cellectis

the life science company

ENGINEERED CAR-T THERAPIES

Workshop on Scientific and Regulatory Challenges of Genetically Modified Cell-based Cancer Immunotherapy Products

November 15-16, 2016

FORWARD LOOKING STATEMENTS

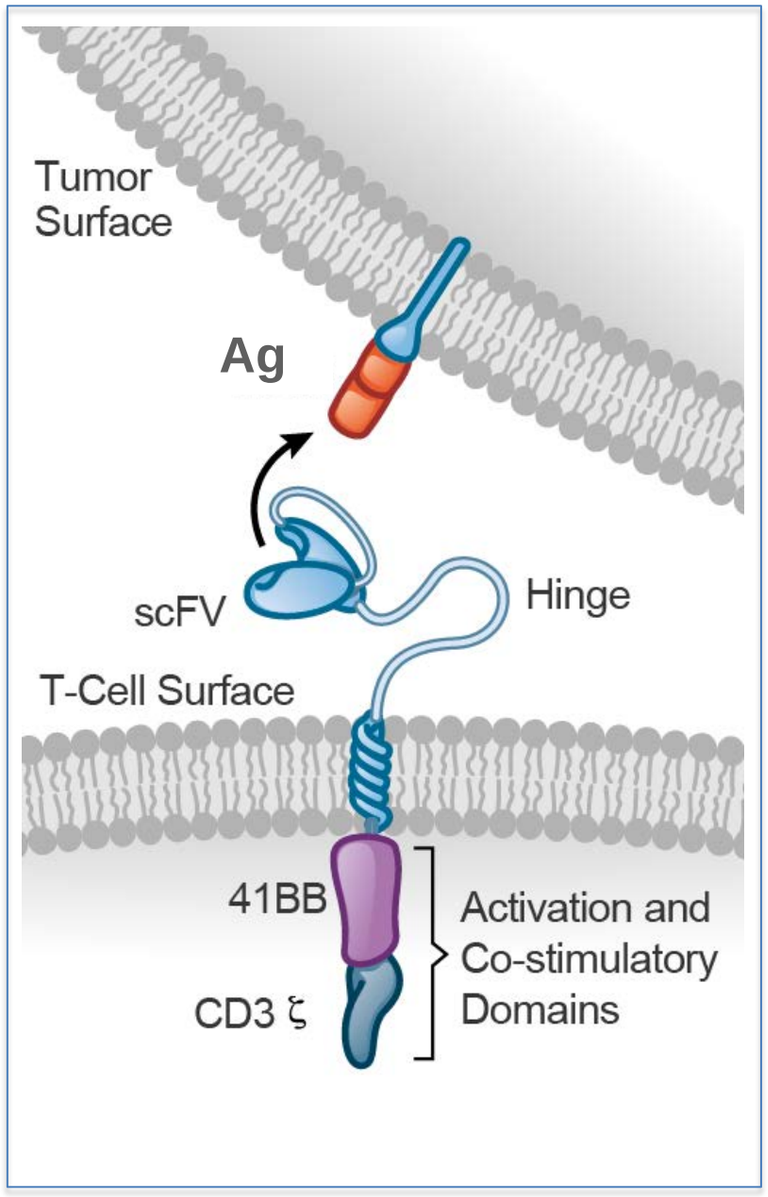
THIS COMMUNICATION EXPRESSLY OR IMPLICITLY CONTAINS CERTAIN FORWARD-LOOKING STATEMENTS CONCERNING CELLECTIS SA AND ITS BUSINESS.

SUCH STATEMENTS INVOLVE CERTAIN KNOWN AND UNKNOWN RISKS, UNCERTAINTIES AND OTHER FACTORS, WHICH COULD CAUSE THE ACTUAL RESULTS, FINANCIAL CONDITION, PERFORMANCE OR ACHIEVEMENTS OF CELLECTIS SA TO BE MATERIALLY DIFFERENT FROM ANY FUTURE RESULTS, PERFORMANCE OR ACHIEVEMENTS EXPRESSED OR IMPLIED BY SUCH FORWARD-LOOKING STATEMENTS.

CELLECTIS SA IS PROVIDING THIS COMMUNICATION AS OF THIS DATE AND DOES NOT UNDERTAKE TO UPDATE ANY FORWARD-LOOKING STATEMENTS CONTAINED HEREIN AS A RESULT OF NEW INFORMATION, FUTURE EVENTS OR OTHERWISE.

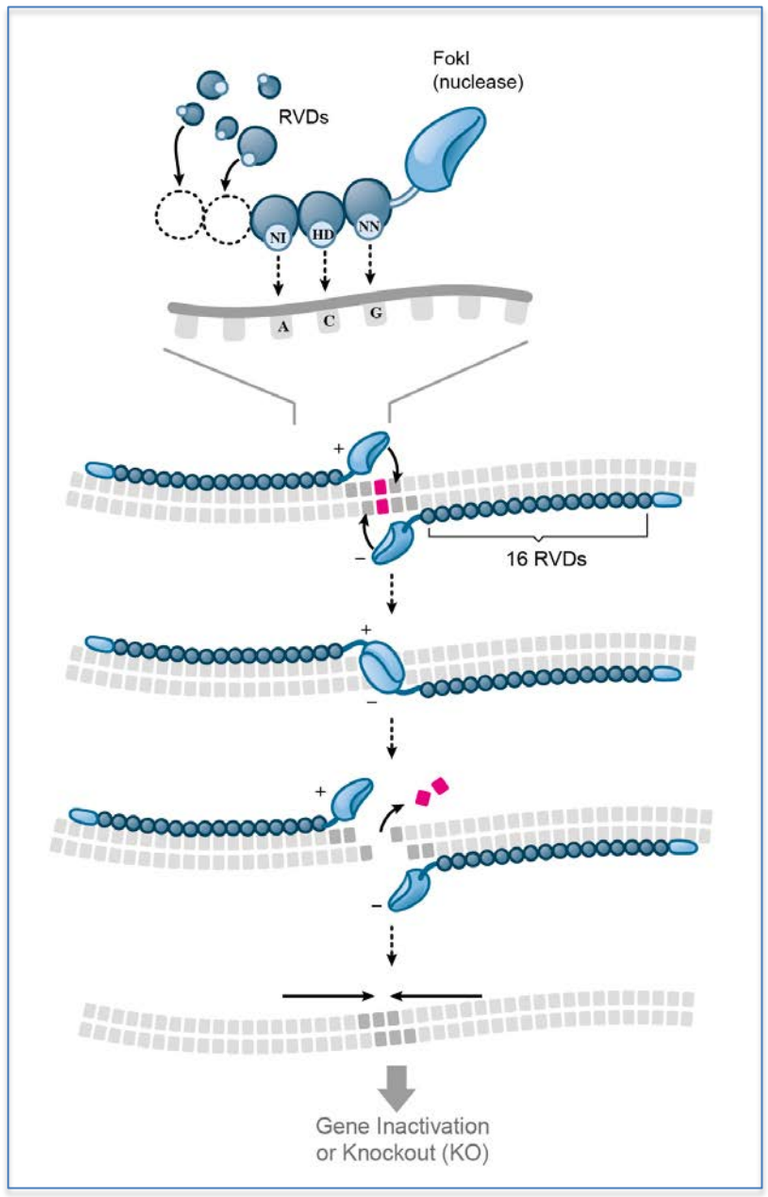
Combining Technology Platforms

To enhance the power of the immune system against cancer



Chimeric Antigen Receptor

Tumors recognition



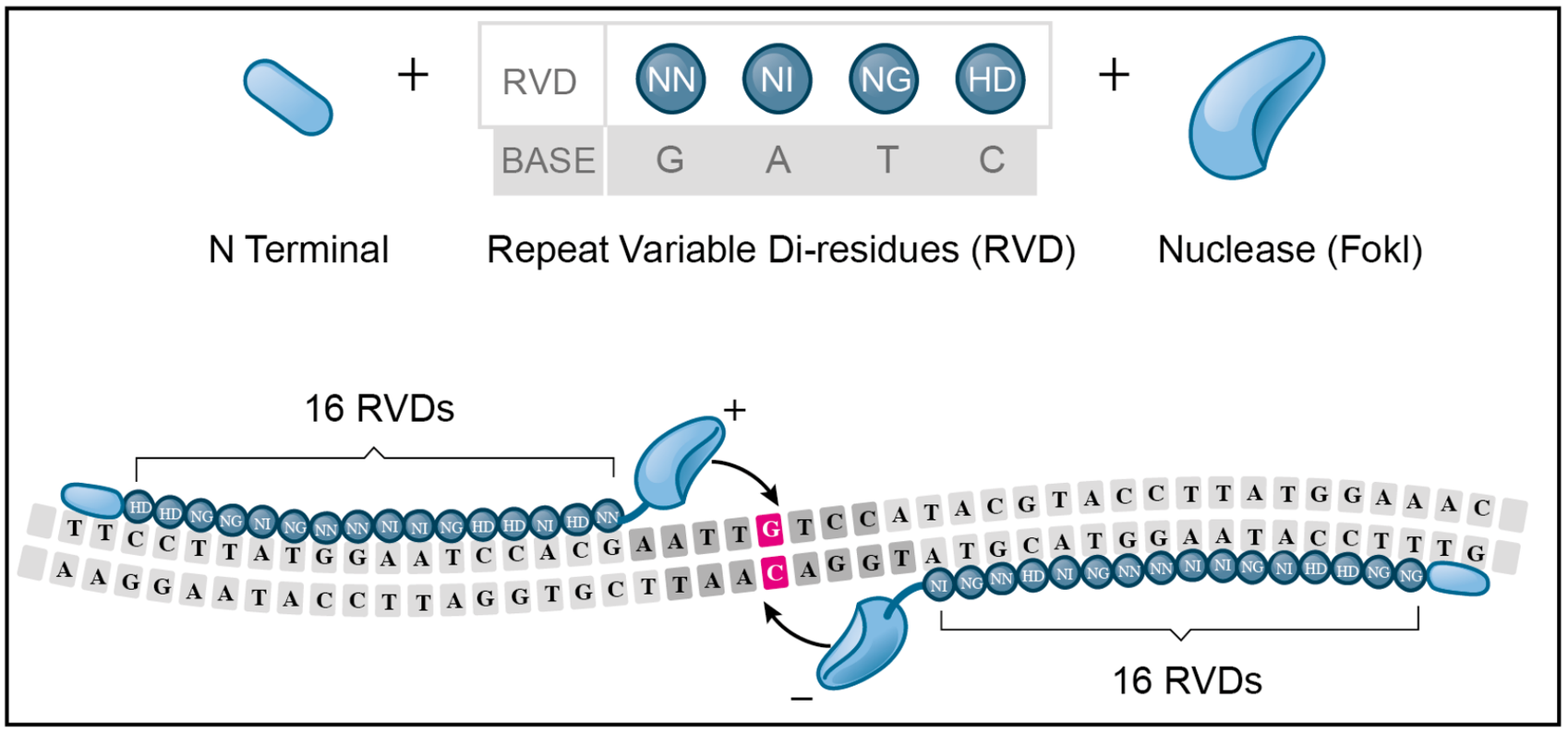
TALEN® Nuclease

T-Cell properties

TALEN® - Gene Editing Tool

TALEN® gene editing tool with best-in-class characteristics:

- **Precision:** 99.8% of chromosome sequences can be targeted using more selective TALEN® scaffolds
- **Efficacy:** Routinely 97% efficiency in single gene knock-out at R+D level
- **Safety:** Industry-leading off-target safety profile with very low toxicity (undetectable off target cleavage)



TALEN® - Gene TALEN® Gene Editing Process

A custom TALEN® is created to target the precise gene sequence

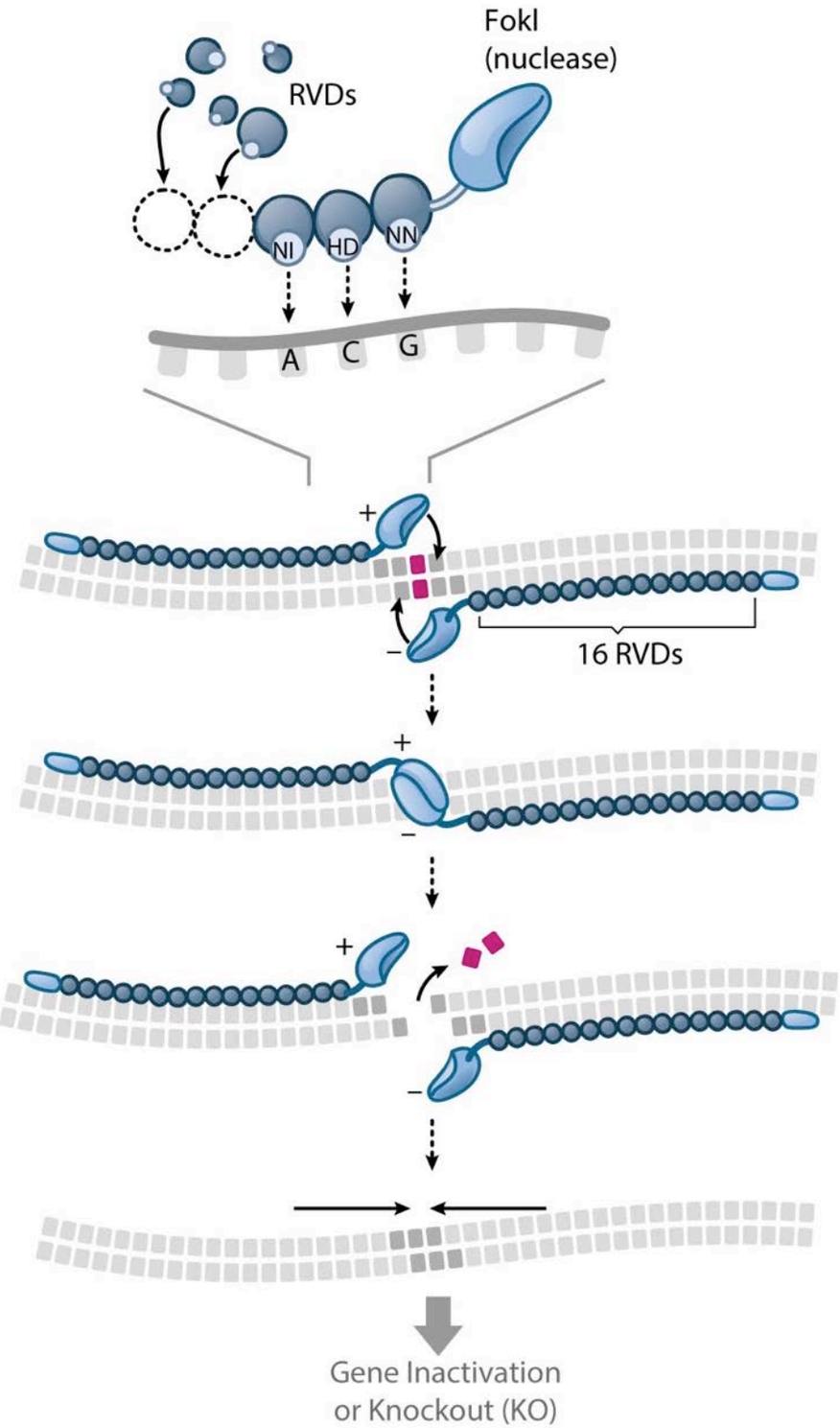
TALEN® binds to its target sequence as a heterodimer, separated by a spacer region

Following binding, FokI nuclease heads clip the DNA at the target sequence

Cleavage generates DNA double-strand breaks that can be repaired by NHEJ

The DNA is degraded at the cleavage site and nucleotides are lost

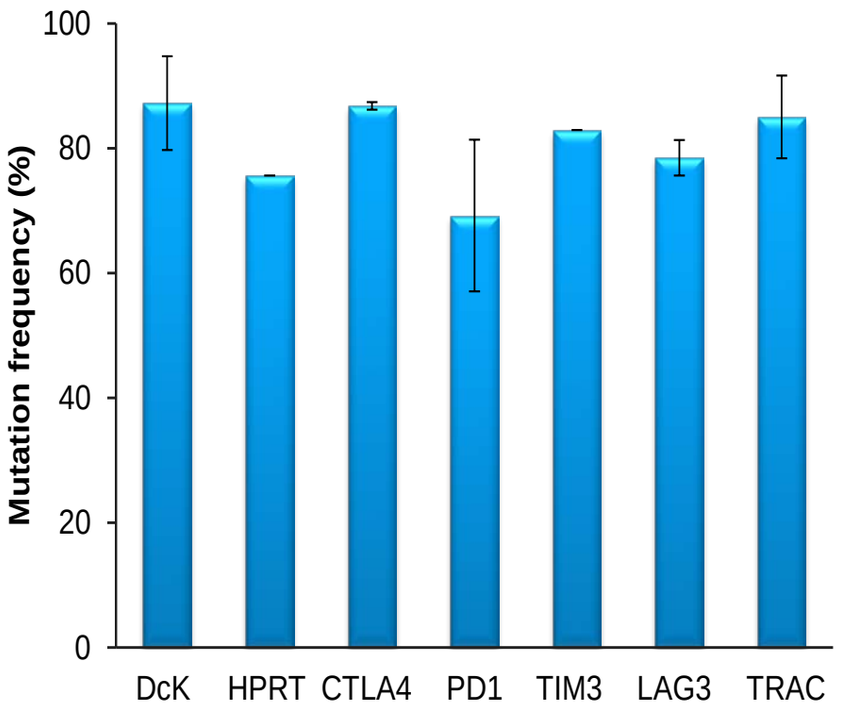
DNA ends are rejoined, resulting in a mutation that inactivates the target gene



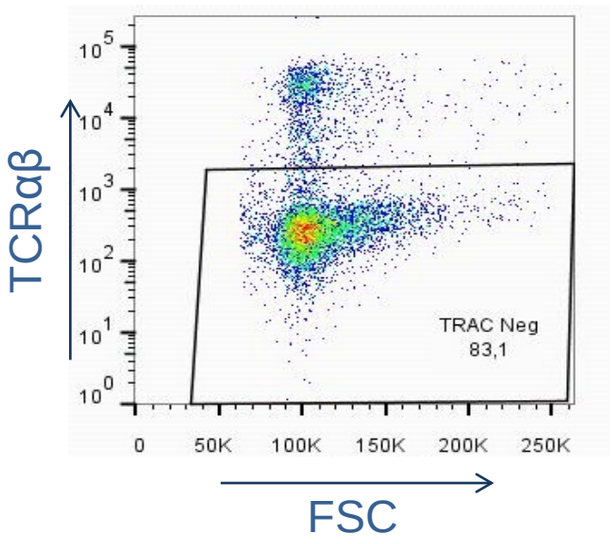
Efficient Gene inactivation using TALEN® mRNA

Pulse Agile Electroporation System

Cuvette or Large volume chamber (12 ml)
$2x10^6$ -10^9 cells

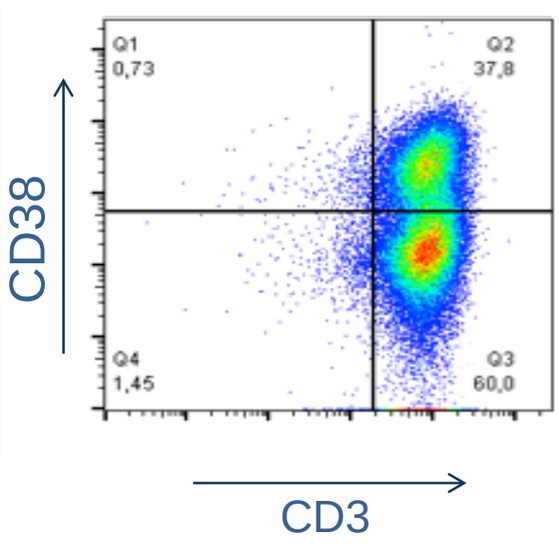


TALEN® TCRα



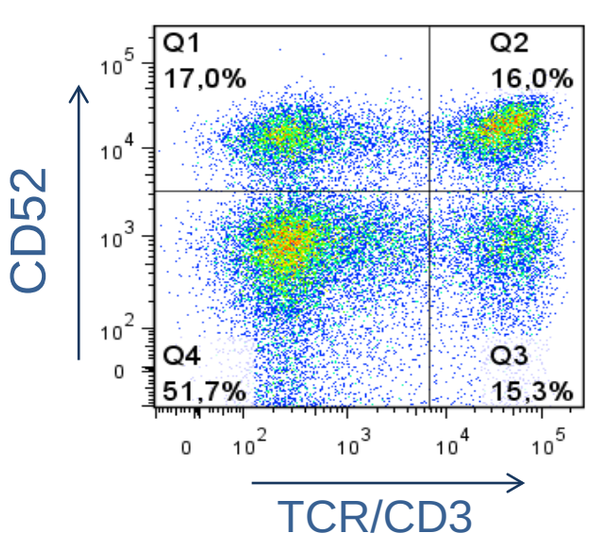
1 allele KO: 83%

TALEN® CD38



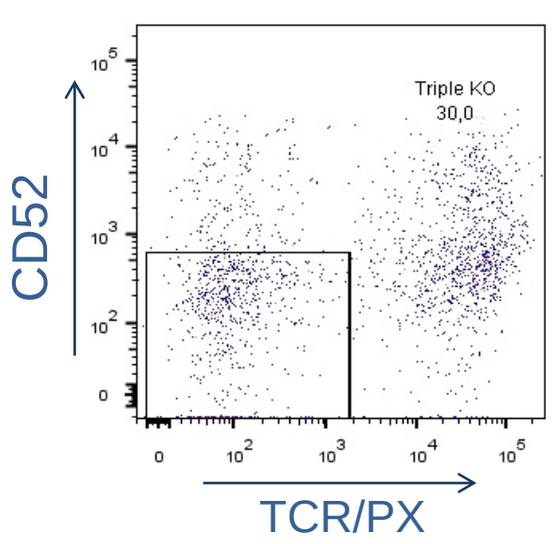
2 alleles KO: 60%

TALEN® CD52+TCRα



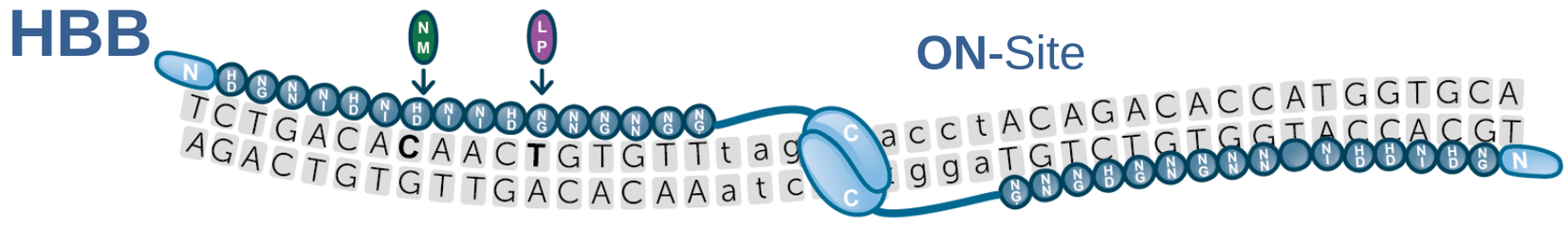
3 alleles KO: 51%

TALEN® CD52+TCRα+geneX

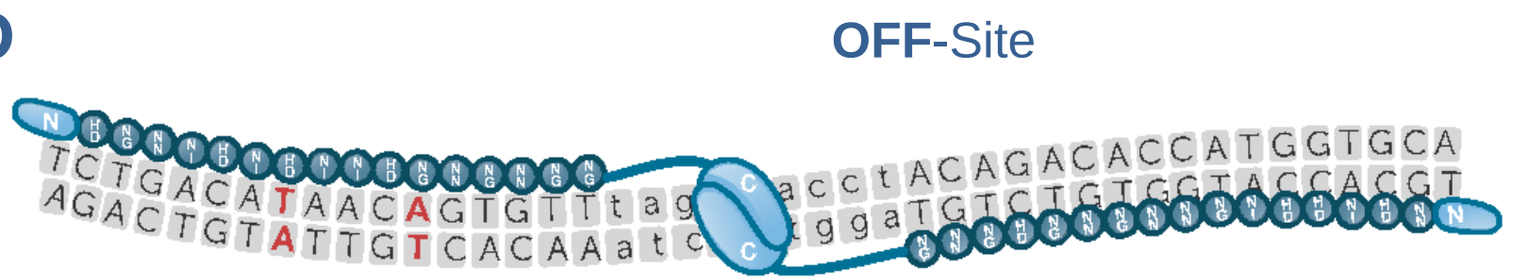


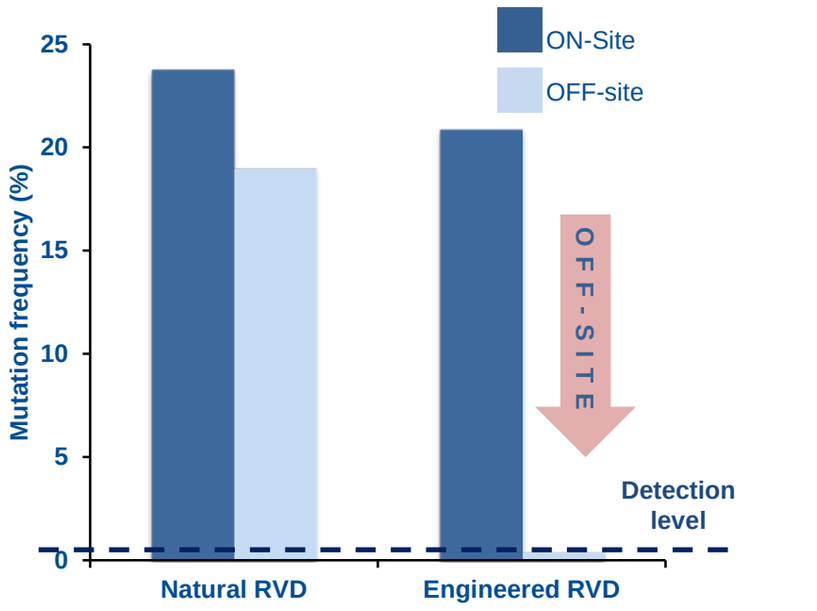
5 alleles KO: 30%

TALEN® Technology permits highly specific cleavage



ON-site/OFF-site > 94 % identity



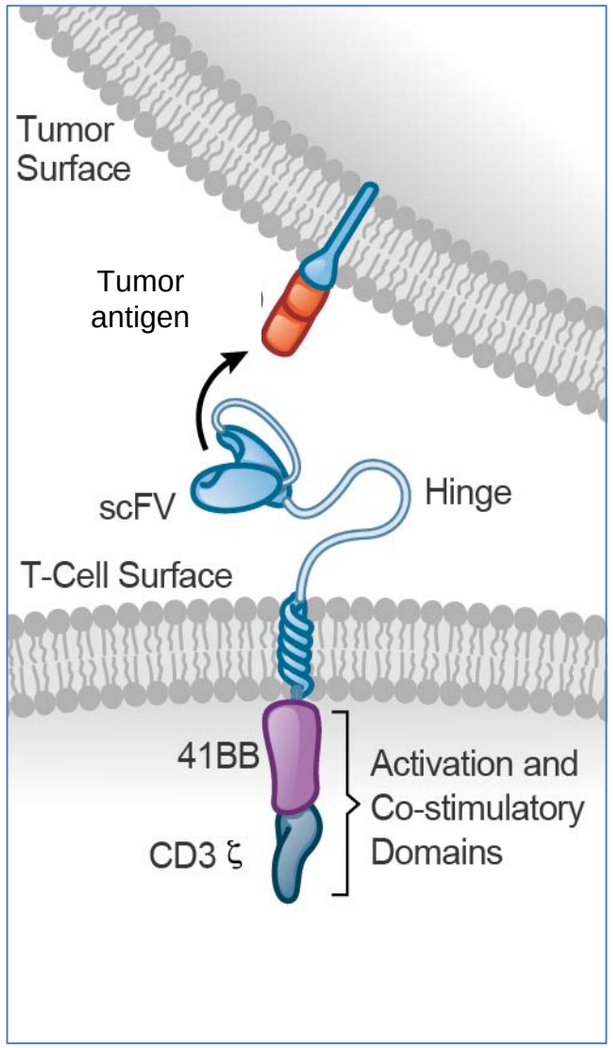


Juillerat et al (scientific report 2015)

Combining Technology Platforms

To enhance the power of the immune system against cancer

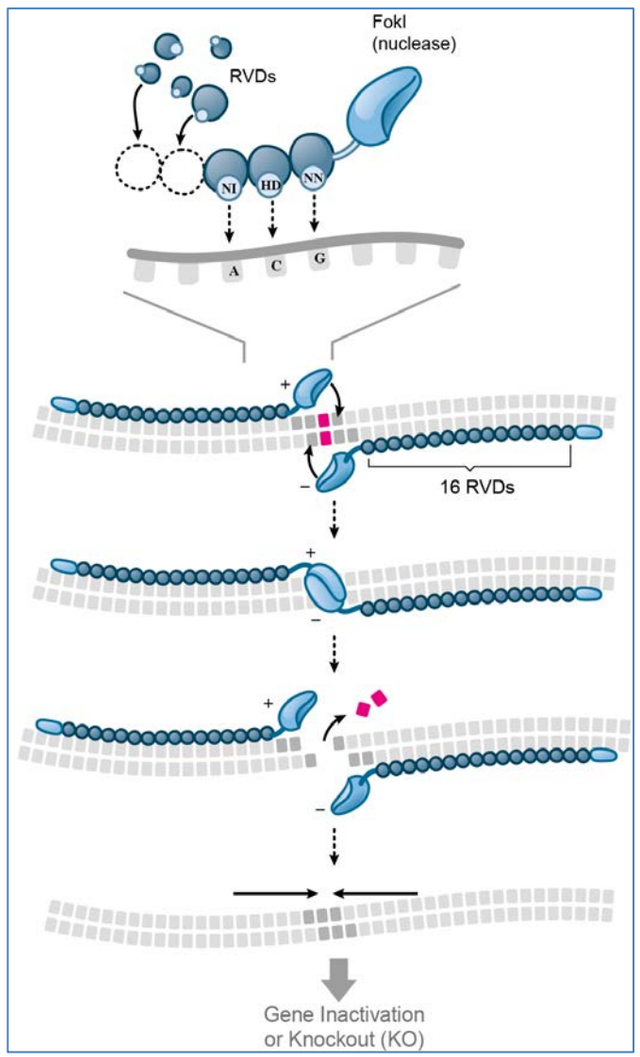
Chimeric Antigen Receptor



Enhancing

Tumor Recognition

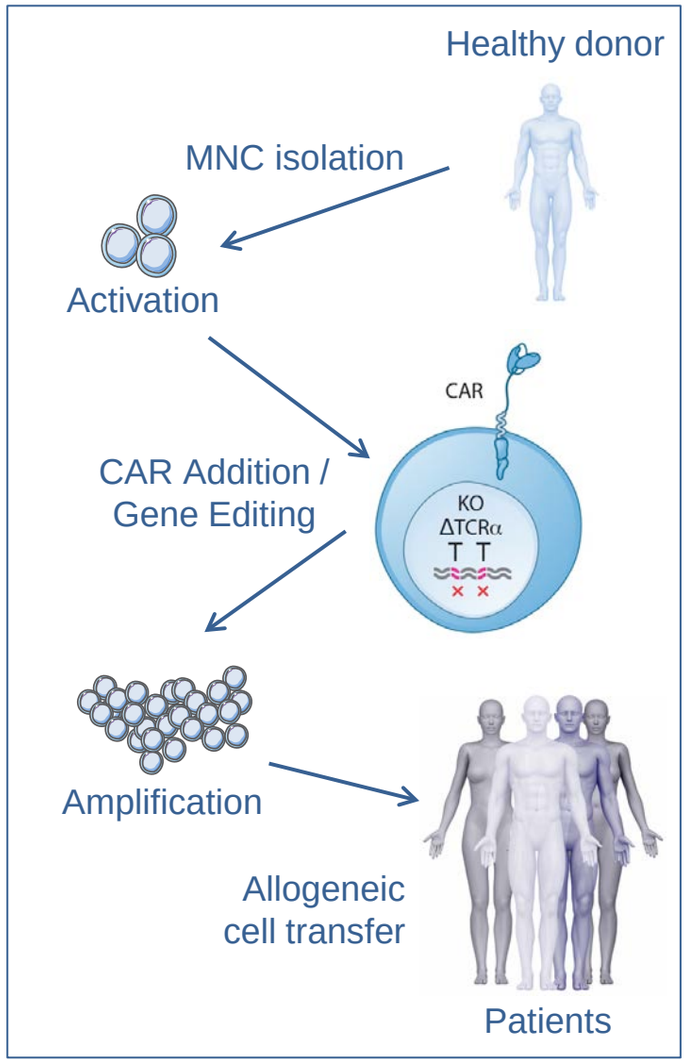
TALEN ® Gene Editing



Enhancing

T-Cell Properties

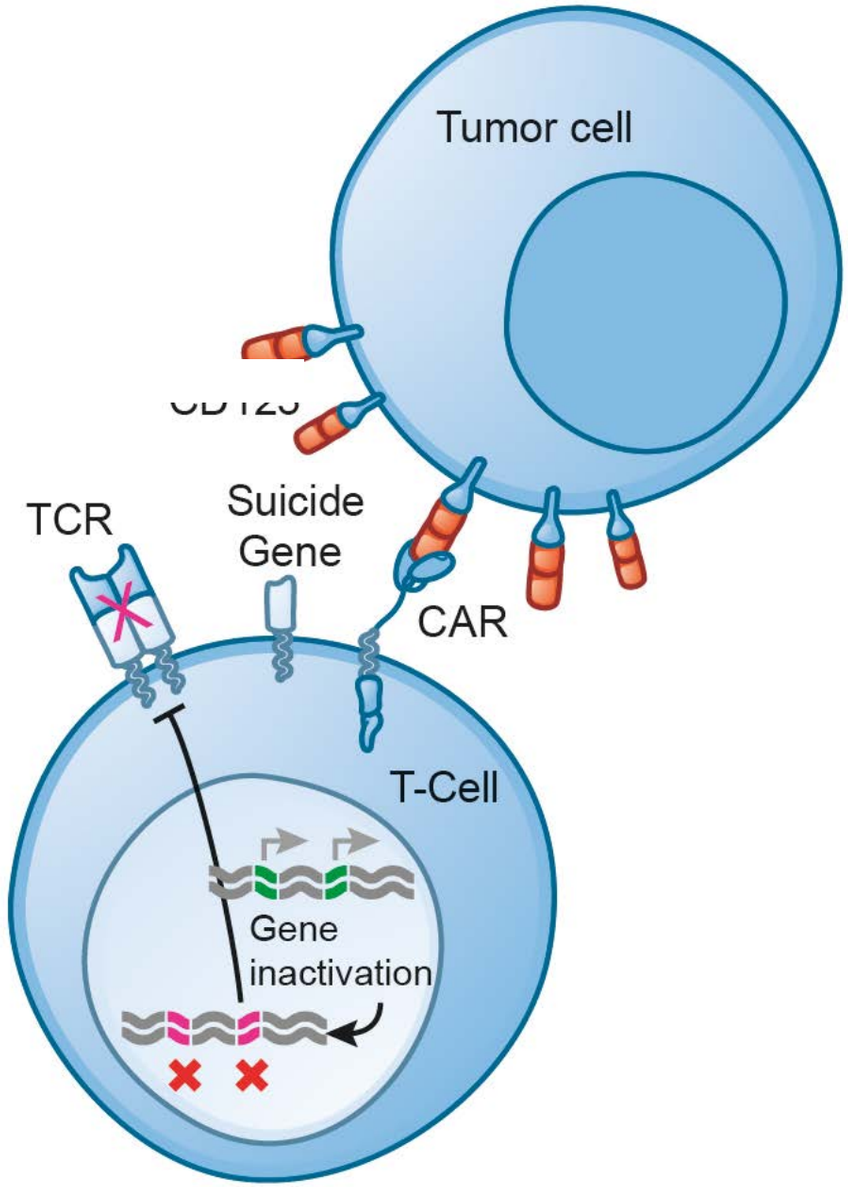
‘Off-The-Shelf’ CAR T-Cells



Expanding

Patient Access

Towards “off-the-shelf” adoptive T-cell immunotherapy



- CAR expression to redirect T-cells to tumor antigens
- Suicide gene for safety
- TRAC disruption using TALEN® to eliminate TCR from the cell surface and avoid GvHD
- Lymphodepletion (alemtuzumab or Cy/ Flu)
- Additional gene editing

Enhancing the power of T-cells by Gene Editing

T-cell Characteristics

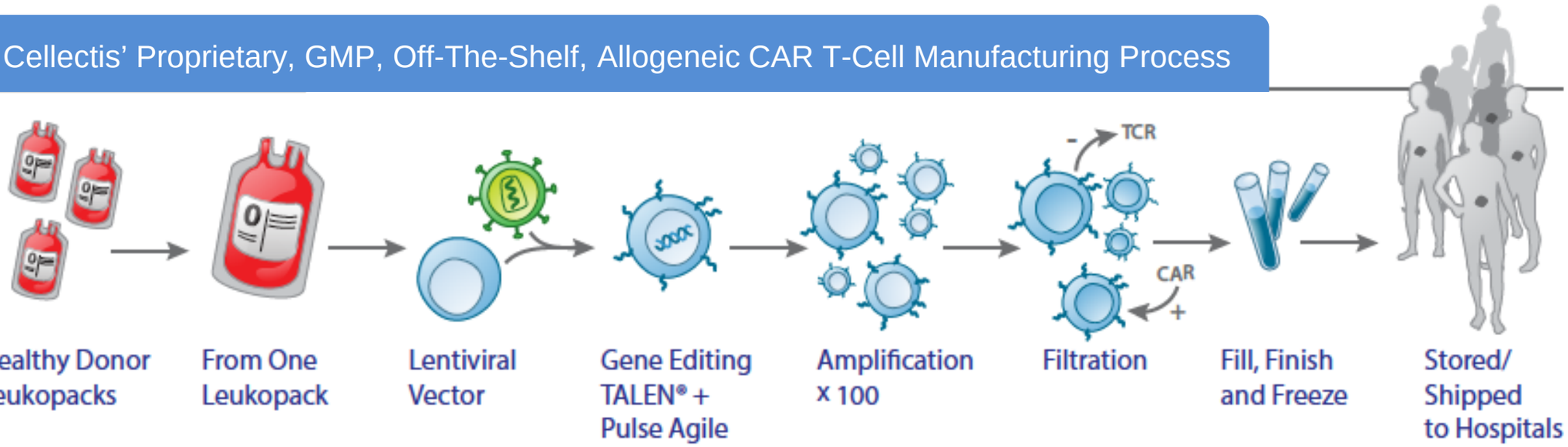
- o Allogeneic, non alloreactive CAR T-Cells
- o Resistance to chemotherapy
- o Resistance to lymphodepleting agents
- o Resistance to tumor inhibition
- o Suppressed cross T-Cell reaction

Targeted Patient Benefits

- ✓ Off-the-shelf product (KO TCR)
- ✓ Compatible with SoC, use in combination therapies
- ✓ Enhanced engraftment (KO CD52, KO DCK)
- ✓ Enhanced efficacy (KO PD1, KO CTLA4,…)
- ✓ Better suited for specific tumors (i.e. CS1/SLAMF7, CD38)

“Off the shelf” CAR T-cell GMP Manufacturing Process

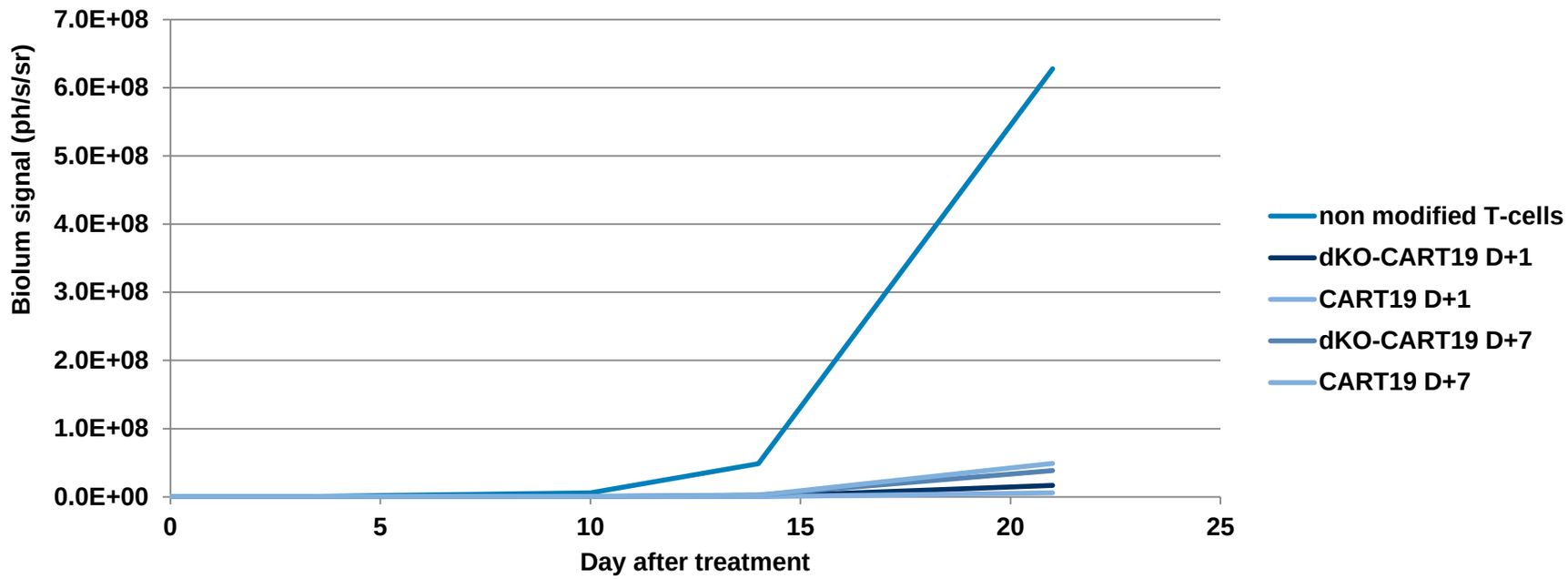
Cellectis’ Proprietary, GMP, Off-The-Shelf, Allogeneic CAR T-Cell Manufacturing Process

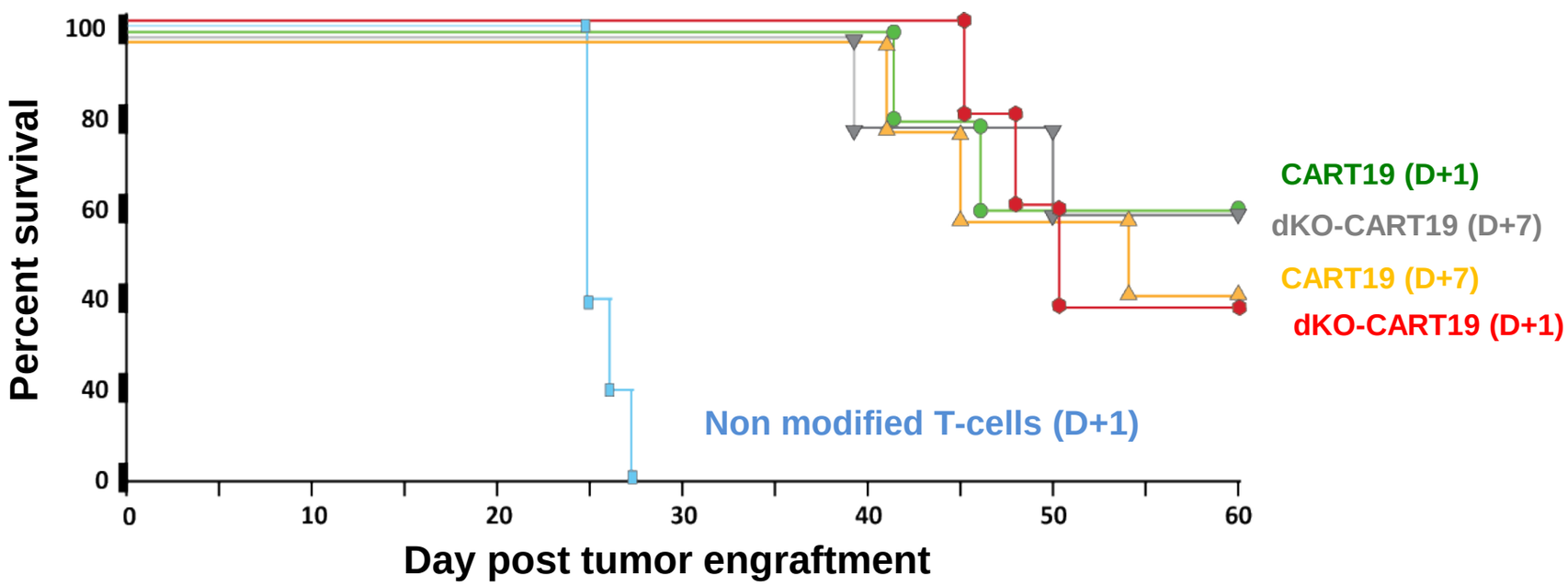


Day 0	Day 3	Day 5	Day 6-17	Day 18	Day 18
▪ On-purpose lymphocytes apheresis ▪ Frozen quality controlled starting material (MNCs)	▪ CAR addition using a viral vector	▪ TALEN® transfer using proprietary Pulse Agile electroporation technology Critical step for : ✓ Efficient and safe gene knock-out ✓ cell 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	

Efficient anti-tumor activity of “off the shelf” CAR T-cells

NSG mice treated with CAR+ T-cells, 1 or 7 days post tumor cell injection (Daudi-luc cells)

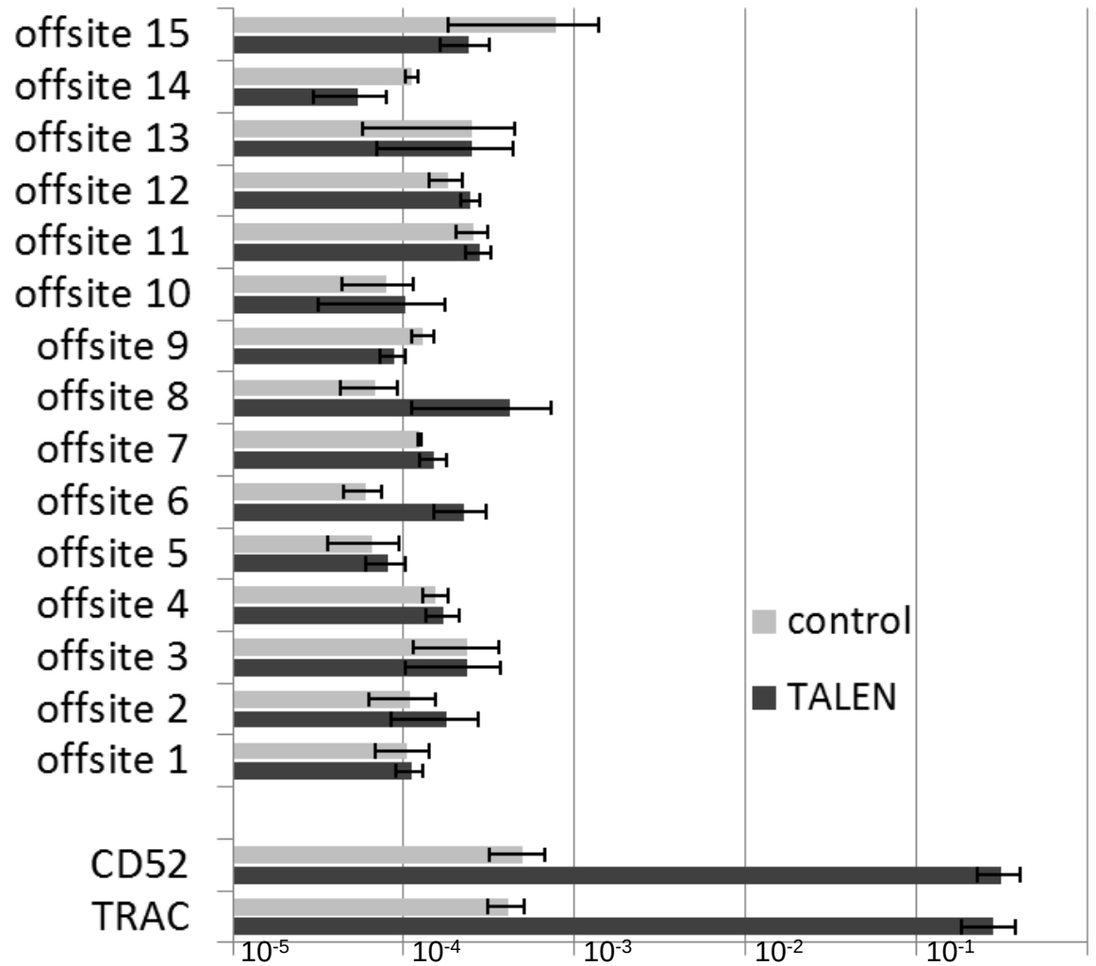




Genomic integrity of TALEN® modified T-cells

Potential offsite targets*: at close match sequences at hybrid sequences from mispairing of half nucleases

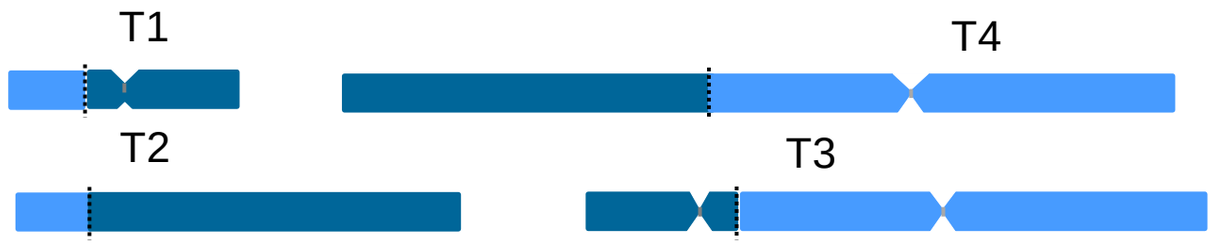
	LEFT HALF TARGET	SPACER	RIGHT HALF TARGET
TRAC	TTGTCCCACAGATATCC	agaaccctgaccctg----------	CCGTGTACCAGCTGAGA
CD52	TTCCTCCTACTCACCAT	cagcctcctggttat----------	GGTACAGGTAAGAGCAA
1	ttgctctCaccAgtaTA	cgtattataccaaagtcaattctcg----	TTtTcaggtaagTgcaa
2	tCActcttacctgGacc	cacctttctgggagcactg----------	CCtacaggtaagGgcCa
3	tctcagAtgAtacacCC	acctcagcctcccaaagtggtggg-----	AgtacaggCaTgagcCa
4	tGAtcccacagaAatAc	ttctgtggaaatacagaa----------	gCatTtctgtgggaTCa
5	ttCctctAacctgtaTT	ttgctcggctctctaagttgtctca----	gAtCcaggtaagGTcaa
6	tAgtcccCcagatatGA	gtggccccaactttgaagg----------	aAggtgTgGaTgaggaa
7	ttgtcAcacaTataCcG	atggcaaagccaattttaaaa--------	TgGtatTtgtgTgacaa
8	tAActcttacctgtaGT	gtccactttaaacaat----------	AgatTtctCtgggGcaa
9	ttActccAactAacTat	ccatgactgtcccatt----------	ccgtTtaccGgctTaga
10	tGgctcAtacctgtaGT	cacagctactcaag----------	aGgAtgagGTggaggaa
11	ttgctcAtacAtgtGcA	cctatgacttatgaataattc--------	atgCtgTgtaggTggTa
12	ttgtcccacagaCatTc	cctgggacaagctgggag----------	ccACgtaGcagctgGga
13	tcAcaCctggtacaTAg	aacccagccaaagacagagcacactca--	GtgTtTagtaggGggaa
14	ttgtcccacagCtaCcc	atgtcagttatctccactaacatttccaa	gAatCtTtgtAggacaa
15	tctcaActgAAacaAgg	caaatcccttccacctatgagcc------	TgtaAagTCaagagcaa

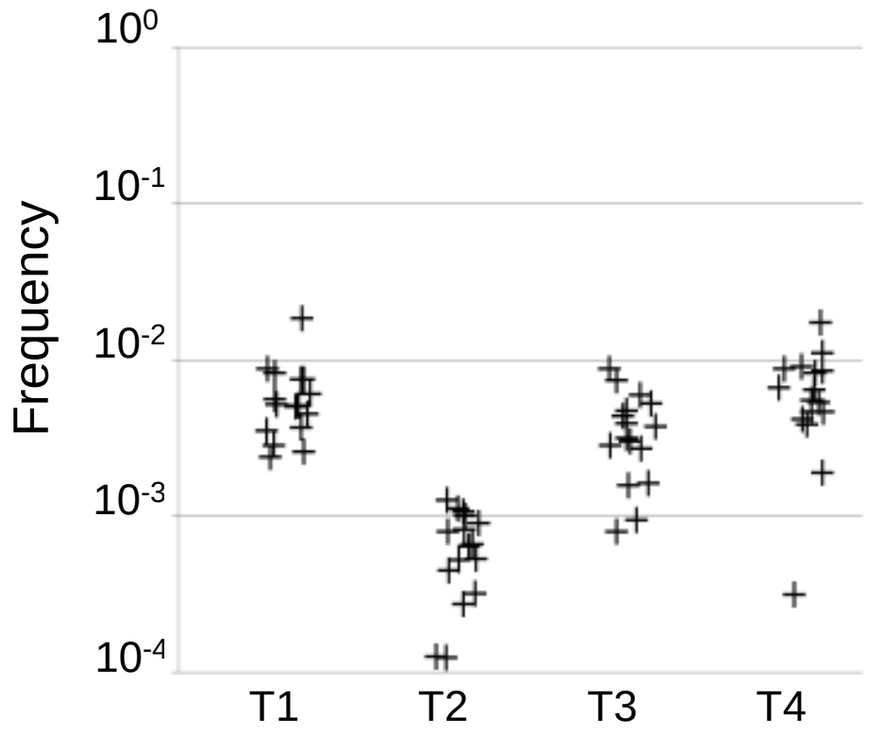


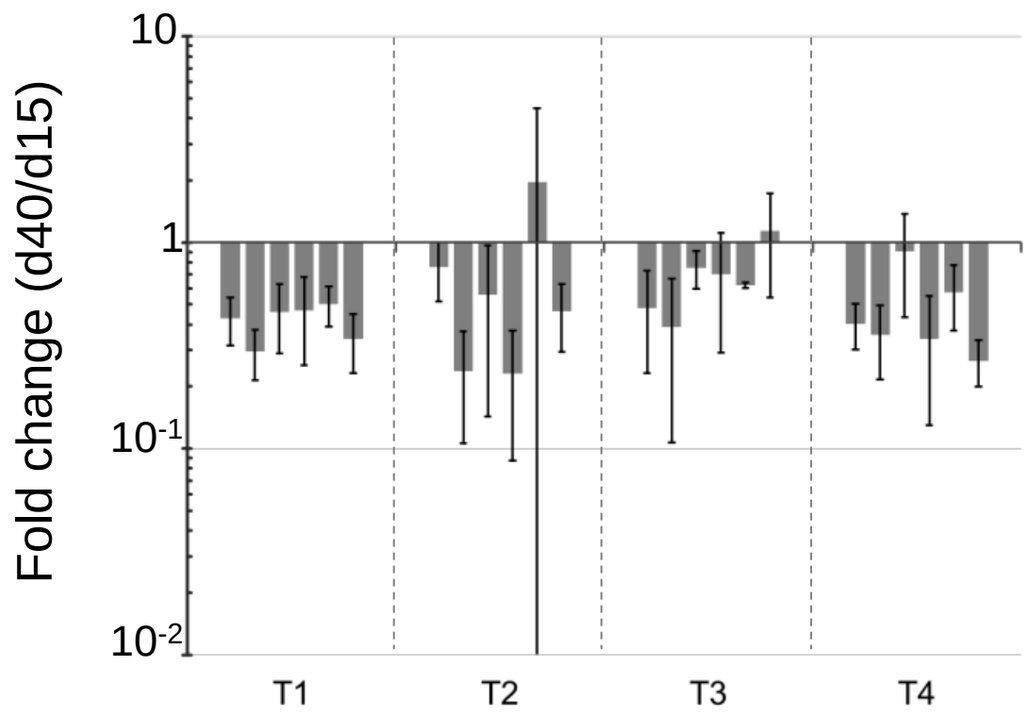
***Juillerat et al. (2014) Nucleic Acids Res. 42:5390**

Genomic integrity of TALEN® modified T-cells

Detection of translocations by qPCR:



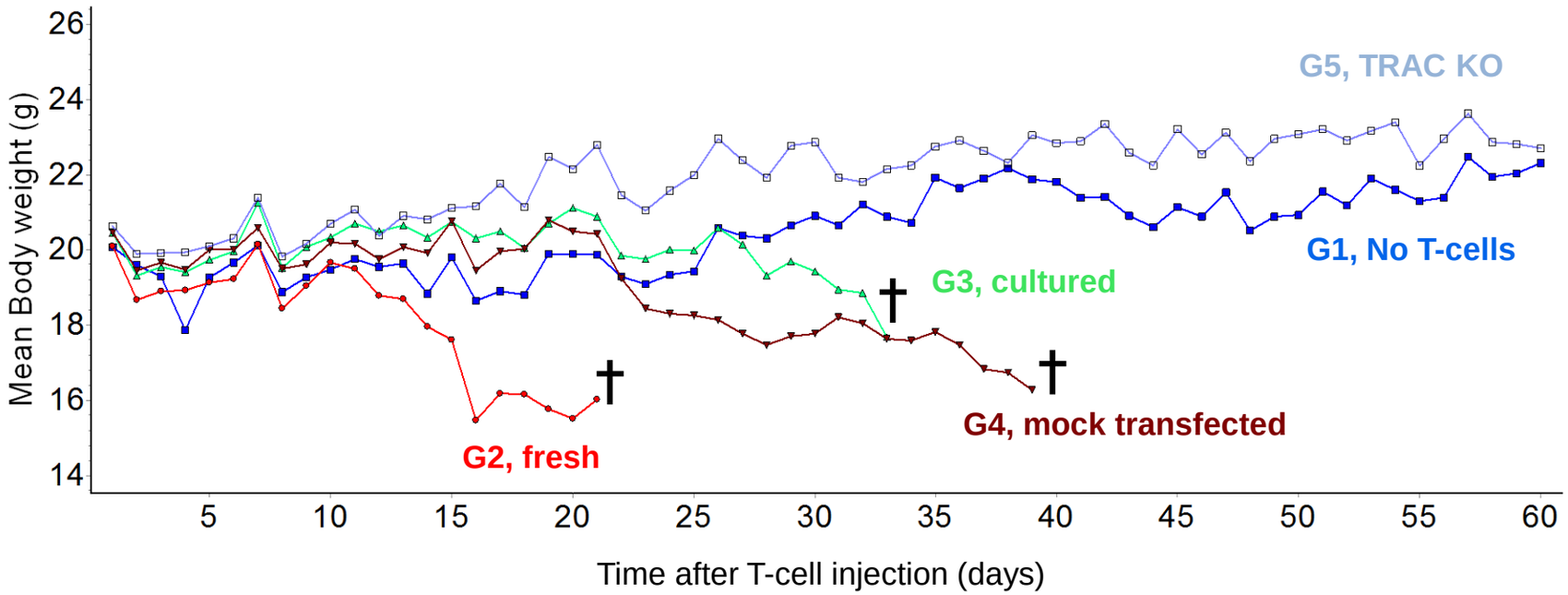


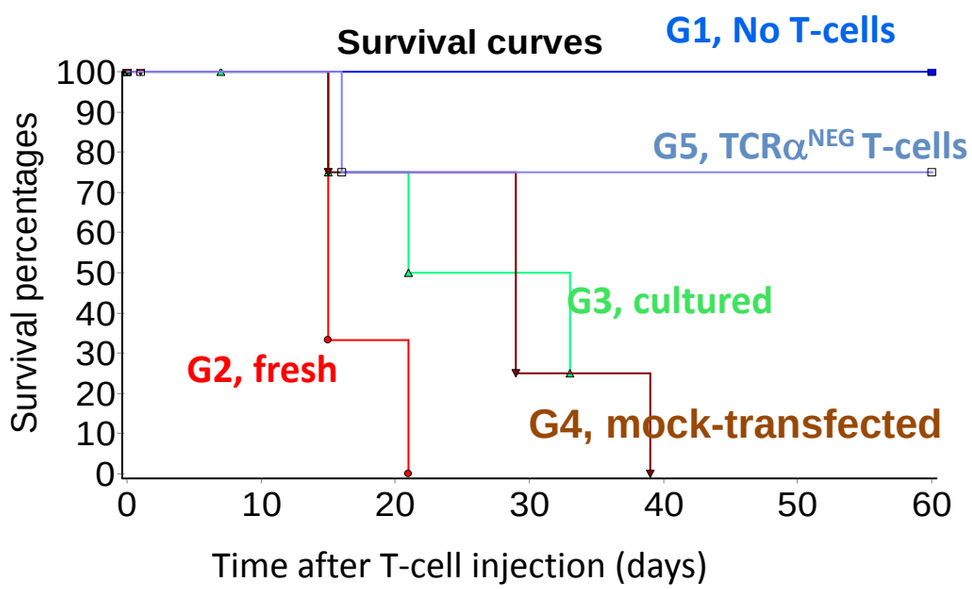


Translocations detectable at 10^{-2}-10^{-4} but no proliferative advantage

TCRα-deficient T-cells do not induce GvHD

NOG mice irradiated (2.5 Gy) 1 day before T-cell injection (i.v., $30x10^6$)





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

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						

* or European equivalent

“Off the shelf”/Gene edited CAR T-Cell therapy

Genomic stability

Off-target cleavage

Best method? Sensitivity?
in-silico prediction, genome wide sequencing, « DSB capture » methods

Translocations

qPCR assays, karyotype/FISH

Other genomic stability assays

IL2 independent proliferation assay

Graft versus host disease (GvHD)

Lymphodepletion strategy

Manufacturing

Choice of starting materials, batch to batch consistency, final product testing, product stability

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