cellectis
EDITING LIFE

Engineering allogeneic immune cells to generate off-the-shelf CAR T-cell immunotherapies

Roman GALETTO, PhD
Preclinical Development

2nd EUFEMED Conference
Lyon, France - 2019

cellectis.com

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.

Forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

The risks and uncertainties include, but are not limited to the risk that the preliminary results from our product candidates will not continue or be repeated, the risk that our clinical trials will not be successful. The risk of not obtaining regulatory approval to commence clinical trials on additional UCART product candidates, the risk that any one or more of our product candidates will not be successfully developed and commercialized.

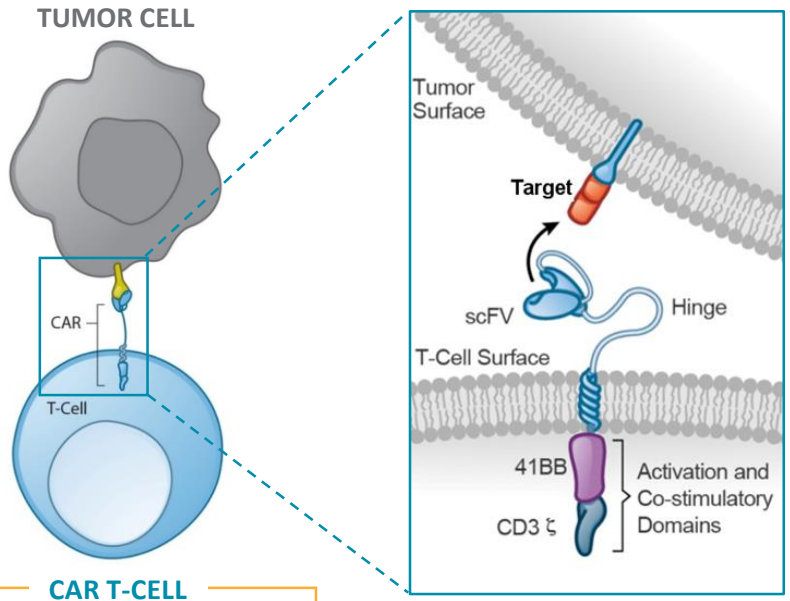
Further information on the risk factors that may affect company business and financial performance, is included in our annual report on form 20-F and other filings Cellectis makes with the securities and exchange commission from time to time and its financial reports.

Except as required by law, we assume no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

OUR MISSION

Leverage our leadership in gene editing and CAR-T therapy
to bring new **hope** to cancer patients
through broadly available, off-the-shelf therapies

CAR T-CELLS: "LIVING DRUGS" IN IMMUNO-ONCOLOGY



CAR T-CELL

T-cells engineered to recognize specific tumor antigens and drive killing of the cancer cells

CHIMERIC ANTIGEN RECEPTORS

CARs: *Cell membrane bound mAbs*

CAR domains are derived from different human proteins, each conferring a particular function to the chimeric protein

Allows MHC-independent antigen recognition (target cell surface proteins)

CAR T-cell activation upon antigen recognition mediates direct killing of tumor cells

T-cells replicate in response to contact with antigen *in vivo*

Clinical trials with CARTs targeting CD19 in patients with B-cell leukemia have shown impressive results, with unprecedented remission rates

CAR T-CELLS: TARGETING CD19

Long term survival based on approximations from available data

Figure 4.2. Comparison of Estimated Outcomes for Tisagenlecleucel and Clofarabine*

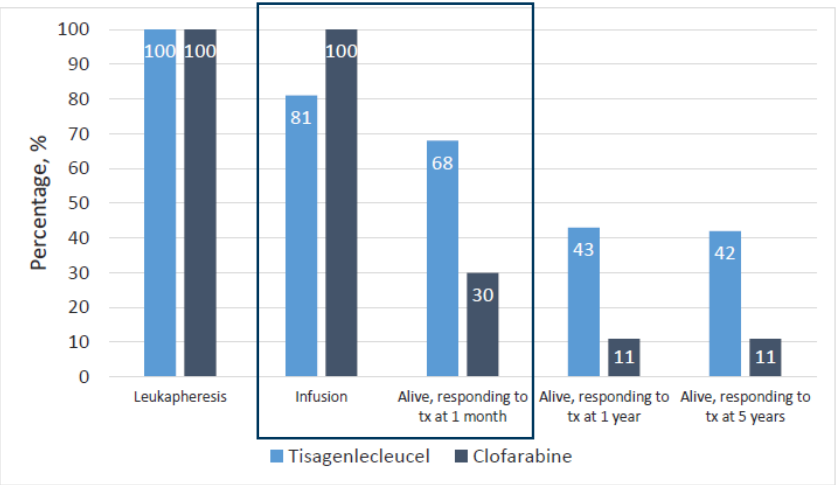
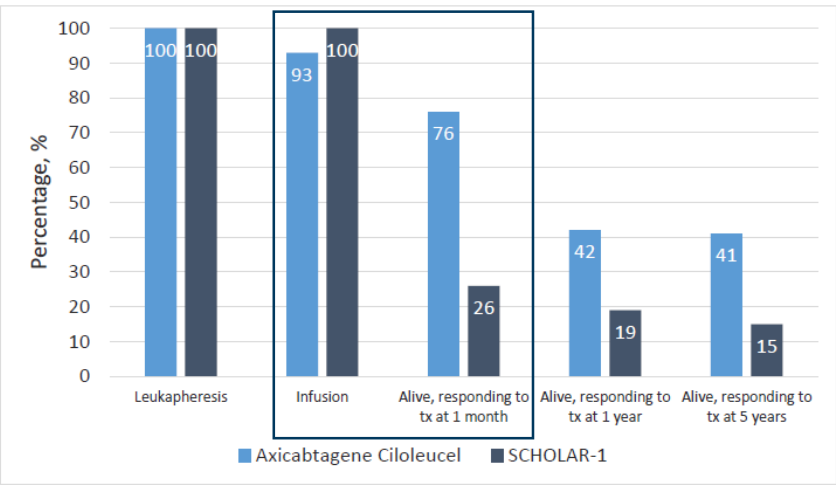
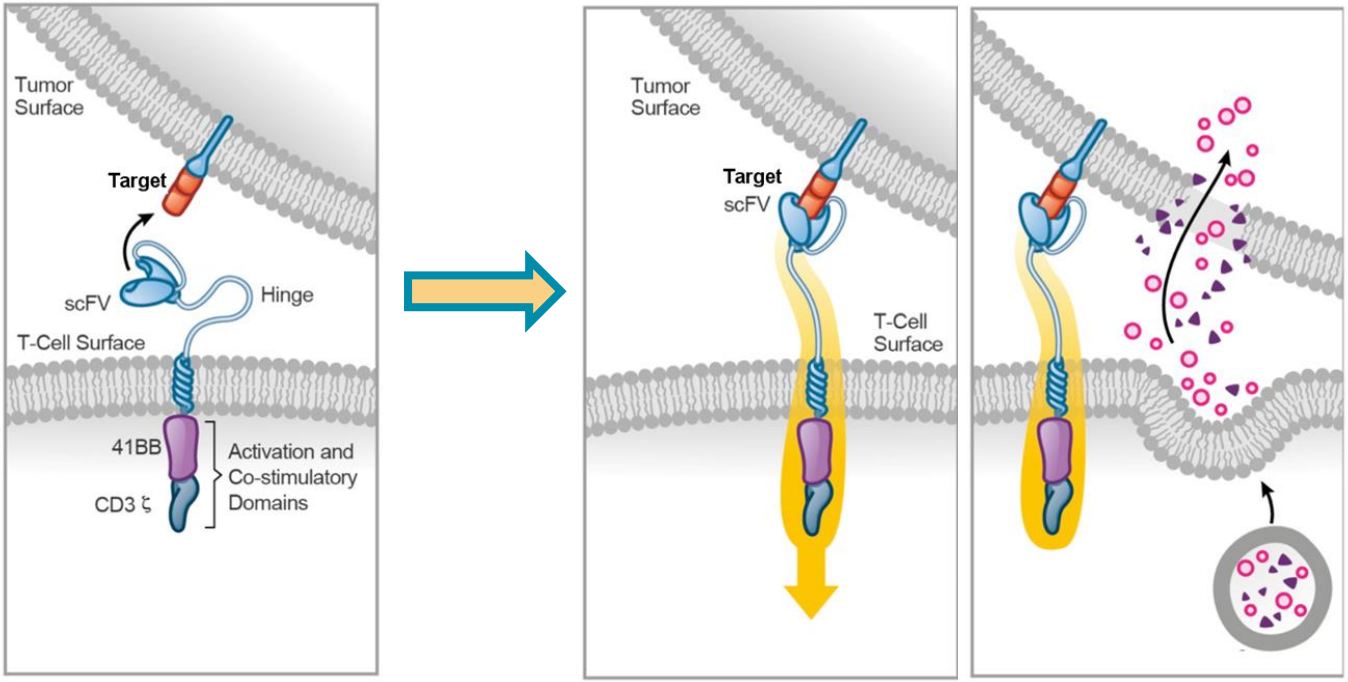


Figure 4.3. Comparison of Estimated Outcomes for Axicabtagene Ciloleucel and SCHOLAR-1*

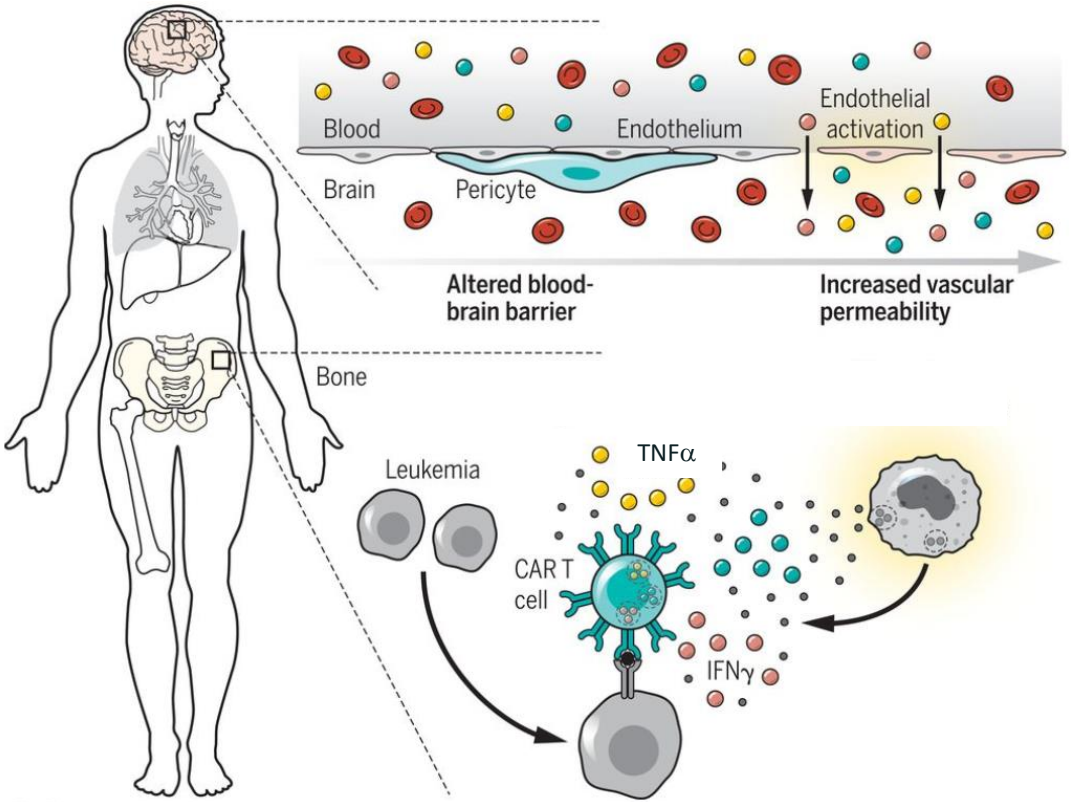


CAR T-CELLS: STRUCTURE AND MECHANISM OF ACTION



- CART cell activation upon antigen recognition mediates direct killing of tumor cells
- CART Therapy is associated with specific toxicities, related to the MoA (that can be successfully managed)

TOXICITIES ASSOCIATED WITH CAR T-CELL THERAPIES



Adapted from June et al; Science, 2018

ICANS (IMMUNE EFFECTOR CELL-ASSOCIATED NEUROTOXICITY SYNDROME)

- **Proportional to circulating cytokine levels and systemic inflammation**
- **Disruption of the BBB following endothelial activation**
- **Increased cytokines levels in CNS compartment due to permeability of BBB**
- **Microglial activation leads to further cytokine release, inducing an inflammatory state and brain dammage**

CRS (CYTOKINE RELEASE SYNDROME)

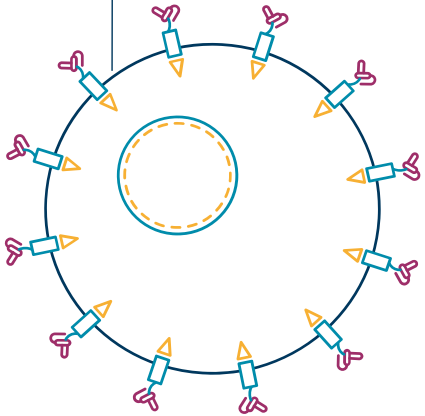
- **Inflammatory cytokine release by CART Cells** *IFNg and TNFa*
- **Activation of bystander immune cells and release of proinflammatory cytokines** *IFNg, IL-6, IL-1 and IL-10*
- **Hyperactivation of immune cells through positive feedback loop**
- **Activation and dammage of endothelial cells**

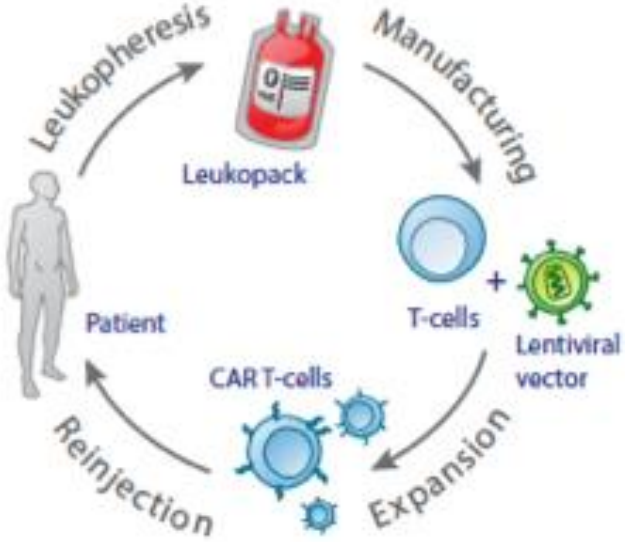
CAR T-CELL MANUFACTURING

MANUFACTURED FROM HUMAN CELLS

GENE THERAPY MEDICINAL PRODUCT
QC RELEASED
CRYOPRESERVED CELL SUSPENSION

CART CELL





ONE PROCEDURE BENEFITS ONE PATIENT

RISK-BENEFIT BALANCE

HUGE FINANCIAL WEIGHT ATTACHED TO EXISTING AUTOLOGOUS PRODUCTS

(TECHNICAL, LOGISTICAL AND ECONOMICAL CHALLENGES)

POTENTIAL LIFE-THREATENING IMMUNE-MEDIATED TOXICITIES REQUIRE URGENT DIAGNOSIS AND THERAPEUTIC INTERVENTION (TARGETED MODULATION OF KEY CYTOKINE PATHWAYS)

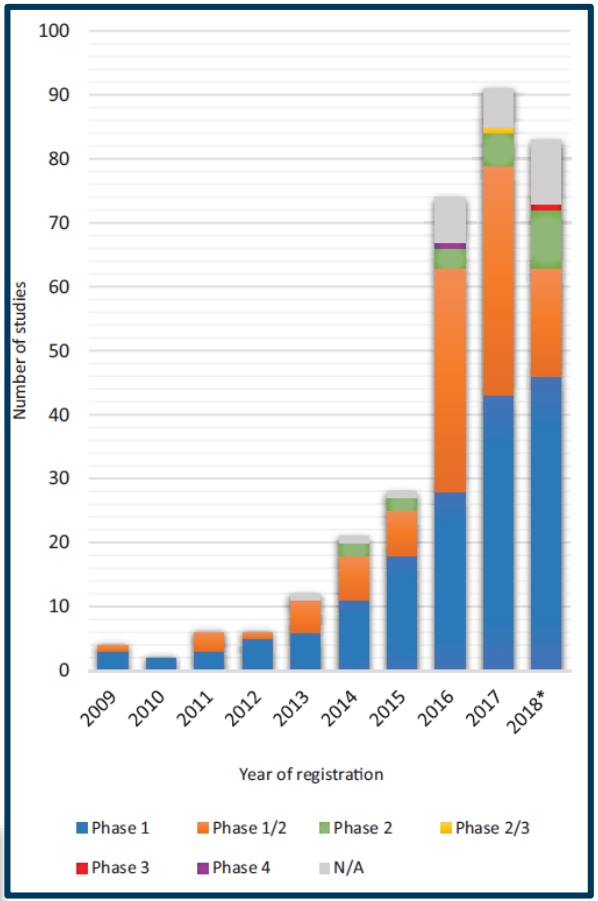
CAR T-CELLS CAN BE MORE EFFECTIVE THAN STANDARD OF CARE, AND COULD OVERCOME THE FINANCIAL BURDEN IMPOSED BY EFFECTIVE BUT NON-CURATIVE THERAPIES

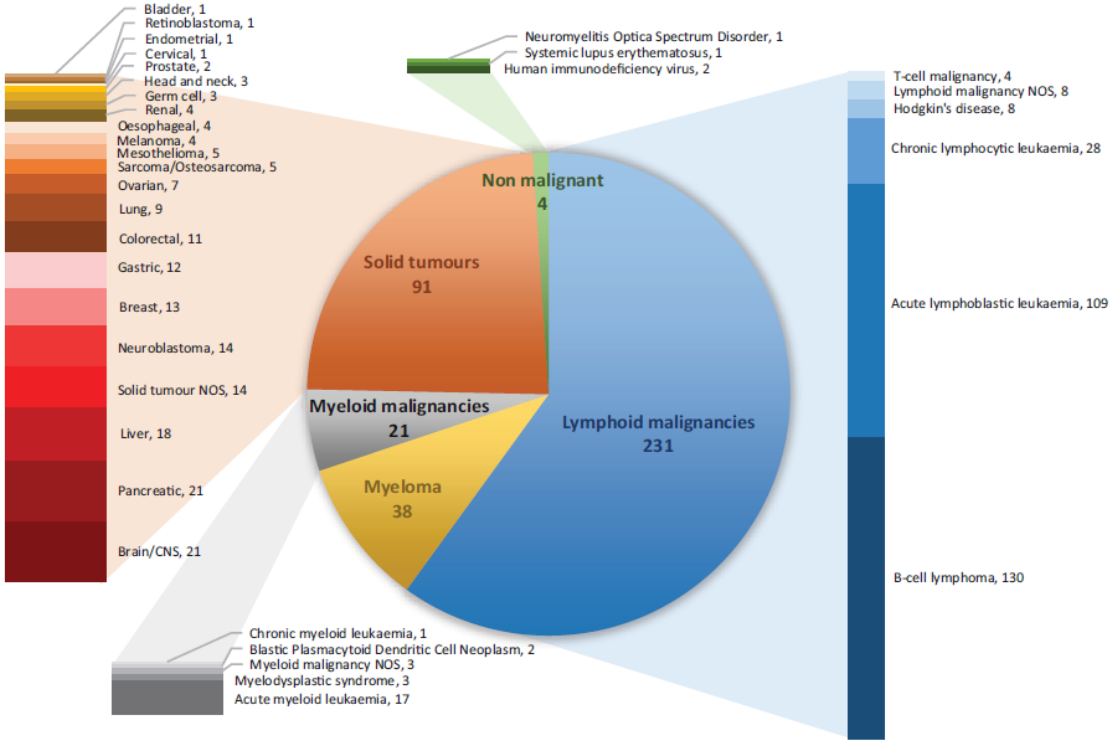
IDENTIFYING PREDICTORS OF RESPONSE WILL IMPROVE THE RISK-BENEFIT BALANCE AND MINIMIZE UNNECESSARY FINANCIAL OUTLAY FOR INDIVIDUAL PATIENTS AND HEALTHCARE SYSTEMS

(PATIENTS PREDICTED TO RESPOND POORLY TO CHEMOTHERAPY BUT WELL TO CAR T-CELLS COULD RECEIVE THEM UPFRONT)

June et al; Science, 2018
Garcia-Borrega et al; HemaSphere, 2019
Charrot and Hallam; HemaSphere, 2019

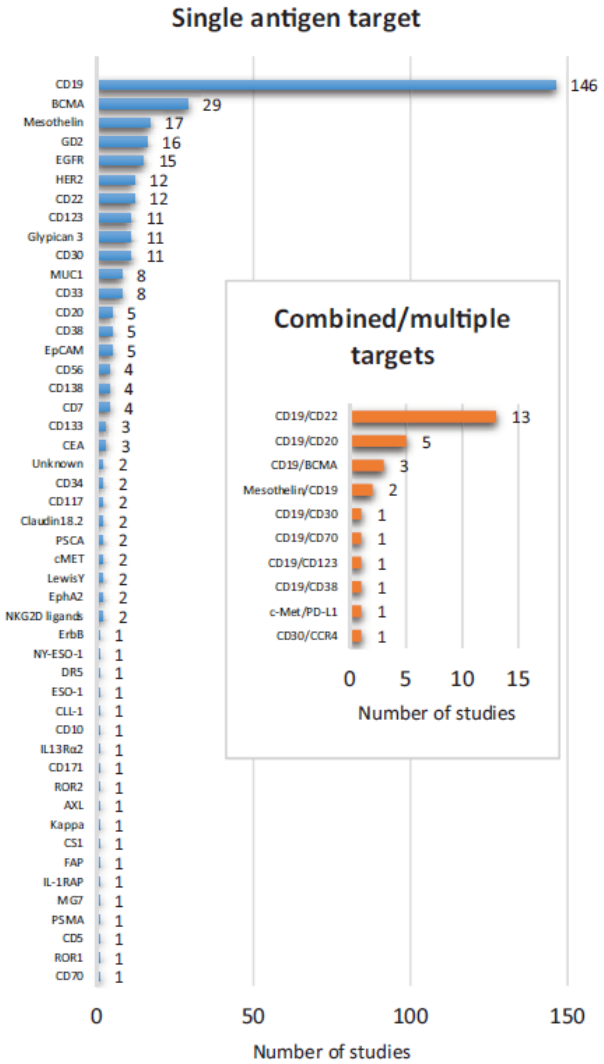
CAR T-CELL CLINICAL TRIALS

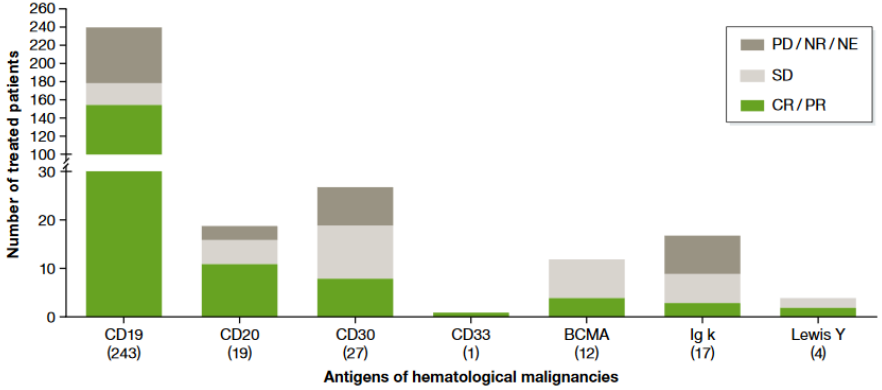


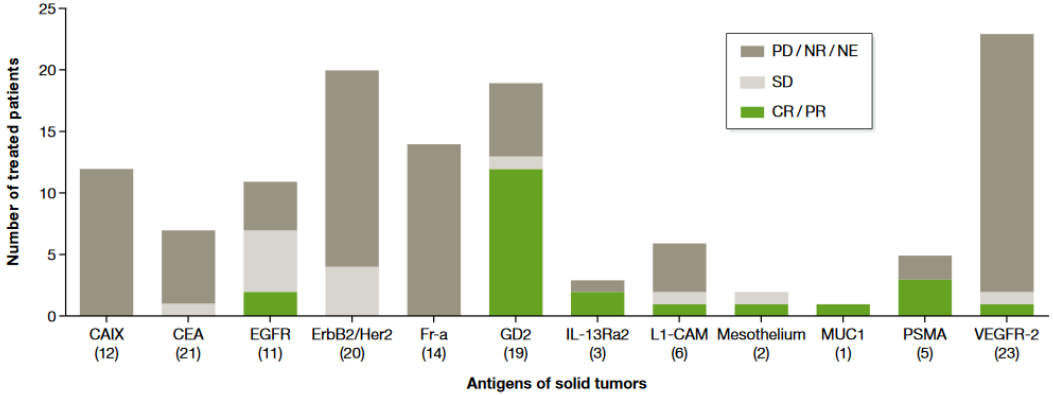


Charrot and Hallam; HemaSphere, 2019

CAR T-CELL CLINICAL TRIALS

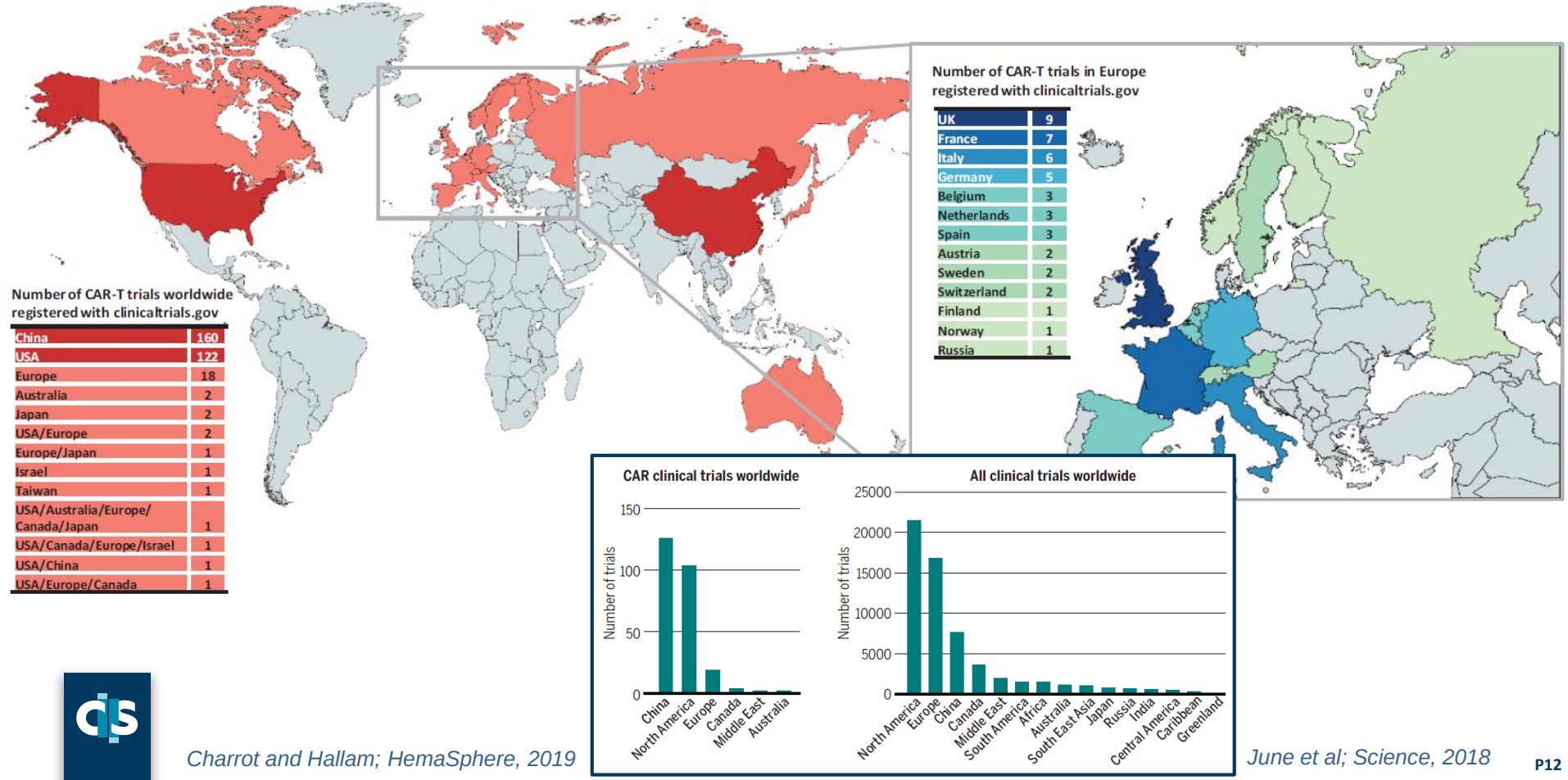






Hartmann et al; EMBO Mol Med, 2017
Charrot and Hallam; HemaSphere, 2019

CAR T-CELL CLINICAL TRIALS



Charrot and Hallam; HemaSphere, 2019

June et al; Science, 2018

FACTORS INFLUENCING EFFICACY AND SAFETY OF CAR T-CELLS

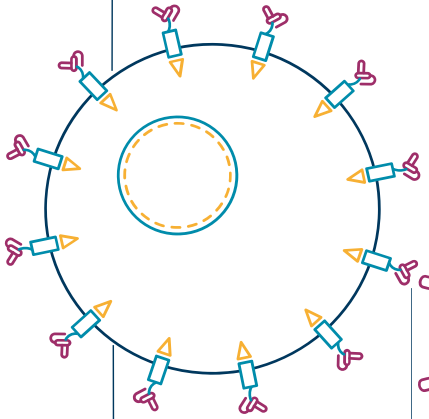
MANUFACTURED FROM HUMAN CELLS

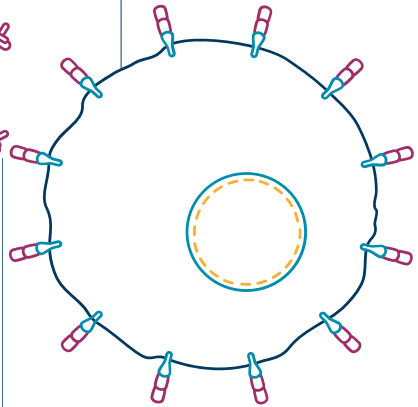
GENE THERAPY MEDICINAL PRODUCT
QC RELEASED
CRYOPRESERVED CELL SUSPENSION

TARGET EXPRESSION
(+ ON-TARGET/OFF-TUMOR ACTIVITY)
TUMOR BURDEN

ACCESS TO TARGET CELLS
IMMUNOSUPRERSSIVE MICROENVIRONMENT

CART CELL





TUMOR CELL

CAR CONSTRUCT
scFv SPECIFICITY

T-CELL SUBSETS
CART CELL VIABILITY
CART CELL EXHAUSTION

LYMPHODEPLETING REGIMEN
DOSING AND SCHEDULE
CART CELL EXPANSION

CELLS CAUSING EFFICACY OR TOXICITY (CRS AND NEUROTOX) MAY NOT BE THE SAME AS THE INFUSED PRODUCT

PHARMACOLOGY OF CART CELLS IS VERY DIFFERENT FROM TRADITIONAL DRUGS

SUMMARY (I)

- Engineering immune cells to seek and destroy cancer cells is a revolution in cancer treatment
- CART cells have a major therapeutic potential against certain types of cancer, with encouraging results for treatment of hematological cancers
- Improvement in the management of secondary effects is easing the clinical implementation of CART cell treatments
- Next generation of CART cells currently in early phases of development will allow to improve safety and limit toxicity of treatments

ADVANTAGES OF ALLOGENEIC VS. AUTOLOGOUS CAR-T

Autologous process:

1. CANCER TREATMENT DECISION

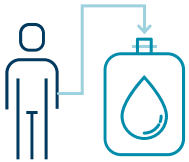
2. CANCER PATIENT APHERESIS

3. MANUFACTURING OF A SINGLE PATIENT PRODUCT

4. INDIVIDUAL CAR-T THERAPY

4-6 weeks before treatment

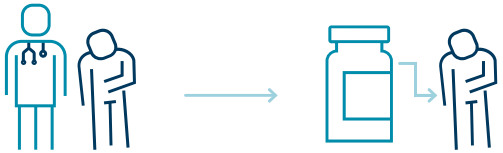
Allogeneic process:



HEALTHY DONOR APHERESIS

SCALABLE MANUFACTURING OF 100+ DOSES/BATCH

MASS PRODUCED OFF-THE-SHELF CAR-T THERAPIES



1. CANCER TREATMENT DECISION

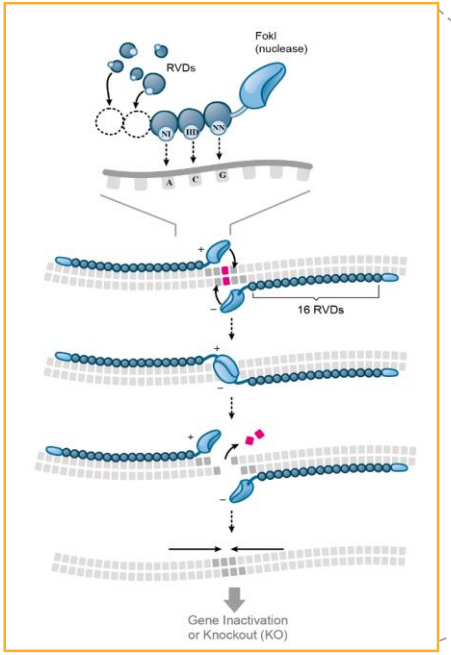
2. OFF-THE-SHELF CAR-T THERAPY

immediate treatment

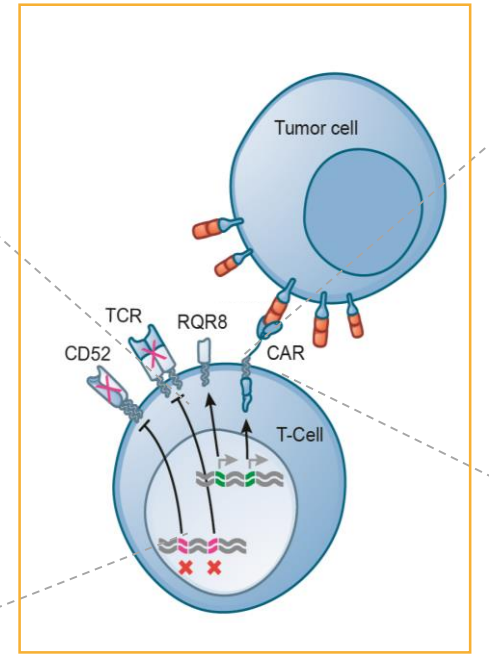
ADVANTAGES OF ALLOGENEIC CAR-T

- Avoid manufacturing delay or failure
  - Ability to release large amount of product in advance
- Improve clinical response
  - Use of T-cells from healthy donors
  - Increase standardization and safety
  - Facilitate retreatment
- Cost efficiencies
  - Multiple doses from one donor
  - Potential to scale production to further reduce cost

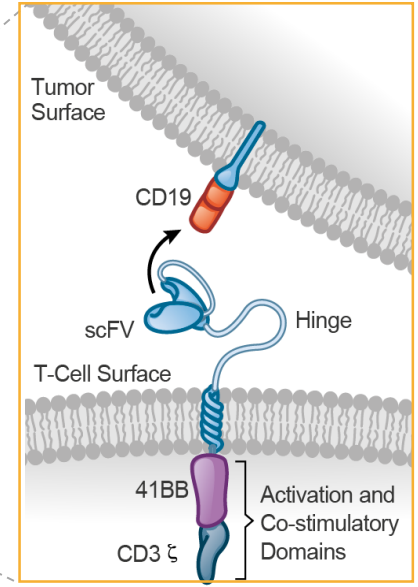
ALLOGENEIC CAR-T CELLS THROUGH GENE EDITING



Gene Editing
TALEN® Nuclease

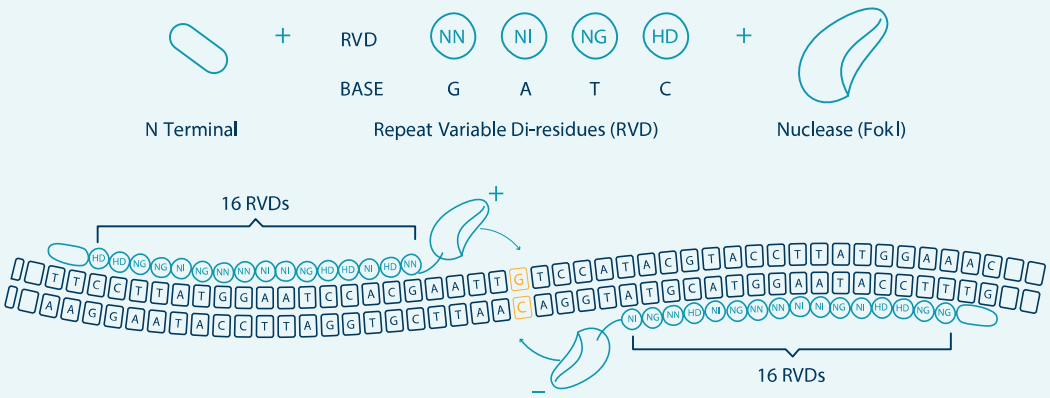


Allogeneic
CAR-T Cell



Chimeric Antigen Receptor
Tumor Recognition

TALEN®: BEST-IN-CLASS GENE EDITING



PRECISION
targeting within 6 base pairs of any target in the genome (effective changes)

SPECIFICITY
recognition site is 32 base pairs long (avoids errors)

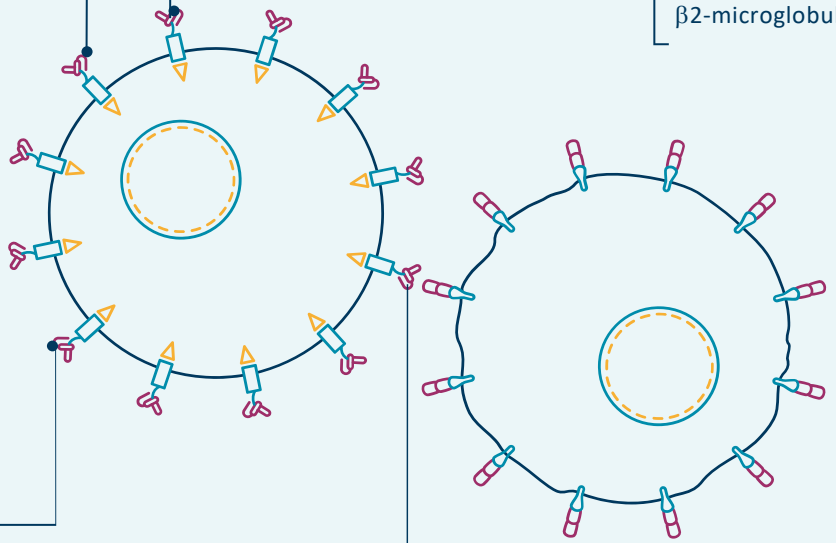
EFFICIENCY
TCR-α can be knocked-out with over 95% efficacy for engineered CAR T-cells (ensures yield)

UCARTs – FIRST & BEST-IN-CLASS ALLOGENEIC CAR T-CELLS

AVOID GvHD
via knock-out of T-Cell Receptor (TCR)

ENHANCED Activity /Persistence
via additional knock-outs (i.e. CD52, β2-microglobulin or CS1)

UCART
Universal Chimeric Antigen Receptor T-cell



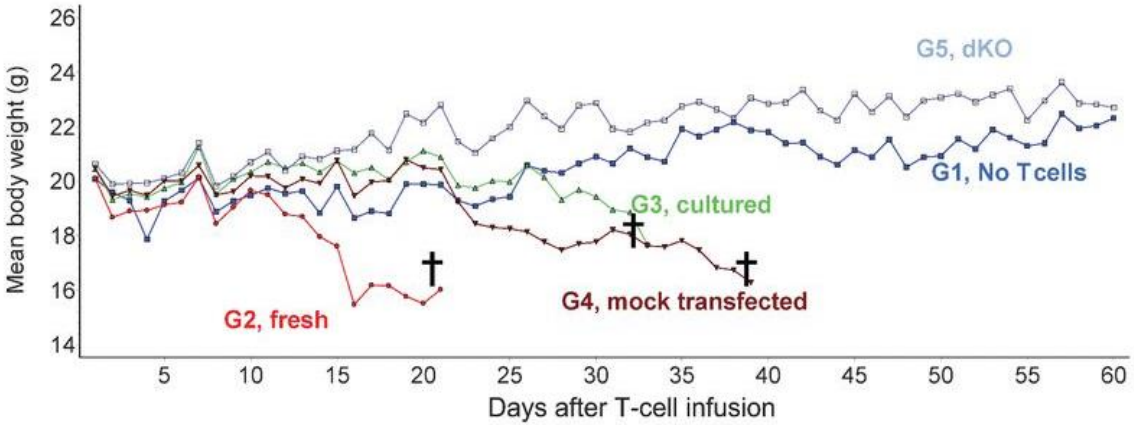
TUMOR CELL

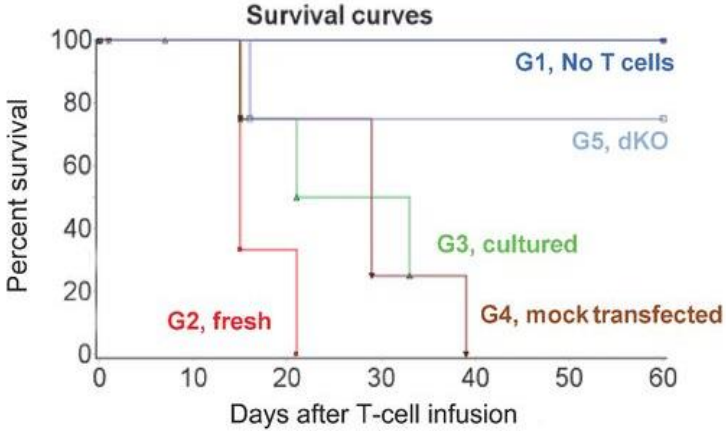
SAFETY SWITCH
CD20 mimotope can be engaged by rituximab treatment

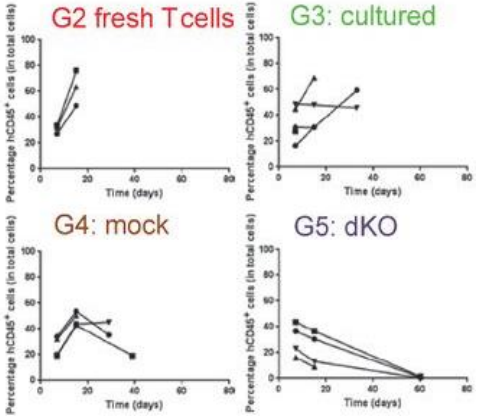
TARGET TUMOR CELLS
via expression of CAR that recognizes tumor antigen

ALLOGENEIC UCART CELLS DO NOT INDUCE GVHD

- GvHD development occurs in all mice injected with non modified T cells
- No clinical symptoms of GvHD were observed in mice injected with TCR deficient T-cells

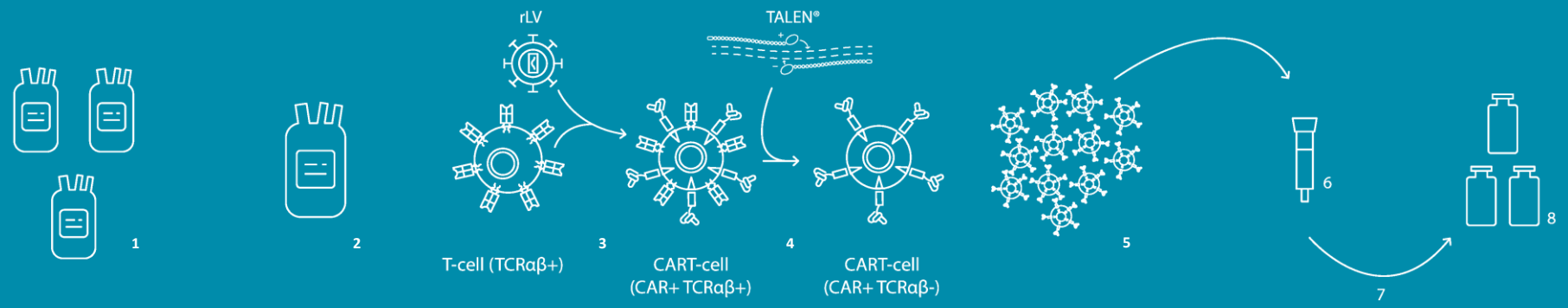






Poirot et al. Cancer Research 2015

UCART MANUFACTURING



1. Frozen leukopaks

2. Thawed PBMCs

3. Lentivector transduction

4. TALEN®-mediated gene editing

5. Cell amplification

6. Purification
7. Fill & Finish

8. Frozen UCART products

- More than 5 years of experience in allogeneic CAR T manufacturing
- Validated gene editing technology for cell manufacturing
- 5 UCART product candidates manufactured so far
- Full QC system in place, 3 wholly-controlled product candidates cleared for 4 clinical trials by the U.S. Food and Drug Administration

PIPELINE: INNOVATIVE CANCER THERAPIES FOR UNMET NEEDS

Program	Indication	Target	Pre-clinical	Phase 1	Phase 2 / 3	2019 Anticipated Milestones
UCART19*	ALL	CD19	Mar. 2016 CTA (MHRA) Mar. 2017 IND (FDA)			
UCART123	AML	CD123	Feb. 2017 IND (FDA)			
UCART22	ALL	CD22	Jun. 2018 IND (FDA)			First dosing expected
ALLO-501*	NHL	CD19	Jan. 2019 IND (FDA)			First dosing expected
UCARTCS1	MM	CS1	Jan. 2019 IND (FDA)			First dosing expected
ALLO-715**	MM	BCMA				IND (FDA) expected
UCART22	NHL	CD22				
UCART123	HL	CD123				
UCARTCLL1	AML	CLL1				
ALLO-819**	AML	FLT3				

Proprietary development program

Licensed development program

* UCART19/ALLO-501 is exclusively licensed to Servier and under a joint clinical development program between Servier and Allogene.

** Product candidates exclusively licensed to Allogene

UCART19*: DESIGN OF PHASE 1 STUDIES IN R/R** ALL***

CD19 is a validated target expressed in B-cell malignancies

Adult ALL (CALM study)

PRIMARY OBJECTIVE
Evaluate safety, tolerability, maximum tolerated dose (MTD) and regimen

SECONDARY OBJECTIVES
Objective remission rate at Day 28. Duration of response, time to remission, progression-free survival

ONGOING

Pediatric ALL (PALL study)

PRIMARY OBJECTIVE
Evaluate safety at a fixed dose in patients aged between 6 months and 18 years old

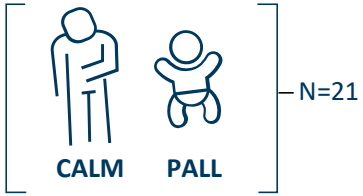
SECONDARY OBJECTIVES
Determine the ability to achieve molecular remission at Day 28

ONGOING

* **UCART19 is exclusively licensed to Servier** and under a joint clinical development program between Servier and Allogene
** Relapsed/Refractory
*** Acute Lymphoblastic Leukemia
**** Dose Level

UCART19*: PHASE 1 R/R ALL – DATA** PRESENTED AT ASH 2018

Safety:



- **14%** Grade 3-4 Cytokine Release Syndrome
- **0%** Grade 3-4 neurotoxicity
- **0%** Grade 3-4 skin Graft vs Host Disease

Efficacy:

- 82% CR/CRi rate in FCA***-treated patients
- 67% overall CR/CRi rate
- 71% of these patients were MRD-
- Redosing with UCART19 resulted in cell expansion and MRD- status in 2/3 patients
- Peak expansion observed mostly at Day 14

* UCART19 is exclusively licensed to Servier and under a joint clinical development program between Servier and Allogene
** Pooled data
*** Lymphodepletion regimen consisting of fludarabine, cyclophosphamide and an anti-CD52 mAb

PIPELINE TARGETS MULTIPLE UNMET NEEDS IN CANCER

AML

UCART123 UCARTCLL1

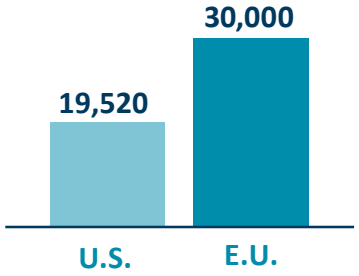
MM

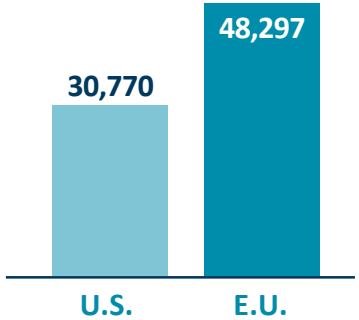
UCARTCS1

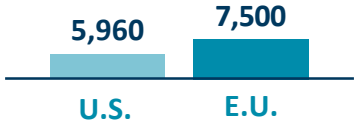
ALL

UCART22

Incidence rates per year







Survival data

27%

5 years OS in adults

6% 5 years OS in adults >55 years old

50%

5 years OS in adults

43-83 months median OS for stages 2-3

20%

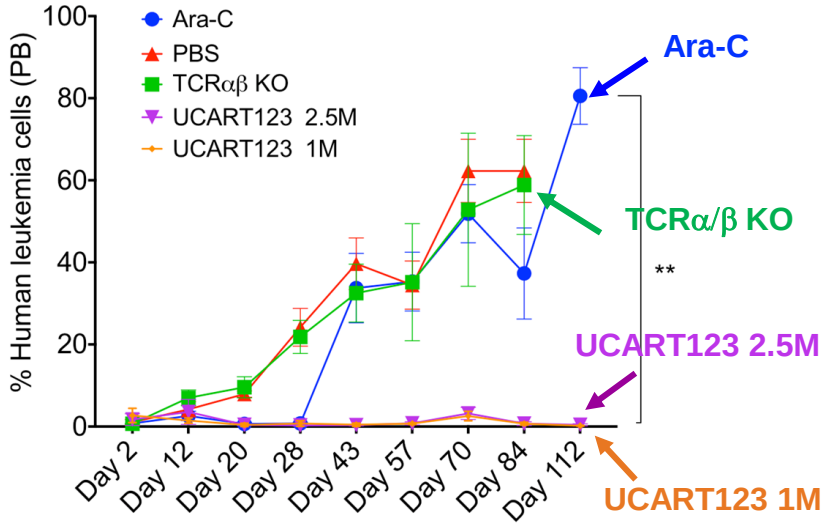
5 years OS* in adults

<6 months median disease-free survival in pediatric patients

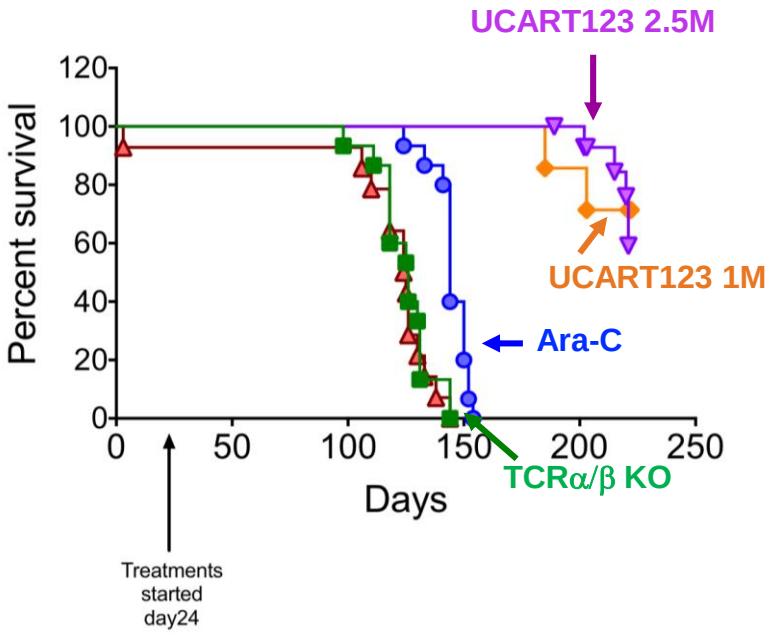
* Overall Survival

UCART123 – *IN VIVO* ACTIVITY AGAINST PRIMARY AML

Peripheral Blood Evaluation

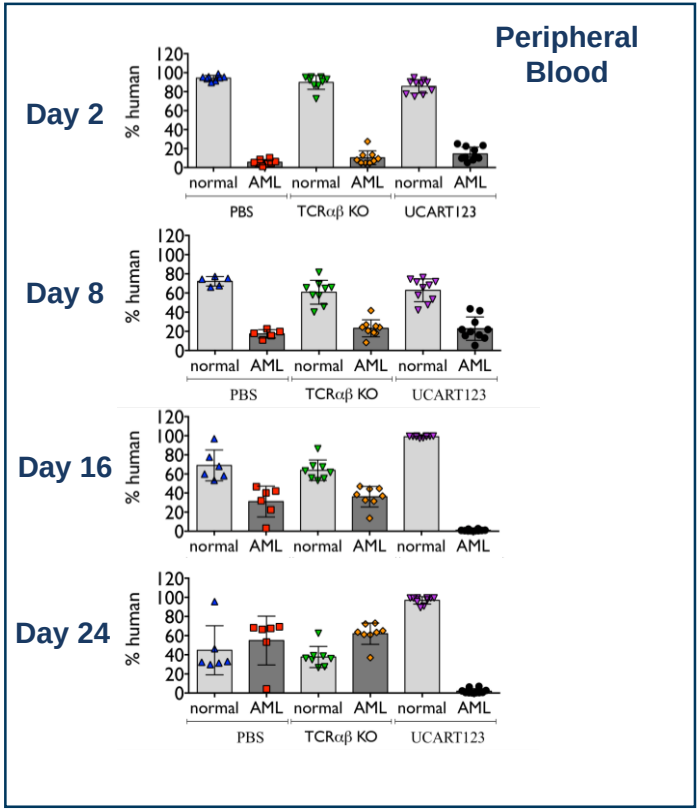


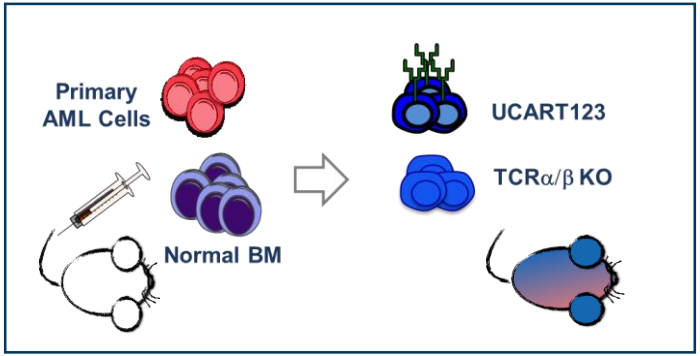
Overall Survival

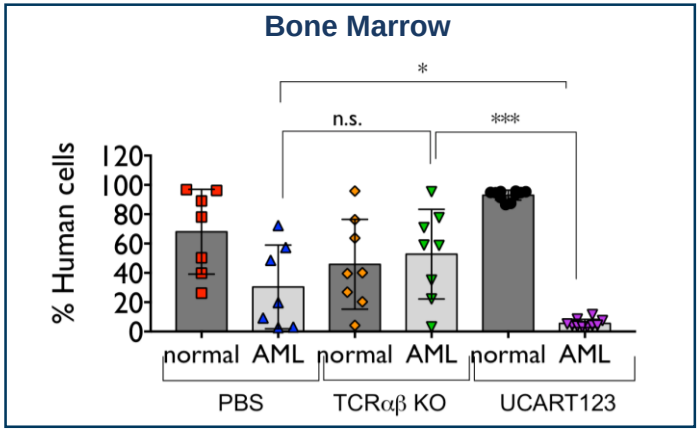


In collaboration with Dr. Monica Guzman, Cornell-Weill

UCART123 - PREFERENTIALLY ELIMINATES AML CELLS

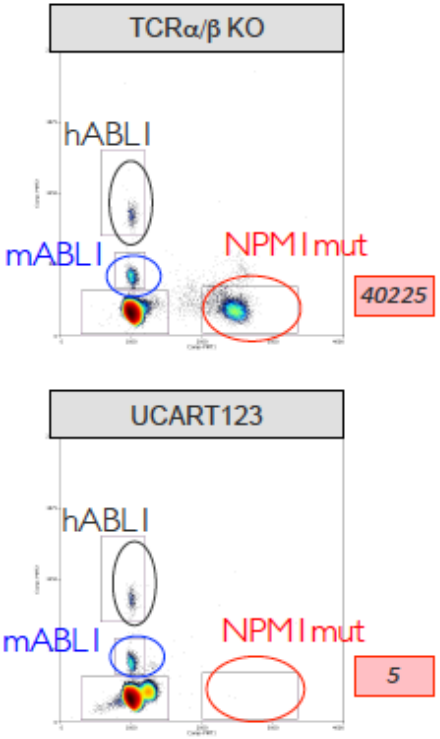


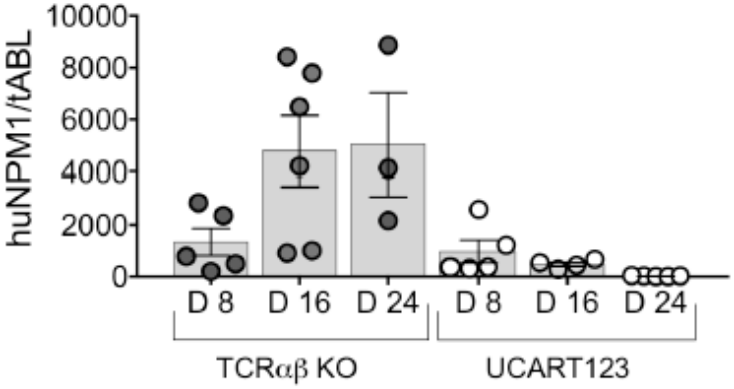




In collaboration with Dr. Monica Guzman, Cornell-Weill

UCART123 - PREFERENTIALLY ELIMINATES AML CELLS





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UCART123 – PHASE 1 STUDY IN AML

Patient characteristics

Age and fitness: R/R in AML
65 years and older, unfit patients

Mutation status:
genetically complex

Progression: rapid progression
following relapse

Dose escalation (mTPI*) phase (R/R AML)

R/R AML
Up to 18
patients

ONGOING at
Weill Cornell MD
Anderson
Moffitt
Dana-Farber

28 days between the first 2 patients for each dose, then 14 days for subsequent patients**

DL1 → **DL2** → **DL3**

Expansion Phase

TOTAL
N=64-144

Expected
in 2020

→

R/R AML
PATIENTS
N=18-37

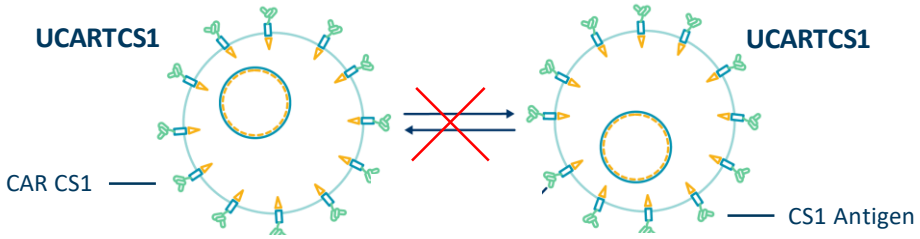
FIRST LINE AML PATIENTS
ELN*** Adverse genetic group
N=46-107

* Modified Toxicity Probability Interval Design
** 42 days if aplasia
*** European Leukemia Net

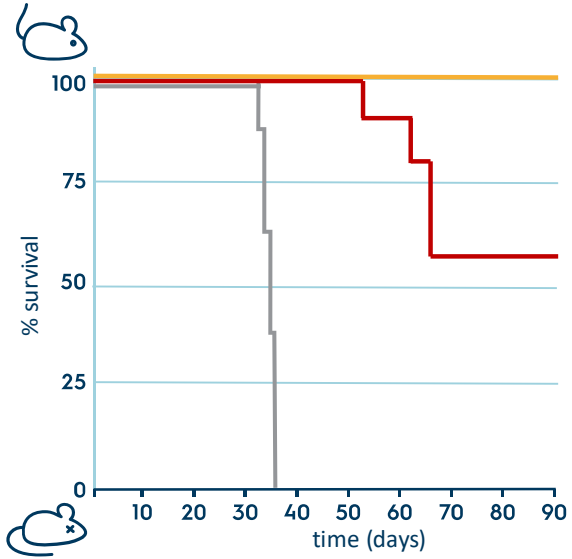
UCARTCS1 – PRECLINICAL RATIONALE IN MULTIPLE MYELOMA

CS1 KO to suppress cross T-cell reaction between UCARTCS1

ENABLE TARGETING OF ANTIGENS EXPRESSED ON T CELLS



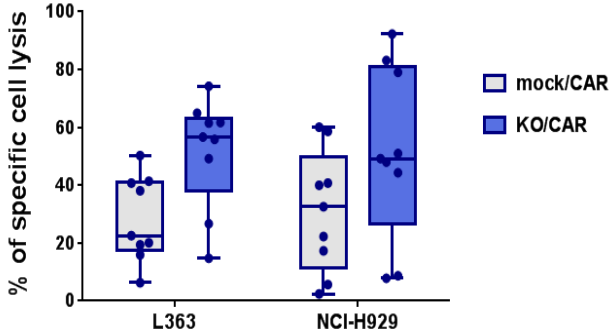
Dose-dependent enhanced survival



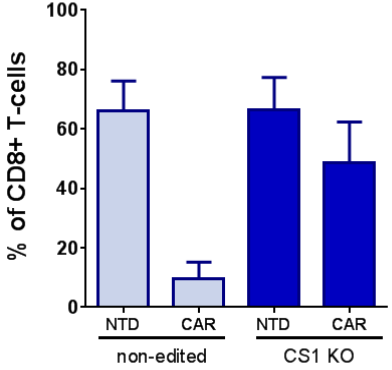
Day -10: **tumor cells injection** Day 0: **treatment**

Vehicle **UCARTCS1** $3x10^6$ **UCARTCS1** $10x10^6$

Higher in vitro anti-tumor activity



Increased yield CD8+ cells



UCART22 – PRECLINICAL RATIONALE FOR ALL

Development rationale:

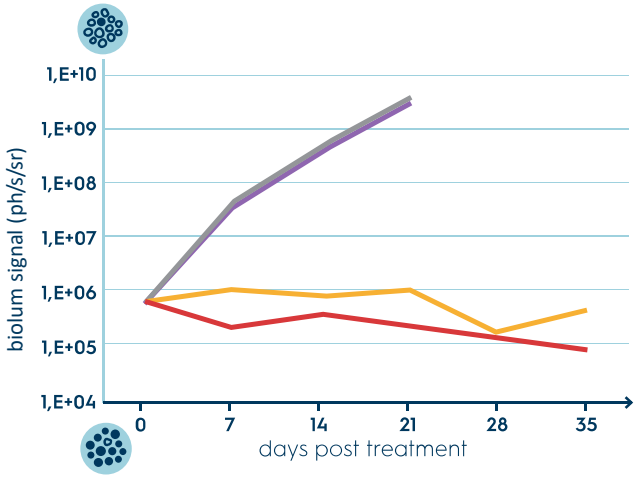
CD22 expression: in CD19 negative blasts

Unmet need: high relapse rates (CD19-) after CD19 CAR-T treatment, poor survival in R/R patients

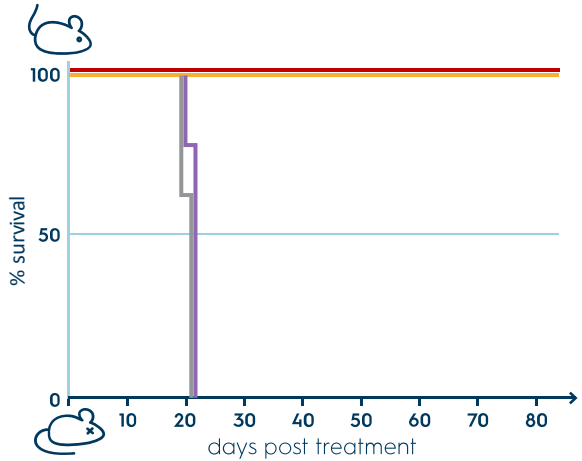
Validated target in ALL and NHL

Expandable market: potential expansion into first-line ALL

Control of tumor progression



Enhanced survival



Vehicle **DKO/NT** 10x10^6 cells **UCART22** 3x10^6 **UCART22** 10x10^6

UCART22

- Is highly efficient at eradicating tumors in vivo
- Result in increased survival in mouse model

SUMMARY (II)

- Gene editing technology can be used to manufacture T-cells from third-party healthy donors to generate allogeneic "off-the-shelf" engineered CAR T-cells
- TALEN mediated inactivation of the TCRα constant (TRAC) gene can be achieved at high frequencies, eliminating the potential for edited T-cells to mediate Graft versus Host Disease (GvHD)
- Additional gene inactivation can be incorporated to further enhance the efficiency or applicability of UCART cells
- First clinical proof-of-concept: UCART19 treated the first pediatric ALL patient in June 2015
- Preclinical data demonstrate strong anti-tumor activity of UCART product candidates
- Phase I clinical trial is currently ongoing with UCART123 in AML
- Additional Phase I trials in ALL (UCART22) and Multiple Myeloma (UCARTCS1A) to be initiated in 2019

THANK YOU

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