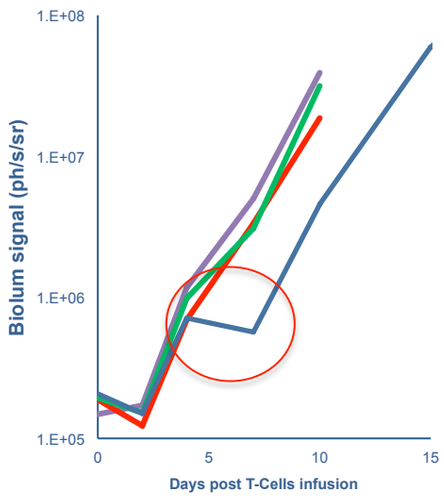


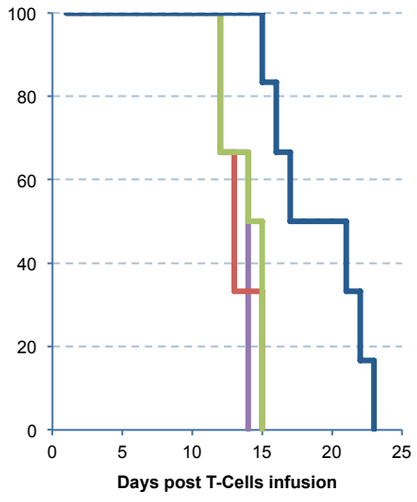


CAR Control

- Non-lethal control of engineered CAR T-Cells to improve the CAR T-cell technology and its safety



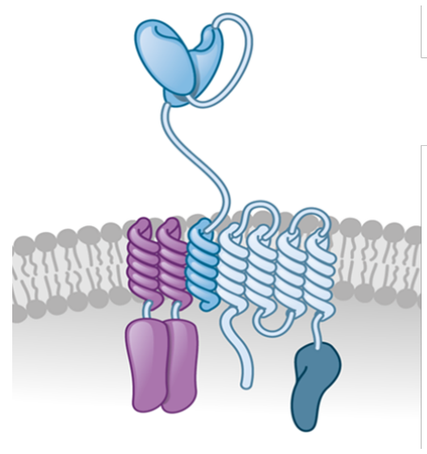


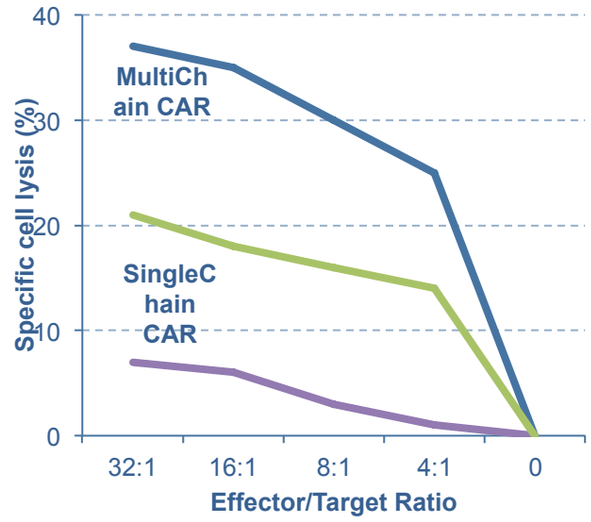


G1: T cell + Vehicle
G2: T cell + small molecule
G3: Switch On + Vehicle
G4: Switch On + small molecule

CAR Design

- Enhanced antigen-specific cytolytic activity and improved target-specific proliferative response





Enhancing CAR T-Cell Capabilities

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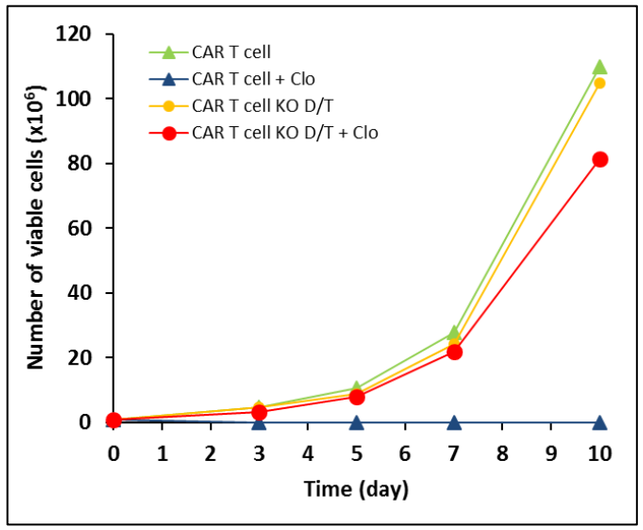
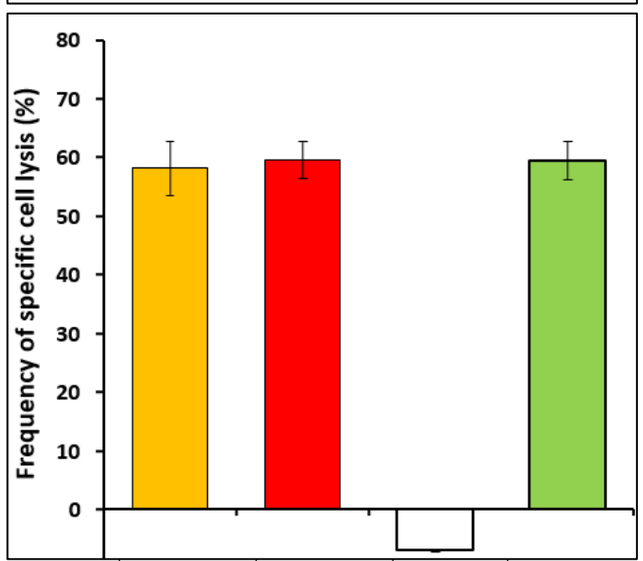
Chemo-resistance

- Gene editing to knock out CD52 or DCK on T-Cell surface in order to induce resistance to Alemtuzumab (ALL/CLL) or PNA (AML)

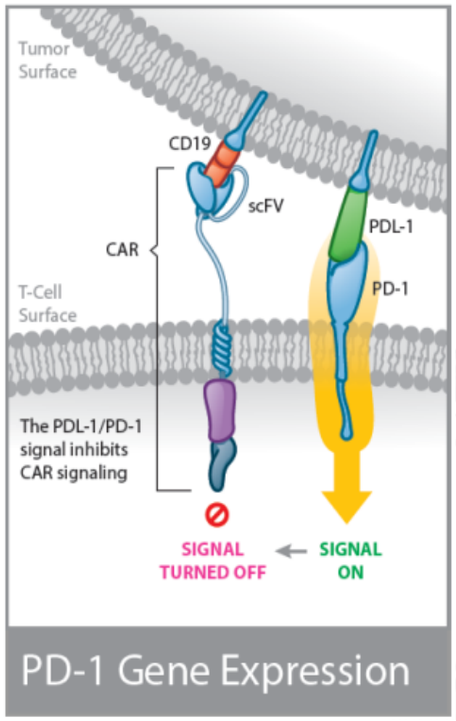




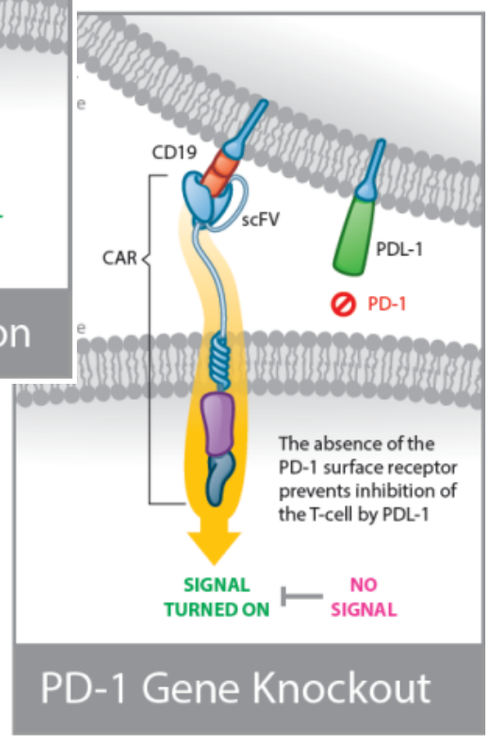
Clofarabine	-	+	+	-
CAR	+	+	+	+
KO DCK/TCR	+	+	-	-

Built-in PD1-deficiency

- Gene editing to render CAR T-Cells insensitive to checkpoint inhibition in order to improve antitumor efficacy

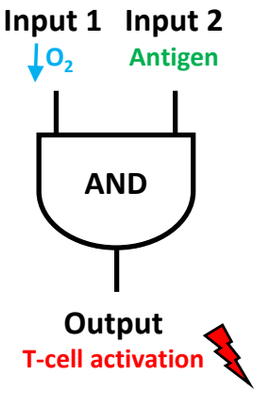


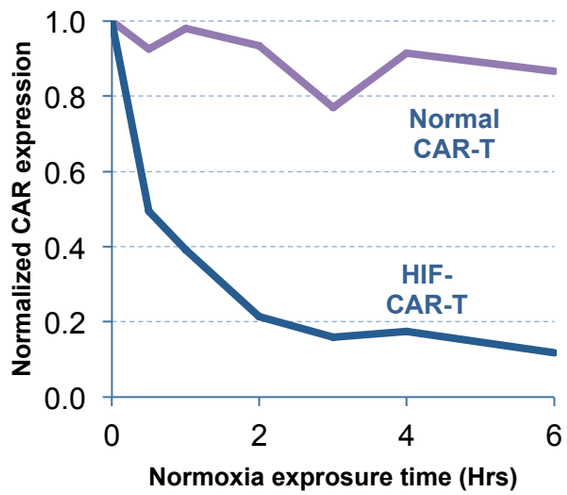
TALEN based PD1 KO



O_2 sensitivity

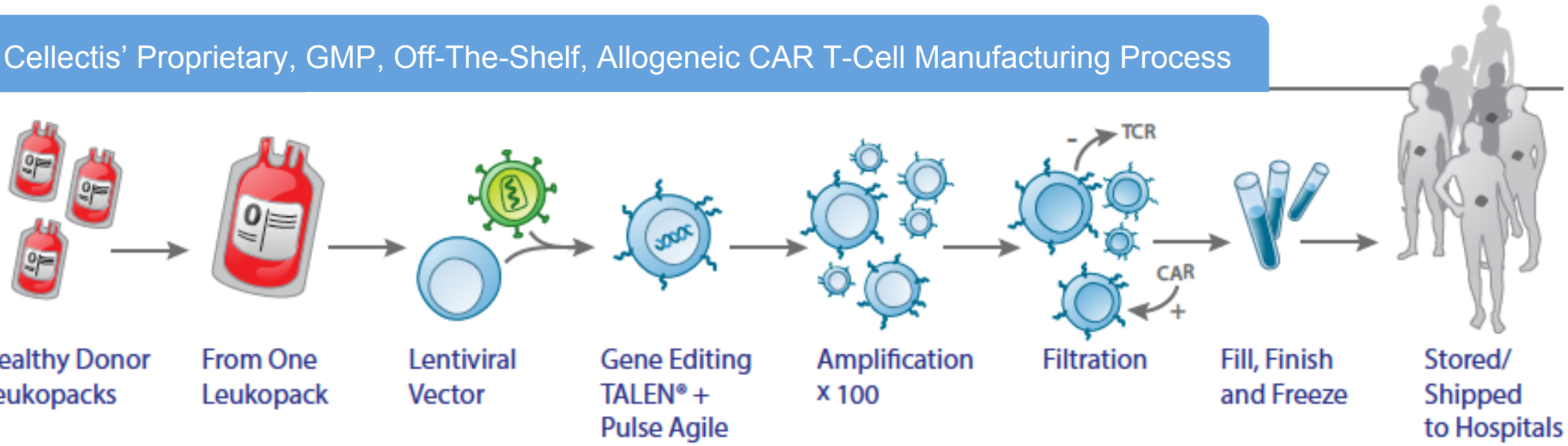
- Integrated, oxygen-based, self decision making T-Cell, regulating the cytolytic properties depending on the tumor microenvironment





Proprietary GMP Manufacturing Process

Cellectis' Proprietary, GMP, Off-The-Shelf, Allogeneic CAR T-Cell Manufacturing Process



Day 0	Day 3	Day 5	Day 6-17	Day 18	Day 18

- On-purpose lymphocytes apheresis
- Frozen quality controlled starting material (PBMCs)

- CAR addition using a viral vector

- TALEN® transfer using proprietary PulseAgile electroporation technology

Critical step for :

- ✓ Efficient and safe gene knock-out
- ✓ cell survival and expansion
- ✓ High efficiency
- ✓ High Yield

- Expansion of engineered cell in controlled culture systems
- Purification of TCR-negative cells
- Fill & finish and controlled rate freezing on the last day
- Full Quality Control after freezing

Pipeline

Servier UCART19	Product development	Pre-clinic	Manufacturing	IND*	Phase I	Phase II
ALL (Pediatric)						
ALL/CLL (Adult)						

UCART123	Product development	Pre-clinic	Manufacturing	IND	Phase I	Phase II
Acute Myeloid Leukemia						
Blastic Plasmacytoid Dendritic Cell Neoplasm						

UCARTCS1	Product development	Pre-clinic	Manufacturing	IND	Phase I	Phase II
Multiple Myeloma						

UCART38	Product development	Pre-clinic	Manufacturing	IND	Phase I	Phase II
Multiple Myeloma						
T-Acute Lymphoblastic leukemia						

UCART22	Product development	Pre-clinic	Manufacturing	IND	Phase I	Phase II
B-NHL / SLL / CLL						

Servier UCART	Product development	Pre-clinic	Manufacturing	IND	Phase I	Phase II
Undisclosed Targets	undisclosed	undisclosed	undisclosed			

Pfizer UCART	Product development	Pre-clinic	Manufacturing	IND	Phase I	Phase II
Undisclosed Targets	undisclosed	undisclosed	undisclosed			

* or European equivalent

Unmet Medical Need in Oncology

2015 US Estimate*	Incidence	Annual Death
AML	20,830	10,460
BPDCN	Estimated < 1% of all hematologic malignancies**	Reported Overall Survival in one group 10-14 months***
ALL	6,250	1,450
Non Hodgkin Lymphoma	71,850	19,790
Multiple Myeloma	26,850	11,240
CLL	18,960	4,660

*American Cancer Society 2015
** Pagano et al, 2013
*** Roos-Weil et al, 2013

UCART123 Targeting AML and BPDCN

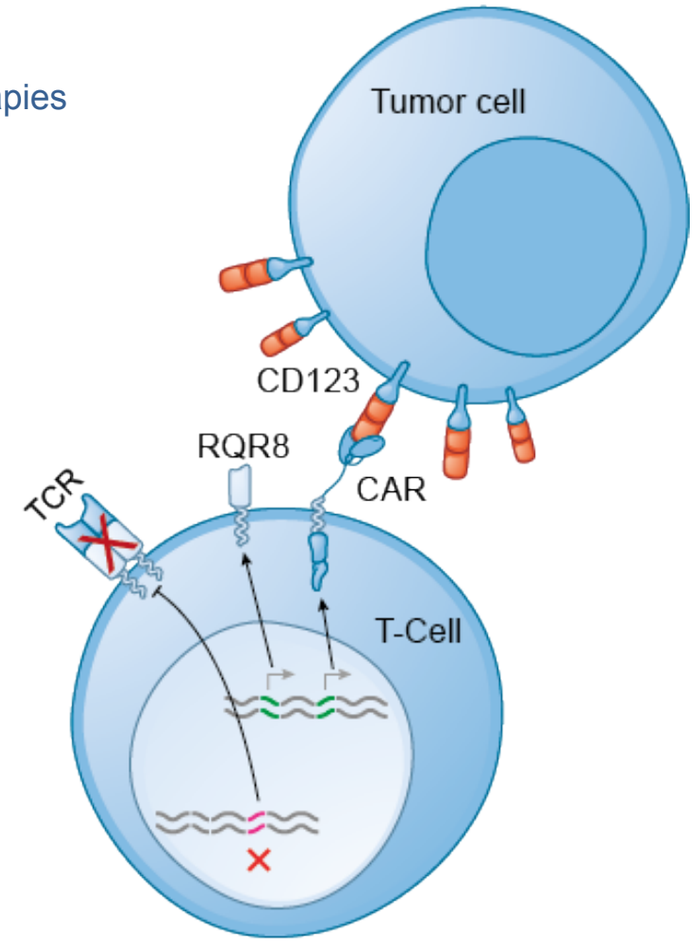
Disease description

Acute myeloid leukemia (AML)

- Five-year survival 15-70%, and relapse rate 33-78%, depending on age and subtype
- No major advances in the treatment of AML in over 40 years
- Limited number of players
- Need for new therapies in the front-line and relapsed setting

Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

- Rare disease involving bone marrow, skin, lymph nodes (US incidence < 100) with no approved therapies
- Classified under myeloid neoplasms and acute leukemia (WHO classification 2016)



Target Antigen

- CD123, IL-3 receptor α-subunit
- highly expressed on leukemia stem cells and AML blasts
- Overexpressed in 100% of BPDCN
- Low expression levels on normal hematopoietic stem/progenitor cells

UCART123 Attributes

- Anti-CD123 CAR expression to redirect T-Cells to tumor antigens
- Suicide gene for safety
- TCR disruption[1] to avoid GvHD

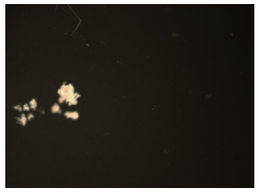
Safety of UCART123

In-vitro and in-vivo data of UCART123 shows **clearance of malignant (AML) cells** and preservation of normal CB CD34+ cells, → indicative of a favorable safety profile

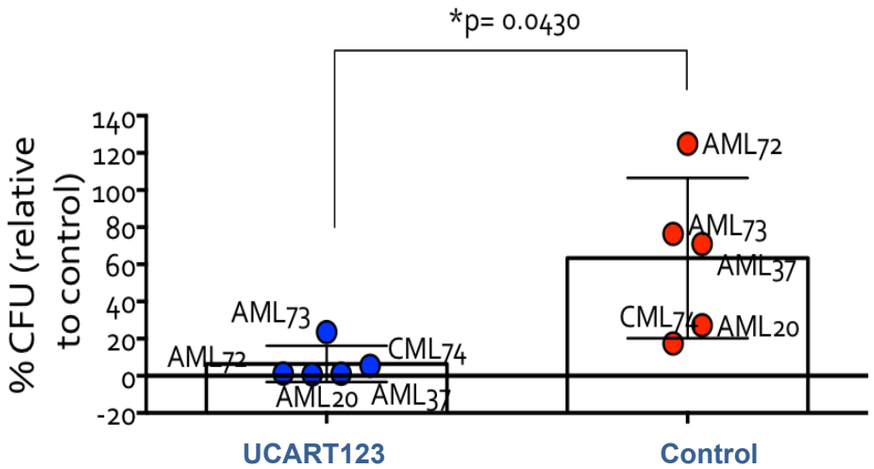
➢ In-vitro clearance of cancer cells and preservation of non cancer cells

AML Cells

Control

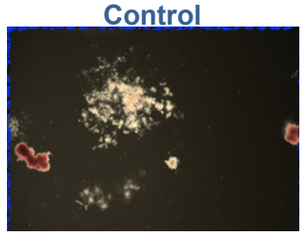


UCART123

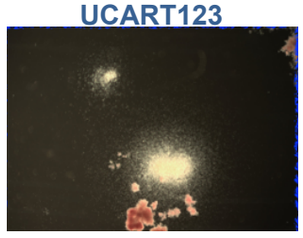


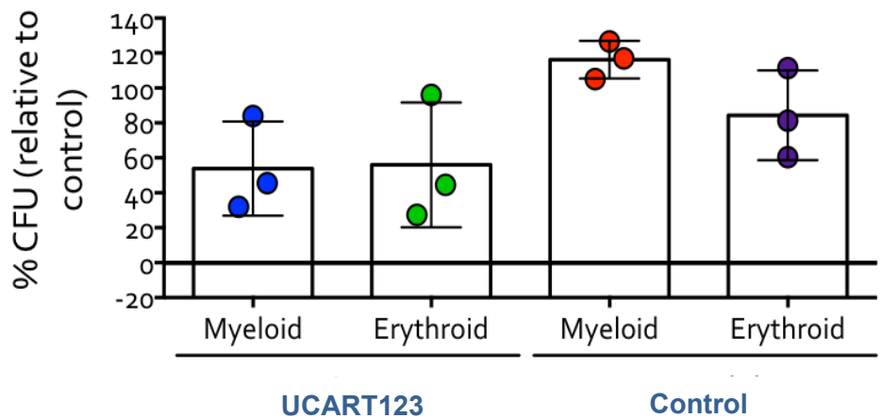
Normal CB CD34+ Cells

Control



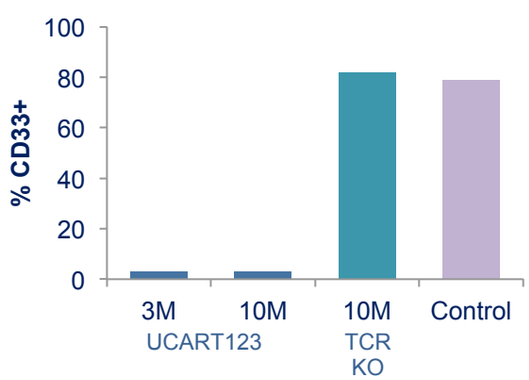
UCART123



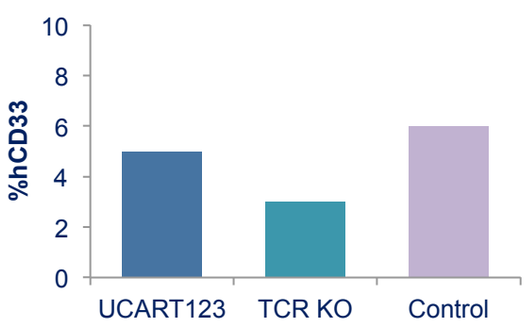


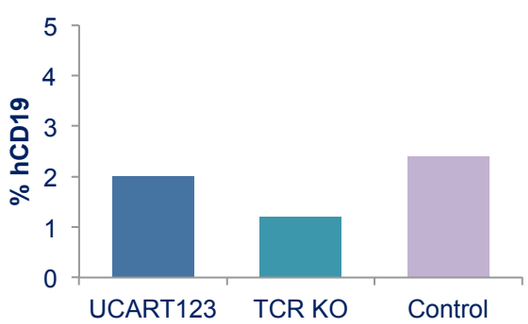
➢ In-vivo data

AML Cells



Normal CB CD34+ Cells



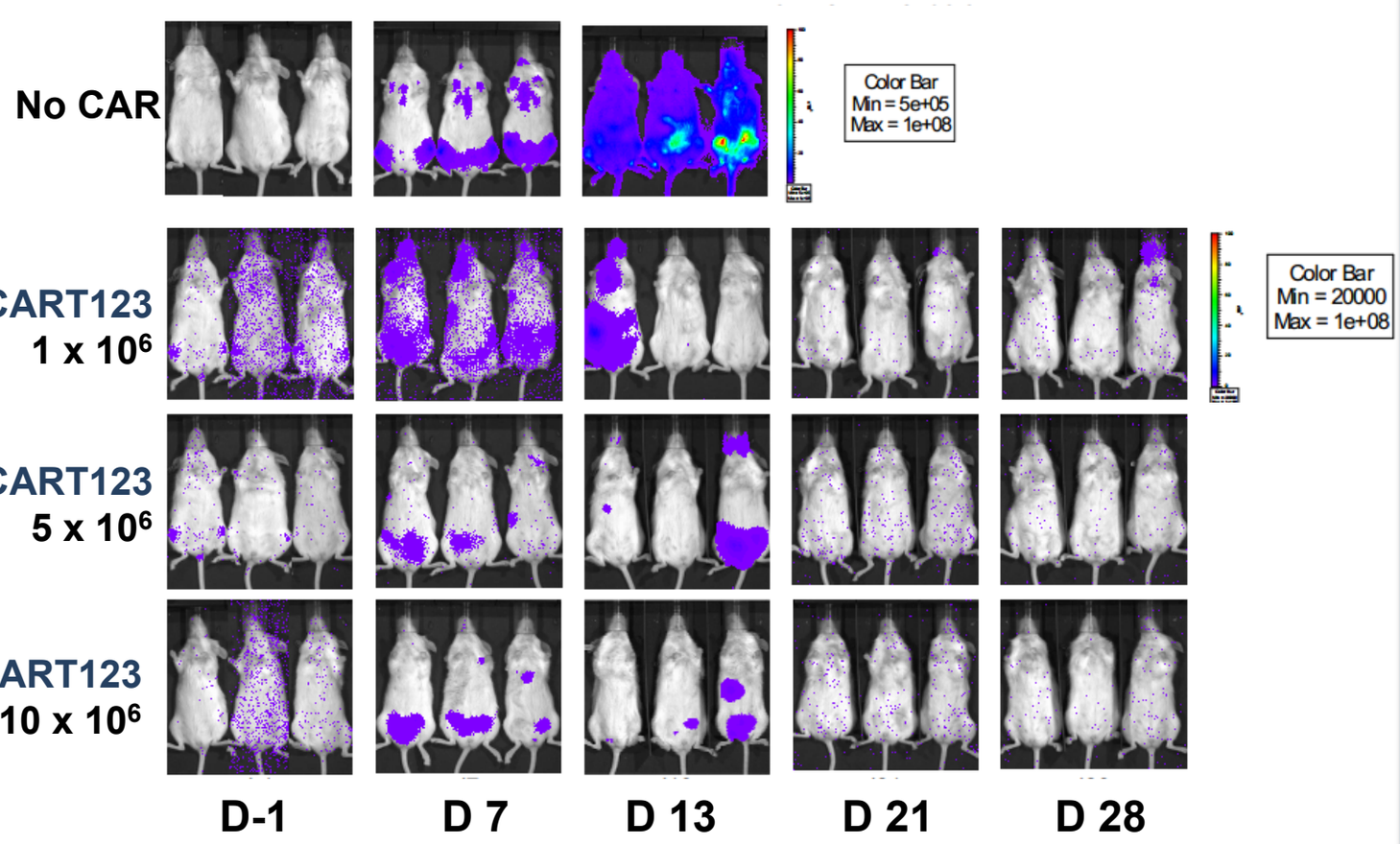


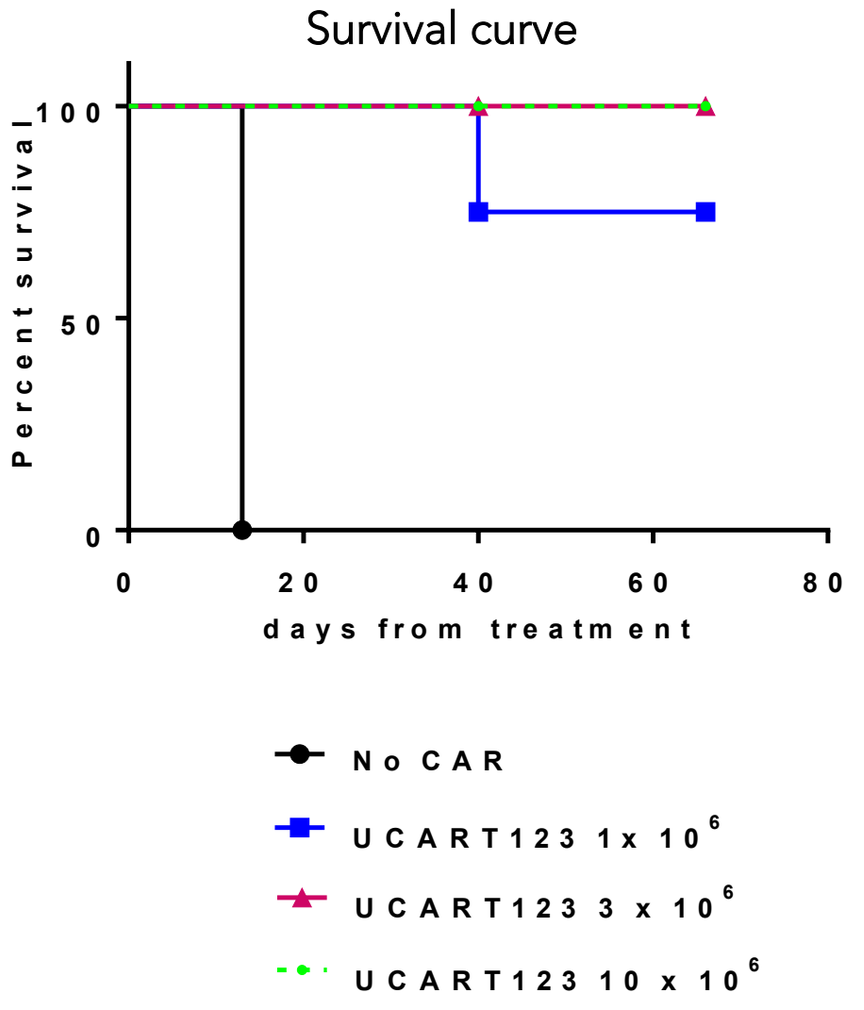
In collaboration with Dr. Monica Guzman, Cornell-Weill

Activity of UCART123

UCART123 in mice:

- Survival beyond 60 days (at a dose of 1x10^6 UCART123 Cells)
- Elimination of the tumor cells in the blood, the spleen and the bone marrow of UCART123 treated mice





Day -7: Intravenous (i.v.) injection of 2.5x10^5 MOLM13-Luc cells in NOG mice
Day 0: CD123 CAR T-Cells i.v. (3 doses: 1x10^6, 5x10^6 and 10x10^6 CAR+ T-Cells)

Development of UCART123

Proof of Concept UCART123

- In-vitro and in-vivo development being finalized

Manufacturing UCART123

- Started in Q2-2016

Intended IND filings

- AML
- BPDCN

Possible future development enabled by Gene editing:

- CD52 inactivation
- Combination therapy
- dCK inactivation (FLAG treatment)
- Overcome immunosuppression (PD1 inactivation)
- Humanized CD123 binding domain

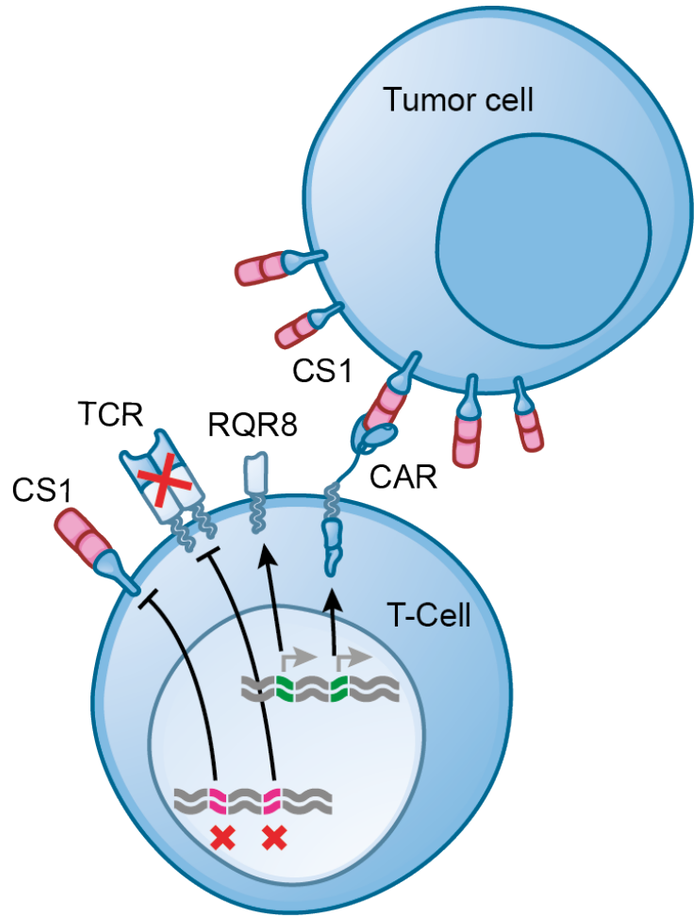
UCARTCS1 Targeting Multiple Myeloma

Disease Description

- Multiple myeloma (MM) is a hematologic malignancy characterized by proliferation of plasma cells.
- In patients relapsing after prior therapy with IMiDs and bortezomib, the median OS rate is 9 months.

Target Antigen

- Elotuzumab (BMS/Abbvie) a monoclonal antibody targeting CS1 as proof of concept for target selection
- CS1 (CD319, SLAMF7) highly expressed on MM cells.
- CS1 antigen not expressed on normal tissues or stem cells
- Low levels of expression on natural killer (NK) cells and a subset of T lymphocytes compared with malignant plasma cells.
- CS1 is expressed on CD8+ T-Cells, to facilitate CAR T-Cell production CS1 can be efficiently inactivated in human T-Cells, using TALEN® mRNA electroporation



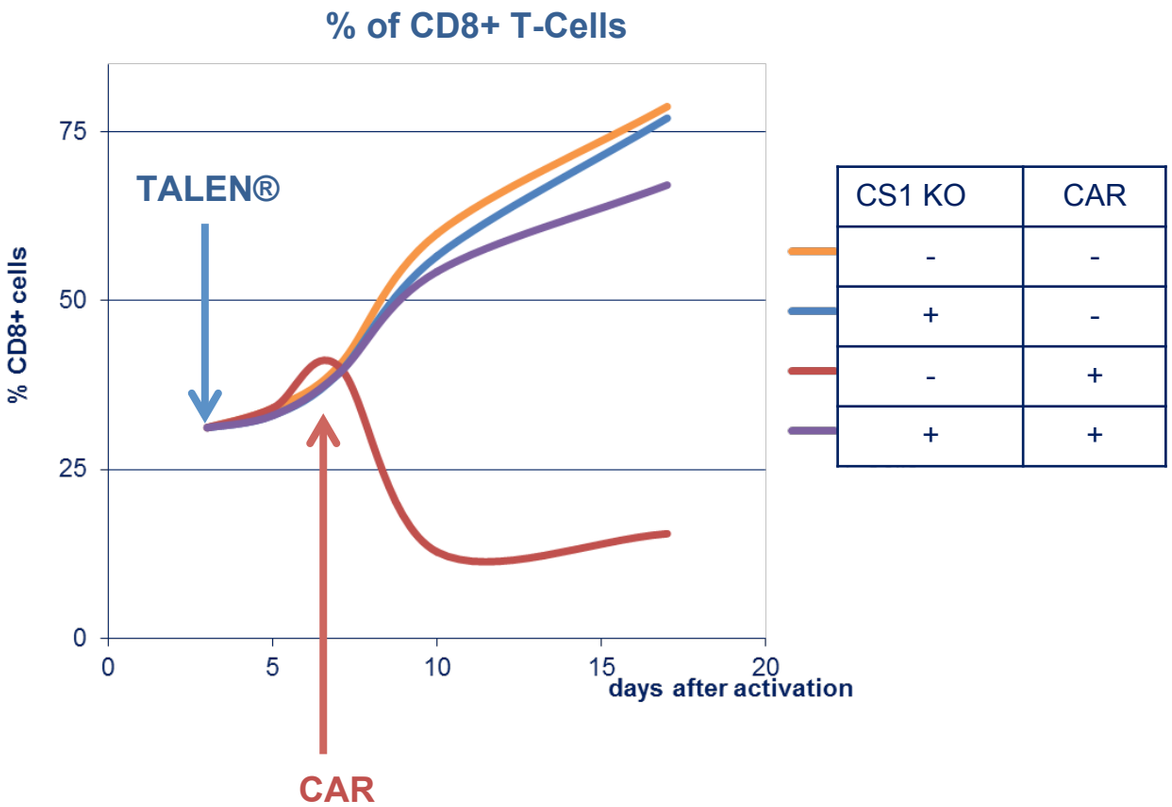
UCARTCS1 Attributes

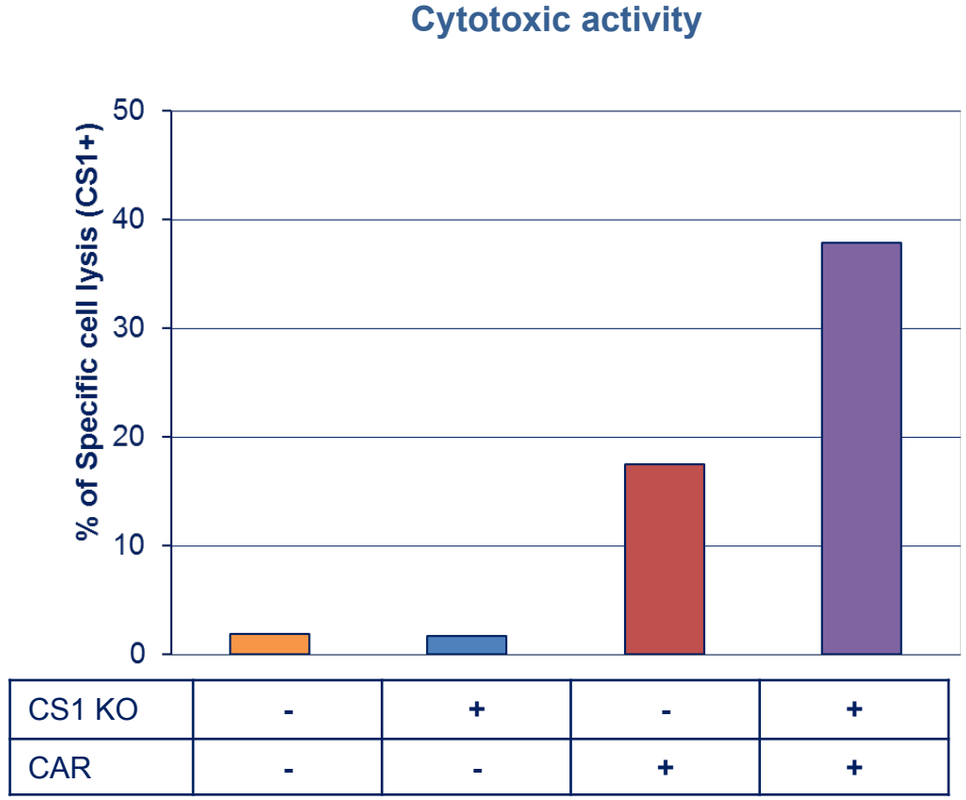
- Anti-CS1 CAR expression to redirect T-Cells to tumor antigens
- Suicide gene for safety
- TCR disruption[1] to avoid GvHD
- CS1 disruption[1] to prevent CAR T-Cell cross reactivity

(1) *Knock-out by using TALEN®*
(2) *American Cancer Society, http://www.cancer.org/acs/groups/content/@editorial/documents/document/acspc-044552.pdf*

Pure-Play Gene Editing to Create UCARTCS1

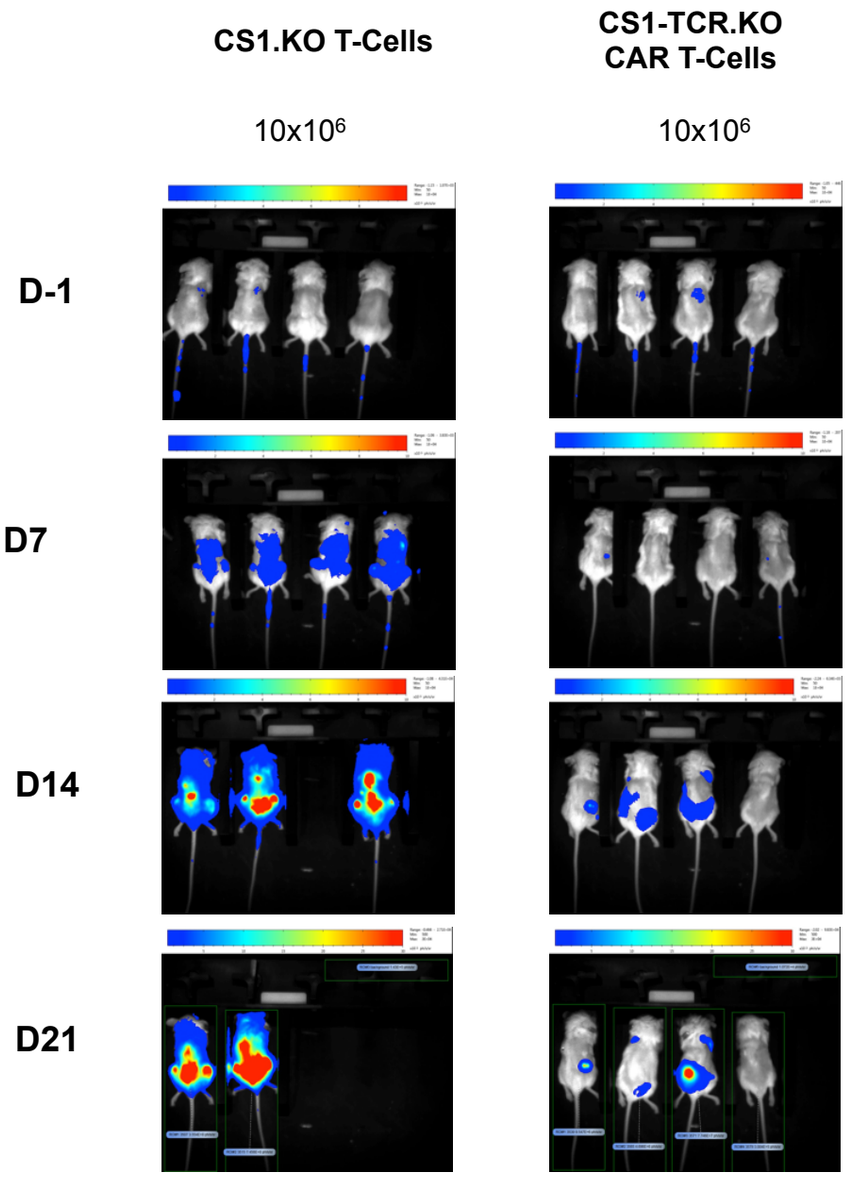
- **Inactivation of CS1 expression** in T-Cells before introduction of the CAR significantly increases yields of $CD8^+$ cells
- **Proof of concept** experiments demonstrate improved cytotoxicity *in vitro* of $CS1^+$ target cells with T-Cells containing a CS1 inactivation.

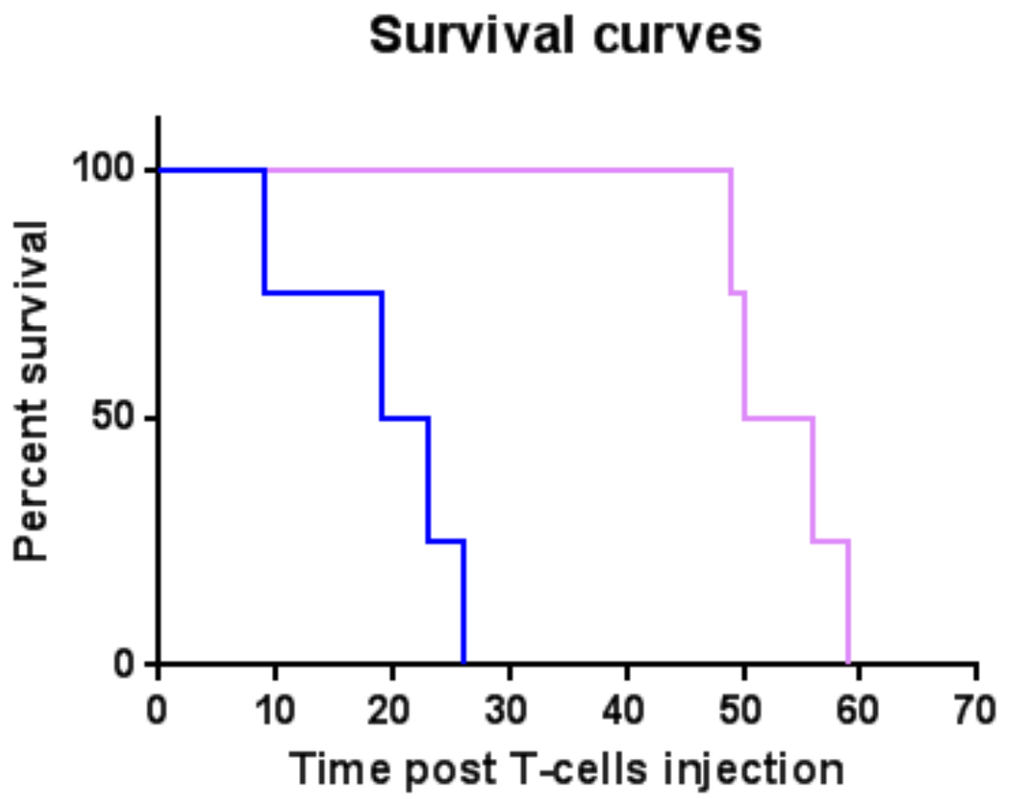




Activity of UCARTCS1

- CS1 CAR T-Cells, inactivated for TCR and CS1, display **significant anti-tumor activity** *in vivo*





Development of UCARTCS1 / UCART38

Proof of Concept UCARTCS1

- Increased cytotoxic activity compared to non-edited T-Cells

In-vivo studies

- Preclinical studies ongoing in collaboration with MD Anderson Cancer Center (Dr. Jing Yang and Dr. Sattva Neelapu)

Manufacturing UCARTCS1

- Development of a modified GMP compatible manufacturing process (inversion of transduction/electroporation steps)

UCART38- Another Target for Multiple Myeloma:

- Pre-clinical development ongoing

UCART22 Targeting ALL and other B-Cell Malignancies

Targeted disease description

- Acute lymphoblastic leukemia (ALL) is a cancer of the white blood cells, characterized by the overproduction and accumulation of immature white blood cells (known as lymphoblasts).

Rationale

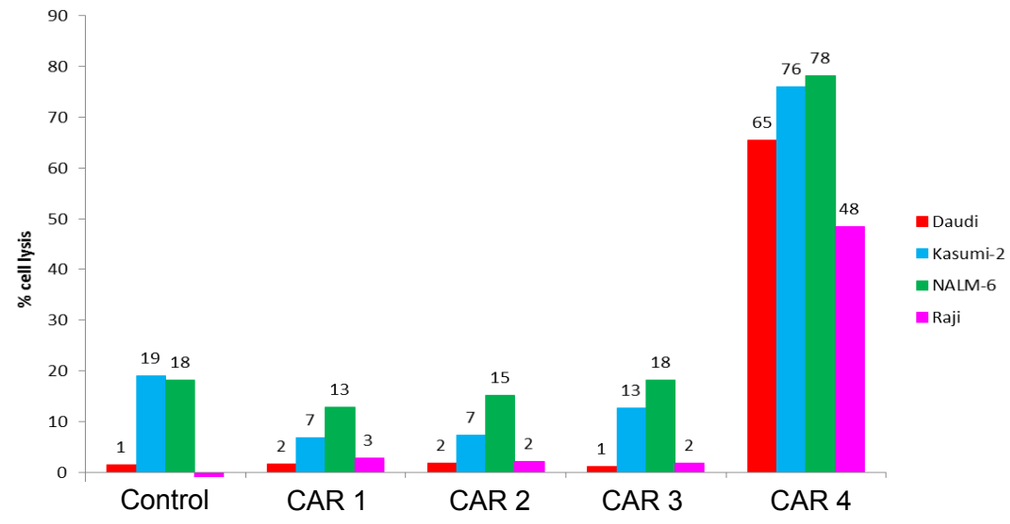
- CD22 and CD19: same expression profile on various B-Cell stages of development
- CD22 expression frequently maintained in CD19-negative blast cells in ALL [ref1 & ref2]

Target expression

- CD22, a single-family lectin, consists of 7 extracellular IgG-like domains and is expressed on the B-cell surface starting at the pre-B-Cell stage, persists on mature B-Cells, and is lost on plasma cells.

Proof of concept

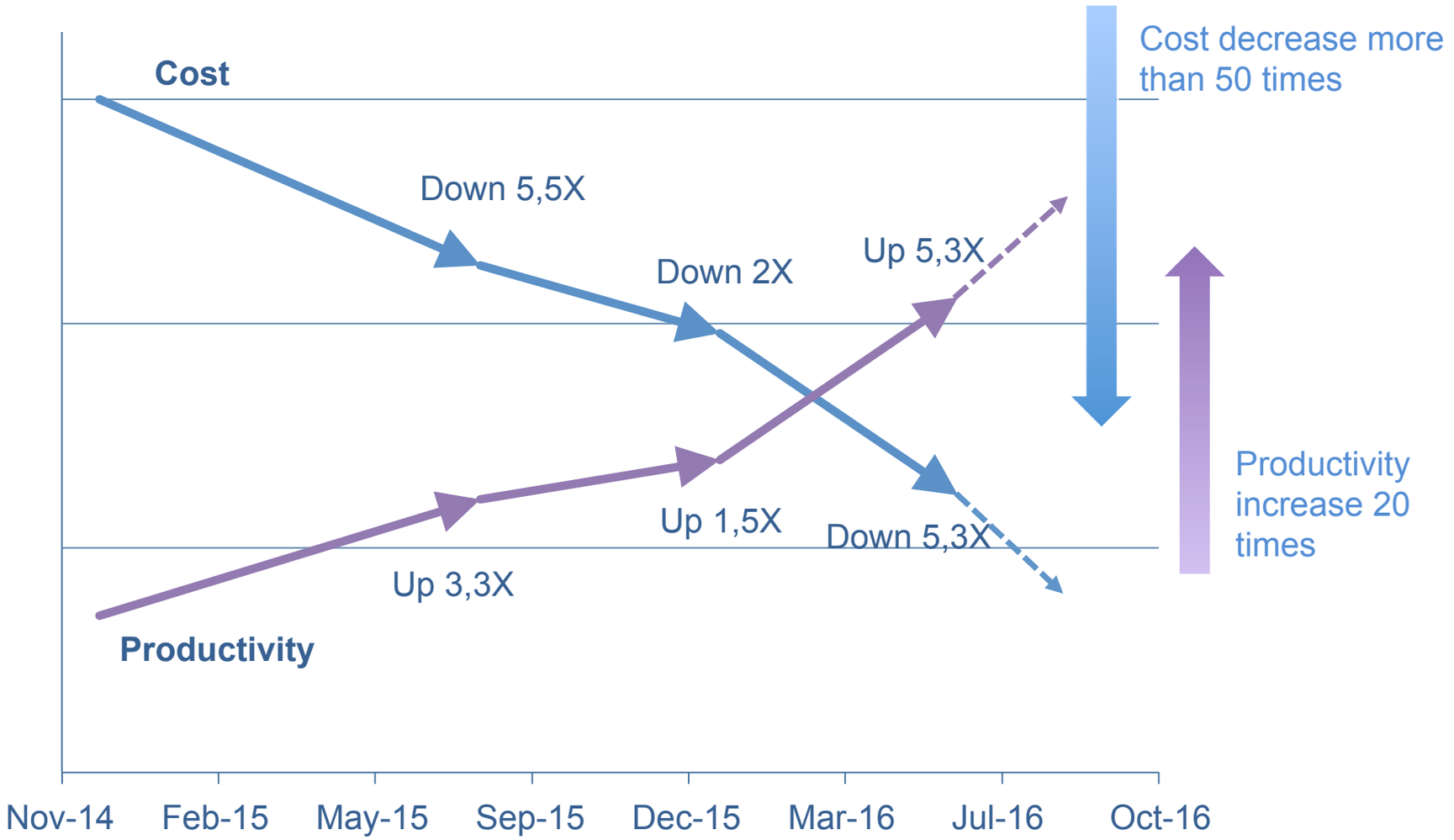
- Anti-CD22 monoclonal antibodies / immunotoxins (e.g. Inotuzumab ozogamicin).
- Autologous CAR-T in development (JCAR018)



Ref 1: TOpp Ms, Kufer P, Gokbuget N Et Al. J. Clin. Oncol. 2011; 29(18):2493-2498
Ref 2: Grupp Sa, Kalos M, Barrett D Et Al, N. Engl. J. Med. 2013;368(16):1509-1518

Worldwide Access to CAR T-Cell Treatment

- Off-The-Shelf, allogeneic CAR T-Cells would give universal, worldwide, immediate access to patients
- Improving robustness and individual steps of manufacturing process
- Process evolution for scalability are driving production costs lower



Maximize CAR T-Cell function

Liquid Tumors

- Insufficient CAR T activation/ persistence in some indications (NHL)
- Concomitant treatment incompatibility

Solid Tumors

- Challenging homing
- Suppressive microenvironment
- Lasting response needed
- T-Cell exhaustion

Enhance Survival

- Screen-based gene inactivation for new drug resistance
- B2M inactivation for prolonged engraftment of allogenic T-Cells
- Combination therapy with PD-1

Optimize T-Cell Function

- Inactivate immune check points TIM3, LAG3, CTLA4
- Combine with mAb therapy
- More complex CAR architectures
- Mobilization of endogenous immune system (on target cytokine secretion)

Immunosuppressive Microenvironment

- Inactivate suppressive pathways
- Cytokine signaling

Enhance Tumor Access

- Inactivate signaling pathways
- Inactivate specific gene

The Future of CAR T-Cell Treatment

➢ Cellectis offers solutions for many of the questions in the CAR T field

Cellectis Innovation	***Targeted Patient Benefits***
○ Allogeneic, non alloreactive CAR T-Cells	✓ Off-the-shelf product (KO TCR)
○ Resistance to chemotherapy	✓ Compatible with SoC, use in combination therapies
○ Resistance to lymphodepleting agents	✓ Enhanced engraftment (KO DCK)
○ Resistance to tumor inhibition	✓ Enhanced efficacy (KO PD1, KO CTLA4,…)
○ Suppressed cross T-Cell reaction	✓ Better suited for specific tumors
○ Controllable CAR expression / activity	✓ Mitigate risks of CAR T-Cell-related toxicities
○ Versatile Gene Editing	✓ Reaching more targets/indications for CAR T-Cells

cellectis

the life science company

THANK YOU

Cellectis S.A.
8, rue de la Croix Jarry
75013 Paris – France

Cellectis, Inc.
430 East 29th Street
10016 New York, NY – USA

Calyxt, Inc.
600 County Rd D
New Brighton, MN 55112 – USA

investors@cellectis.com