# 774

# Repurposing endogenous immune pathways to improve chimeric antigen receptor T-cell potency


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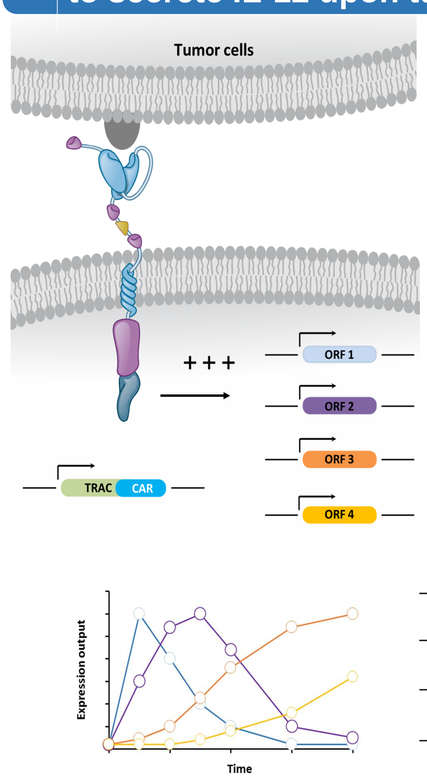
## #1 Abstract


CAR T-cell therapies hold great promise for treating a range of liquid malignancies but are however challenged to access and eradicate solid tumors. To overcome this hurdle, CAR T-cell were engineered to secrete different cytokines known to improve T-cell antitumor activity, prevent T-cell anergy and reduce activation induced cell death. While cytokine-expressing CAR T-cell were shown to be highly active against solid tumor in in vivo models, they have also led to toxicity associated with the systemic release of cytokine. Therefore, new engineering strategies enabling the fine tuning of cytokine secretion by CAR T-cell are warranted.

We sought to explore one of these engineering strategies by integrating an IL-12 chimeric heterodimer expression cassette under the control of the endogenous promoters regulating PD1 or CD25. Because both genes are known to be activated upon tumor engagement by CAR T-cells, they could be repurposed to secrete cytokine only in the vicinity of a given tumor. This approach would reduce the potential side effects induced by systemic secretion while maintaining their capacity to improve antitumor activity.

By combining TALEN® technology with AAV6 repair vectors delivering the CAR to the TRAC locus and the IL-12 to the CD25 or PD1 loci, we have engineered CAR and IL-12 expressions under the respective control of TCR and CD25 or PD1 regulatory elements. This double targeted insertion led to the disruption of PD1 and TRAC genes, to the non disruptive modification of CD25 gene, to the expression of a CAR along with the conditional secretion of IL-12 in the media. Such secretion was found to be transient, dependent on tumor engagement and to follow the regulation patterns of CD25 or PD1 genes, commonly observed upon T-cell activation. In addition, it was also found to enhance the antitumor activity and the proliferative capacity of CAR T-cells.

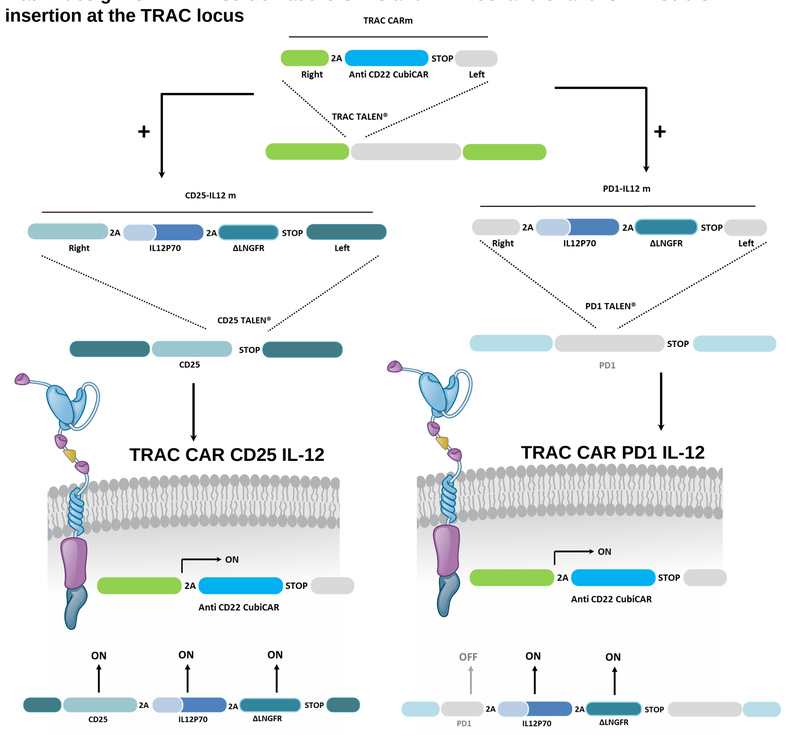

## #2 Repurposing CAR T-cell immune pathways to secrete IL-12 upon tumor engagement




**A whole array of genes with various expression kinetics could be repurposed by TALEN®-mediated targeted insertion of IL-12.**

## #3 Repurposing TCR, CD25 and PD1 gene expression

**Matrix design for IL-12 insertion at the CD25 and PD1 loci and of anti-CD22 CubiCAR insertion at the TRAC locus**




## #4 Efficient TALEN®-mediated targeted insertion of CAR at the TRAC locus

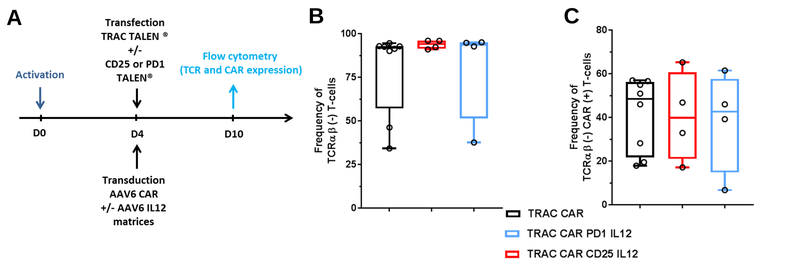



**Figure 1.** (**A**) Experimental workflow for targeted insertions of the CAR at the TRAC locus and of IL-12 at the CD25 or PD1 loci. 4 days after activation using CD3/CD28 beads, cells were treated with TRAC TALEN® and the CARm alone (TRAC CAR) or in the presence of CD25 or PD1 TALEN® and CD25_IL-12m or PD1_IL-12m. T-cell were analyzed by flow cytometry 6 days later using CD3 and CAR-specific antibodies (QBEND10). (**B**) and (**C**) Frequency of TCRα/β (-) T-cells and of CAR+ cells within TCRα/β (-) T-cells.

## #5 TALEN®-mediated insertion of IL-12 disrupts PD1 and spares CD25 expressions

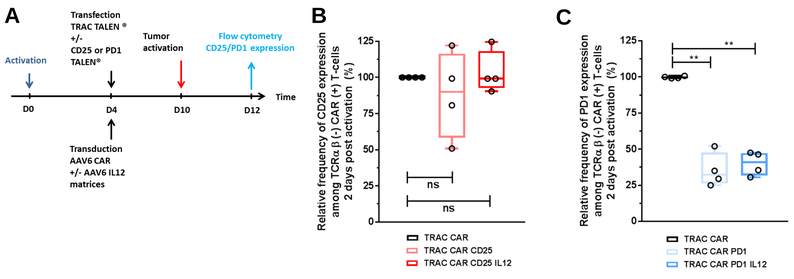



**Figure 2.** (**A**) Analysis of the impact of double targeted insertions on the expression of CD25 and PD1. Following the protocol described in figure 1, CAR T-cells were activated by CD22 expressing tumor cells at E/T ratio of 1 and analyzed 2 days later by flow cytometry for surface expression of CD25 and PD1. CAR TRAC T-cell treated with CD25 or PD1 TALEN® in the absence of IL-12 matrices were used as controls. (**B**) and (**C**) Frequency of CD25 and PD1 positive cells among TCRα/β (-) CAR (+) T-cells. One way ANOVA was used for statistical analysis (**, p-value<0.001).

## #6 Converting CAR T-cell/tumor engagement into IL-12 secretion

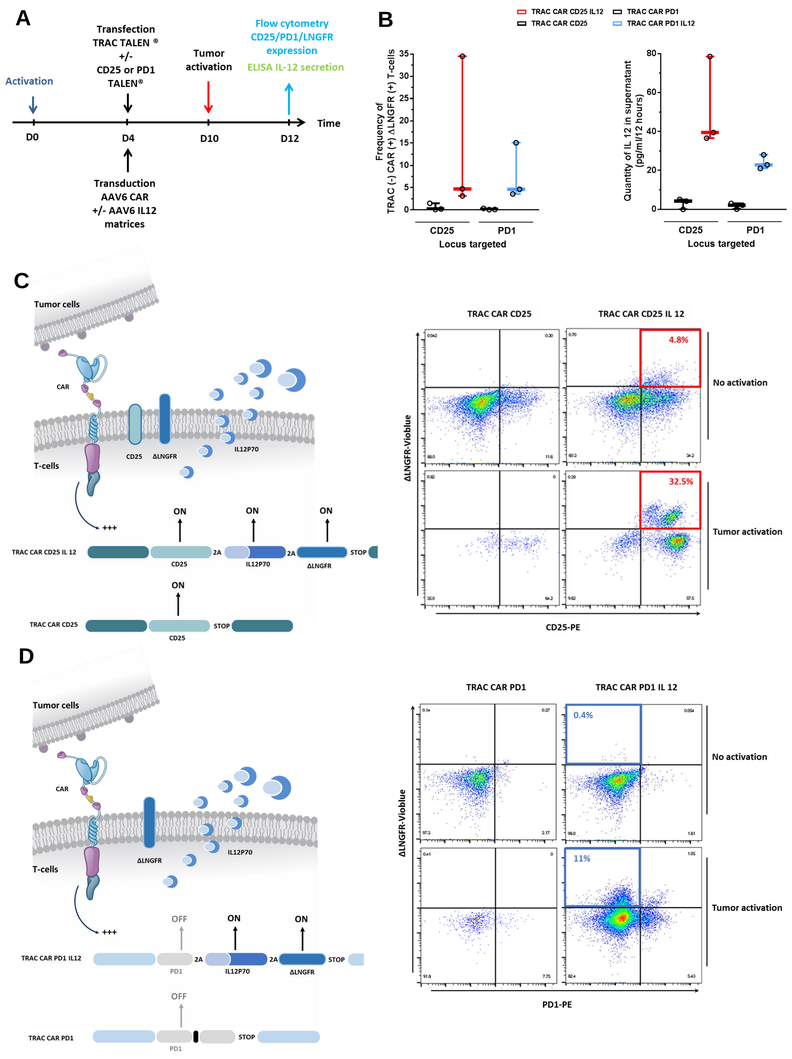



**Figure 3.** (**A**) Protocol used to characterize the expression of CD25, PD1 and LNGFR reporter and IL-12 upon tumor engagement. (**B**) **Left**: Frequency of LNGFR (+) cells among TCRα/β (-) CAR (+) T-cells. **Right**: Quantity of IL-12 in the media after 12 hours of CAR T-cell incubation with tumor cells (1:1). (**C**) and (**D**) Representative flow cytometry plots illustrating co-expression of CD25 and LNGFR and expression of LNGFR by PD1(-) cells respectively (gated on TCRα/β (-) CAR (+) T-cells).

## #7 Il-12 secretion is tightly regulated and follows CD25 and PD1 expression patterns

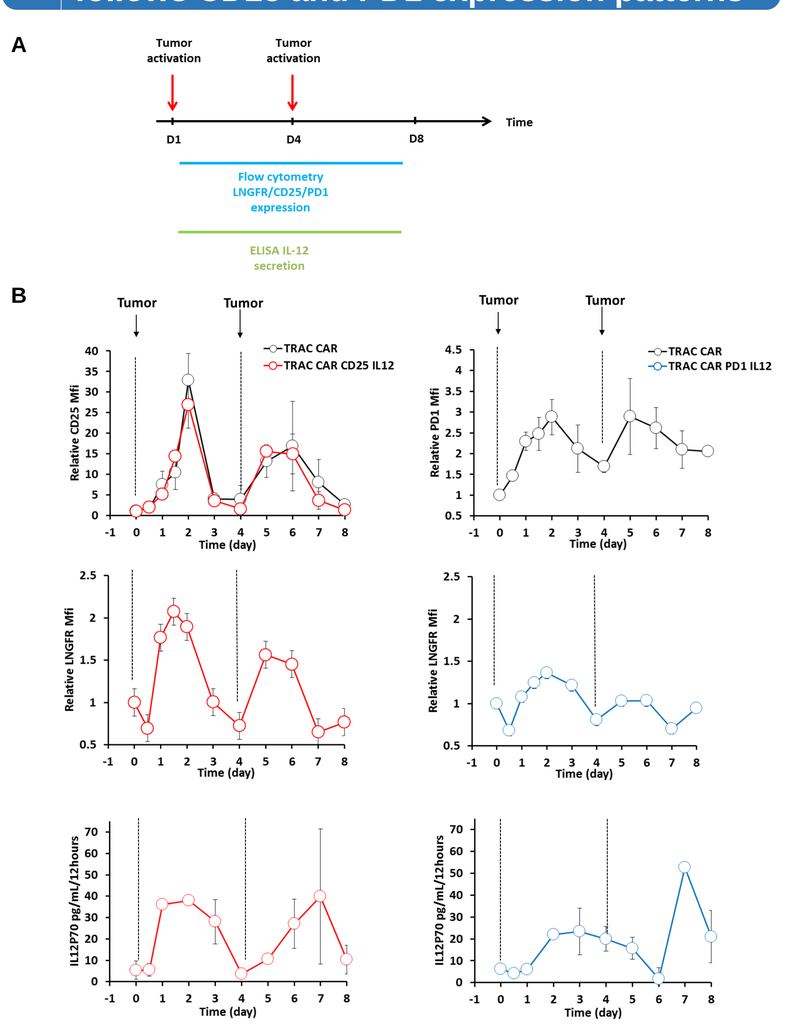



**Figure 4.** (**A**) Analysis of the kinetic co-regulation of CD25, PD1, LNGFR and IL-12 expression. $10^6$ CAR T-cells were activated by CD22(+) tumor cells at D1 and D4 (E/T=1). CD25, PD1 and LNGFR surface expression was measured by flow cytometry. Media was changed every 12 h so that the quantity of IL-12 detected by ELISA in the supernatant is the amount secreted in the last 12 hours. CAR TRAC T-cell treated with CD25 or PD1 TALEN® in the absence of IL-12 matrices were used as controls. (**B**) Evolution of relative CD25, PD1 (**upper panel**) and LNGFR MFI (**middle**) among TCRα/β (-) CAR (+) T-cells. **Bottom panel**: Evolution of IL-12 secretion in supernatant recovered every 12 hours.

## #8 Conditional secretion of IL-12 increases the antitumor activity of CAR T-cells *in vitro*

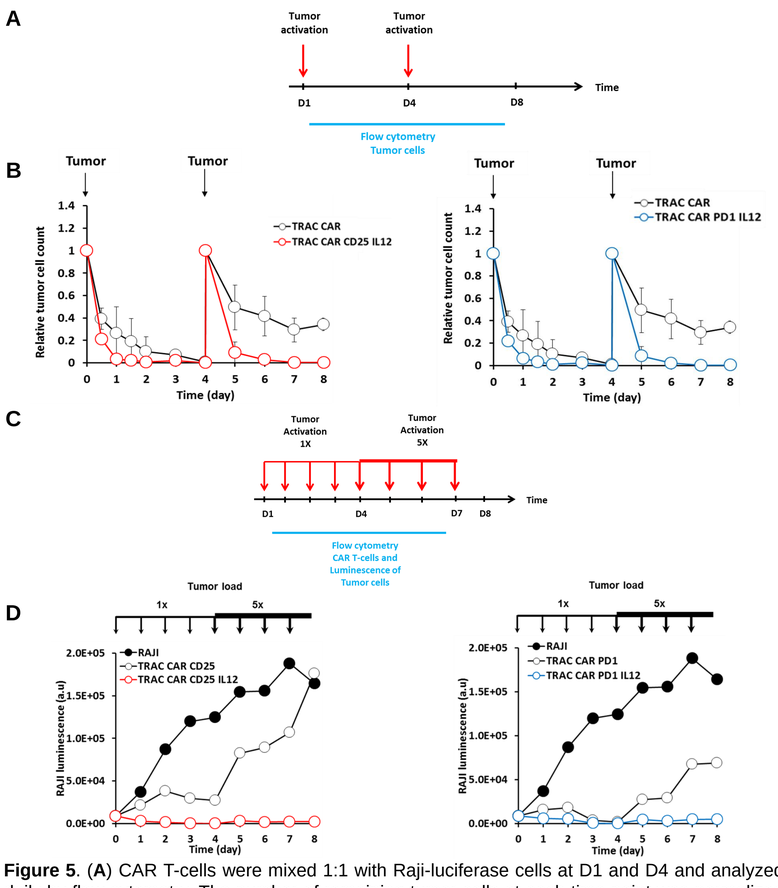



**Figure 5**. (**A**) CAR T-cells were mixed 1:1 with Raji-luciferase cells at D1 and D4 and analyzed daily by flow cytometry. The number of remaining tumor cells at each time point was normalized to the initial number of cells added. (**B**) Kinetic of tumor cell depletion by TRAC CAR T-cell edited at the CD25 locus (**left**) or PD1 locus (**right**) with or without IL-12m. (**C**) Long-term cytotoxicity assay: CAR T-cell were challenged daily with Raji-luciferase cells ($2x10^5$ for the first 4 days and $10^6$ cells for the next 4 days). Every day, the luminescence signal of the remaining tumor cells was measured and cell mixtures were centrifuged and resuspended in fresh media containing Raji-luciferase cells. (**D**) Evolution of luciferase signal.

## #9 Local and tumor dependent secretion of IL-12 by CAR T-cells *in vivo*

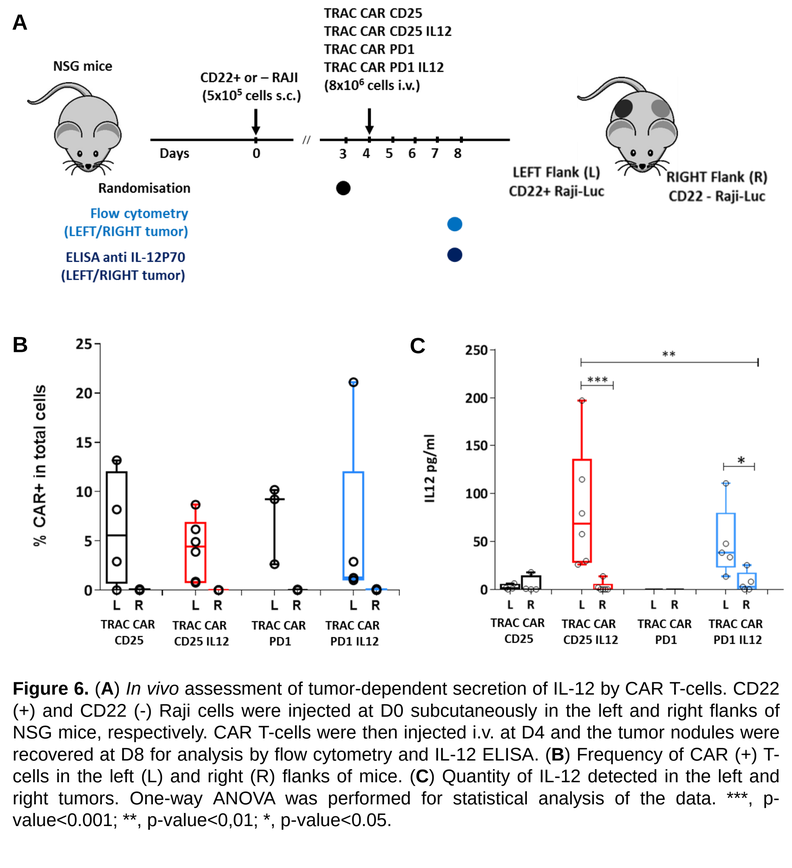



**Figure 6.** (**A**) *In vivo* assessment of tumor-dependent secretion of IL-12 by CAR T-cells. CD22 (+) and CD22 (-) Raji cells were injected at D0 subcutaneously in the left and right flanks of NSG mice, respectively. CAR T-cells were then injected i.v. at D4 and the tumor nodules were recovered at D8 for analysis by flow cytometry and IL-12 ELISA. (**B**) Frequency of CAR (+) T-cells in the left (L) and right (R) flanks of mice. (**C**) Quantity of IL-12 detected in the left and right tumors. One-way ANOVA was performed for statistical analysis of the data. ***, p-value<0.001; **, p-value<0,01; *, p-value<0.05.

## #10 Conclusions

- We combined TALEN® technology with AAV6 repair vectors to simultaneously engineer:
  - CAR expression under the control of TRAC regulatory elements
  - IL-12 expression under the control CD25 or PD1 regulatory elements.
- This strategy successfully disrupted PD1 and TRAC genes while maintaining CD25 expression.
- We efficiently induced CAR expression and conditional secretion of IL-12.
- IL-12 secretion is transient, local, dependent on tumor engagement and follows the expression patterns of CD25 or PD1 genes.
- Activation-dependent IL-12 secretion markedly enhances the short and long term antitumor activity of CAR T-cells.
- This work provides a proof of concept that T-cell immune pathways could be engineered to efficiently translate a given input (CAR/tumor engagement) into a tailored output (IL-12 secretion).
- This engineering strategy could be applied to repurpose a myriad of other genes to deliver therapeutically relevant factors in a conditional and tightly regulated manner.

# Engineering CAR T-Cells with an Integrated off Switch to Enhance Safety Performance

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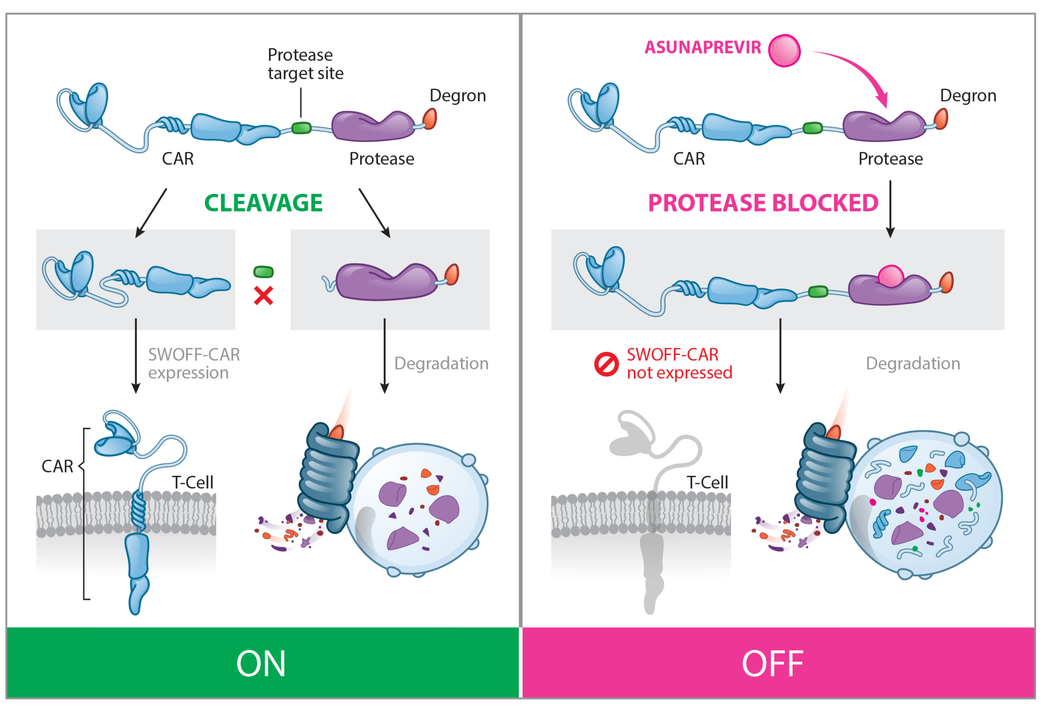
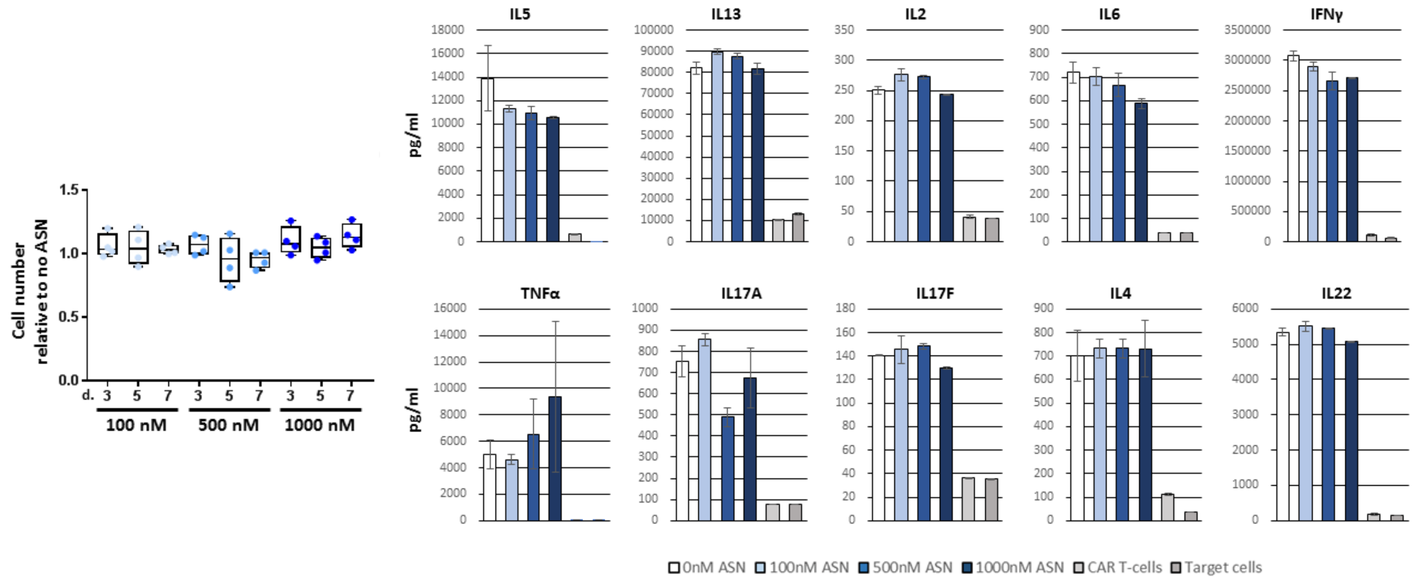
## #1 | Abstract

The last years have seen the adoptive transfer of engineered T-cell as a key player in the development of new treatments against cancer. The high remission rates observed in clinical trials are however mitigated by potentially life-threatening side effects potentially due to CART-cells attacking healthy tissues, with low levels of targeted tumor-associated antigens (on-target, off-tumor effects).
Therefore, endowing T-cells with a therapeutically relevant CAR could be a challenging process as few true tumor specific antigens have been identified. In order to work around this bottleneck and to improve the overall safety of these therapeutic approaches, several strategies including combinatorial targeting and suicide switches have been developed. The possibility to spatio-temporally regulate CAR T-cell functions in a non-lethal fashion using small molecules could allow better mitigating potential toxicity, improving the overall therapeutic outcome.
Here, we developed a single component system to control CAR T-cell cytolytic properties with a small molecule drug in a switch OFF fashion. We utilized an approach combining a protease and a degron to control CAR stability in primary T-cells via a protease inhibitor. The addition of the Asunaprevir (ASN) protease inhibitor led to the selective and dose-dependent, decrease of CAR surface presentation and CAR T-cell cytolytic properties. We foresee that such a CAR control approach would benefit to the safety of clinical applications and the ex vivo production of CAR T-cells.

## #2| Exogenous small molecule CAR T-cell control

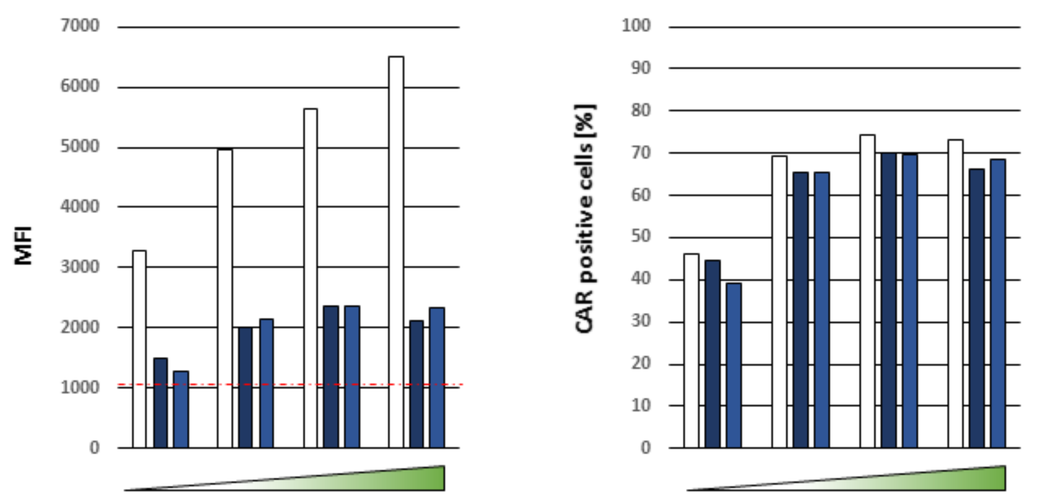



## #3| Asunaprevir has no functional impact on T-cells



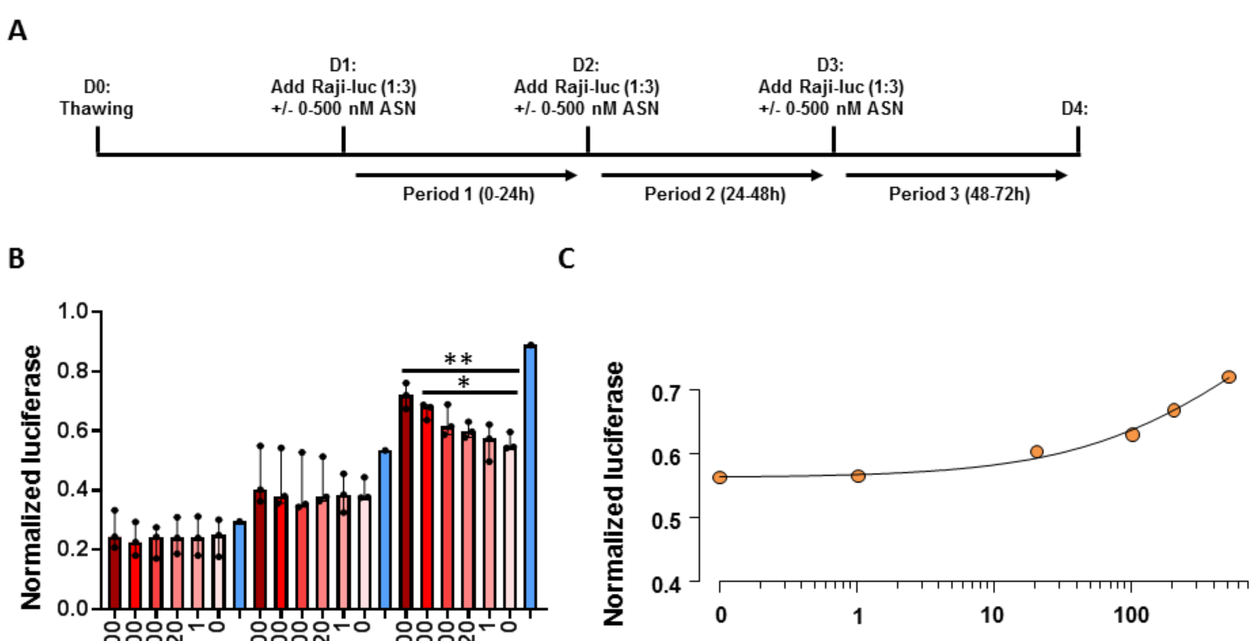

Treatment with Asunaprevir (ASN) has no effect on the proliferation and viability of the T-cells (100 nM to 1 µM ASN).
Treatment with ASN does not result in notable variations (increases or decreases) in cytokine production.
In all, these results show that ASN has no meaningful effects on T-cell function that would preclude its further development as a modulator of CAR T-cell expression.

## #4| SWOFF-CAR surface expression is controlled with Asunaprevir



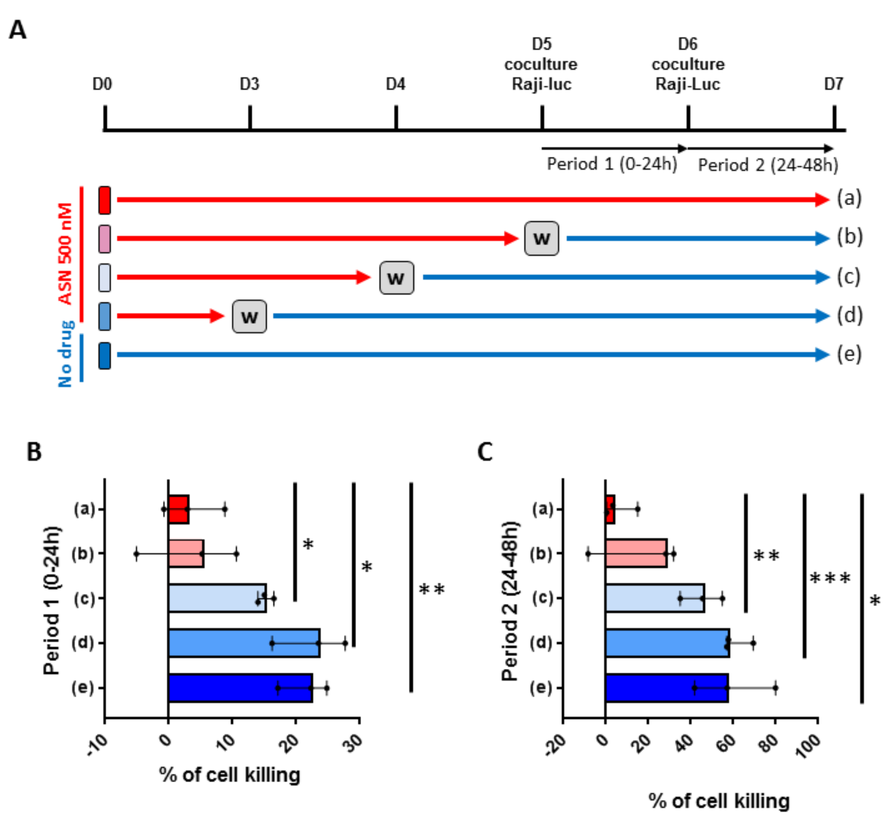

The addition of ASN (blue bars) to the culture medium markedly decreases the MFI of the CAR-positive population (right panel), while the percentage of CAR-positive cells is only slightly decreased (left panel).

## #5| Successful tuning of SWOFF CAR T-cell cytolytic activity with Asunaprevir



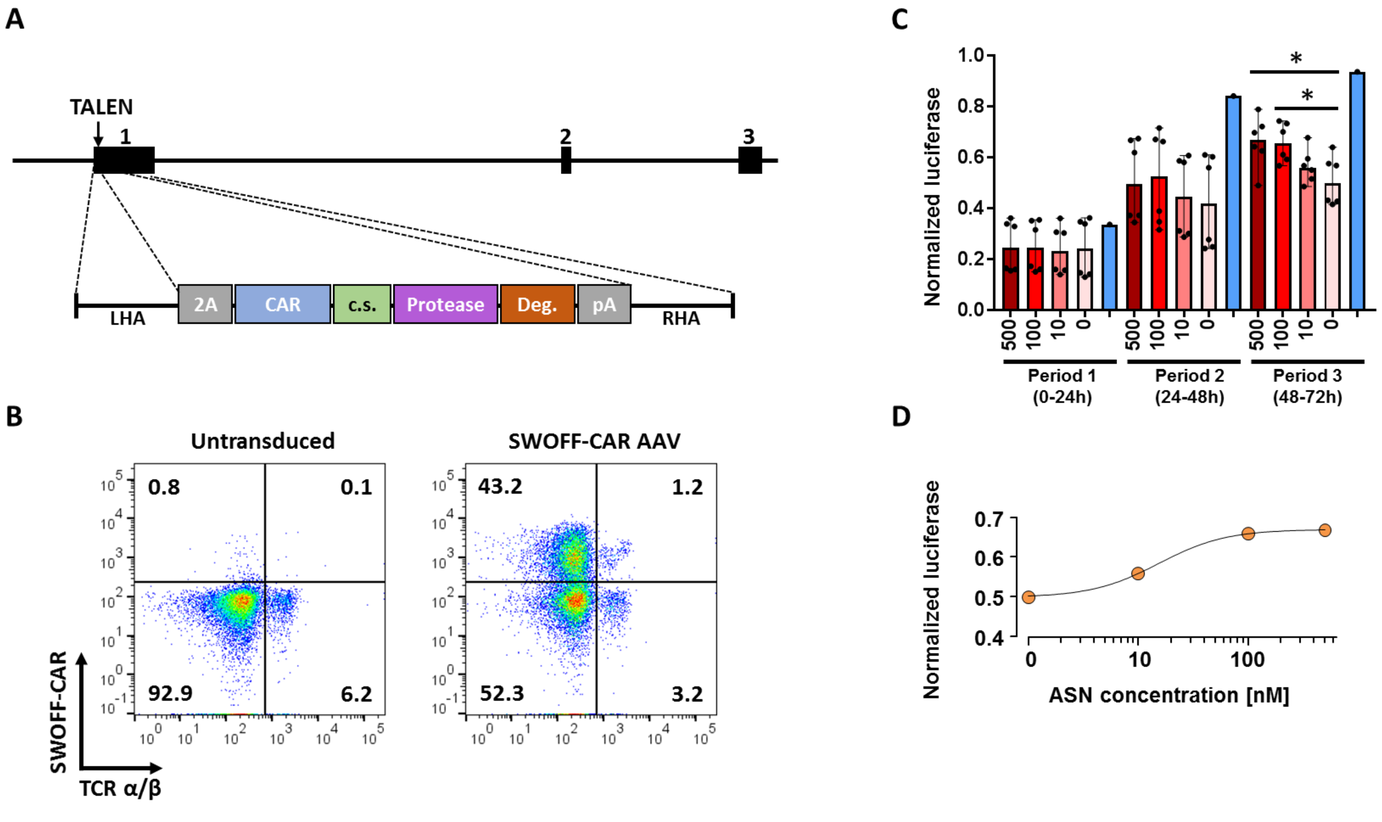

A clear correlation between target cell survival (luciferase signal, control target cells in blue) and the amount of ASN can be observed, showing that CAR T-cell cytotoxic responses can be modulated by ASN using this approach.

## #6| The Asunaprevir-based inhibition of cytolytic function is reversible




Washing out ASN 48h prior to the coculture (CAR T-cell cytotoxicity assay) allowed for a recovery of cytolytic activity to the level of untreated SWOFF-CAR T-cells.

## #7| Targeted integration of the SWOFF-CAR at the TRAC locus improves control




When targeted at the TRAC locus (>90% TRAC KO, 50% SWOFF-CAR KI), the calculated IC50 is within the range of concentrations that have been reported in the plasma of rodents, dogs and humans administered with ASN, suggesting that this system may be sensitive to concentrations of ASN that are clinically relevant.

Abstract #130

# Universal CAR T-cell targeting CS1 (UCARTCS1) for the treatment of Multiple Myeloma

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& [3]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, USA

## #1 Summary

CS1 (also called CD319 or SLAMF7) is highly expressed on multiple myeloma (MM) tumor cells and has limited expression in a subset of hematopoietic cells among normal tissues, making it a rational target for chimeric antigen receptor (CAR) T-cell therapy.

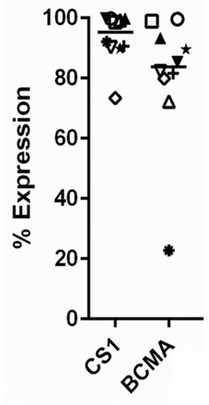
We have designed **allogeneic "off-the-shelf" engineered anti-CS1 CAR T-cells** (derived from normal healthy donor mononuclear cells), which contain an inactivation of the *TCRα constant* (*TRAC*) gene using TALEN® gene-editing technology to minimize the risk of GvHD. As CS1 is expressed on activated CD8+ T-cells, the *CS1* gene is also knocked-out using TALEN® in order to avoid fratricide of CS1-specific CAR+ T-cells.

The inactivation of the *CS1* gene in T-cells prior to the introduction of the anti-CS1 CAR construct effectively prevents the elimination of CD8+ CAR+ T-cells, maintains a naïve phenotype in the CAR+ T-cell population and induces higher anti-tumor activity compared to non gene-edited CAR+ T-cells. In addition, cytotoxicity assays show that UCARTCS1 did not induce significant lysis of normal donor peripheral blood mononuclear cells or CD34+ hematopoietic cells from bone marrow aspirates of healthy donors.

Studies examining *in vivo* anti-tumor efficacy have been performed using MM1.S tumor cells engrafted in NSG mice showing that mice treated with UCARTCS1 cells control the tumor progression. Furthermore, all mice treated twice with 10 x $10^6$ UCARTCS1 showed a very efficient and sustained control of the tumor progression with undetectable M protein levels in their serum 67 days post-treatment and with all mice alive up to 100 days post adoptive transfer.

Finally, UCARTCS1 cells have been shown to specifically target and lyse primary MM tumor cells *in vitro* and *in vivo* using primary MM xenografts in human fetal bone implanted into NSG mice (NSG-hu).

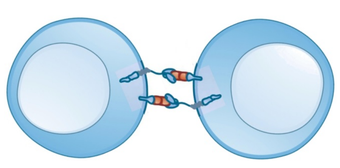
## #2 CS1 is a rational target for CAR T-cells therapy




- **CS1 is highly expressed on MM cells:** CS1 and BCMA expression (determined by flow cytometry) on plasma cells from Multiple Myeloma patients (untreated and treated MM patients bearing different cytogenetic abnormalities).
- On normal cells: low levels of CS1 expression only on natural killer (NK) cells and a subset of B and T lymphocytes.

## #3 Efficient production of anti-CS1 CAR T-cells requires gene-editing

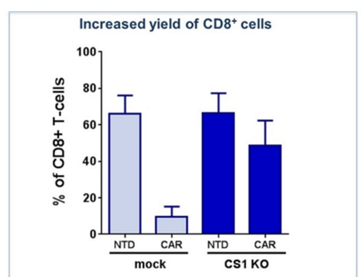
**CS1 is expressed on CD8+ T-cells**, and these cells can be targeted during amplification of CAR T-cells.

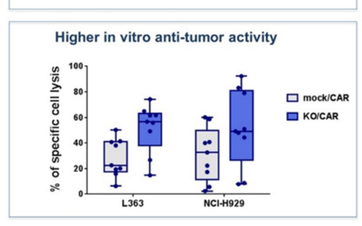


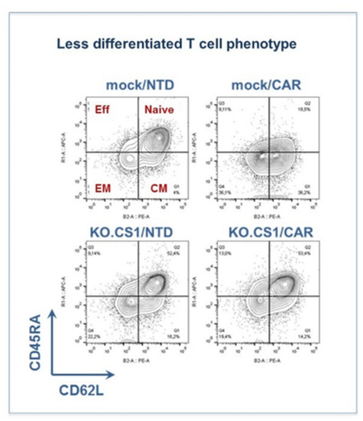
In UCARTCS1, allogeneic anti-CS1 CAR T-cells product, TALEN® gene editing technology is used to:
- inactivate the *CS1* gene, allowing a more efficient production of anti-CS1 CAR T-cells.
- disrupt expression of the TCRαβ, allowing the use of any donors' T-cells and minimizing the risk of GvHD

## #4 *CS1* inactivation using TALEN® allows efficient CS1CAR T-cells production

Gene-editing (*CS1* KO) of T-cells using TALEN® and PulseAgile electroporation technologies prior to the introduction of the anti-CS1 CAR construct:
- **prevents the elimination of CD8+ CAR T-cells** (upper left panel),
- **maintains a less differentiated phenotype** (right panel),
- **induces higher anti-tumor activity** *in vitro* compared to non gene-edited CAR T-cells (lower left panel).

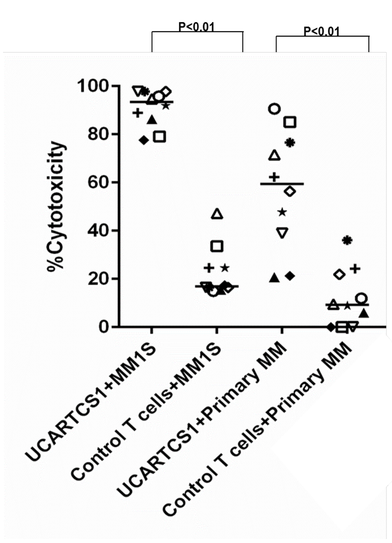



*In vitro* cytotoxic activity was evaluated by flow cytometry following 4h co-culture of T-cells with CS1+ (NCI-H929 and L-363) and CS1- (MOLM-13) cell lines. NTD: non-transduced. CAR: T-cells transduced with the rLV encoding the anti-CS1 CAR. CS1 KO: T-cells transfected with the mRNA encoding the CS1 TALEN®. mock: mock transfected, non-edited T-cells.

## #5 UCARTCS1 shows high cytotoxicity *in vitro* against primary MM cells

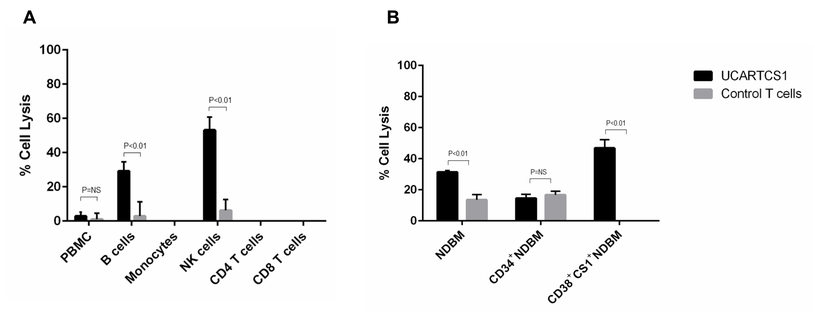



**High cytotoxic activity of UCARTCS1 against an MM cell line (MM1.S) and primary MM samples *in vitro*.**

Percent cell lysis of MM1.S and individual primary tumor cells after 16h co-culture with UCARTCS1 cells or control T-cells (non-transduced TRAC and CS1 TALEN® treated T-cells from the same donor, purified for TCRαβ-negative cells) at a 10:1 E:T ratio. Results of each of the experiments performed with different patients' samples.

## #6 UCARTCS1 does not show toxicity *in vitro* against CD34+ cells

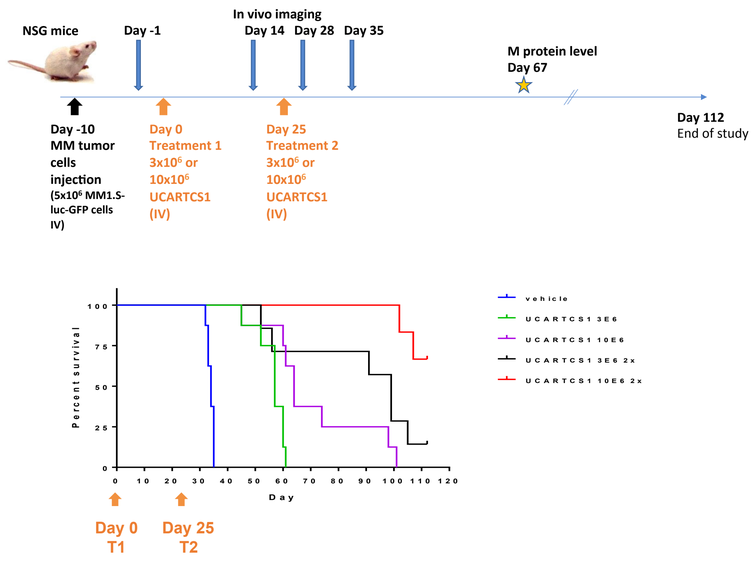
**UCARTCS1 does not induce significant lysis of CD34+ hematopoietic cells**




Cytotoxic activity of UCARTCS1 cells against PBMCs from healthy donor (A) and NDBM (normal donor bone marrow in B).

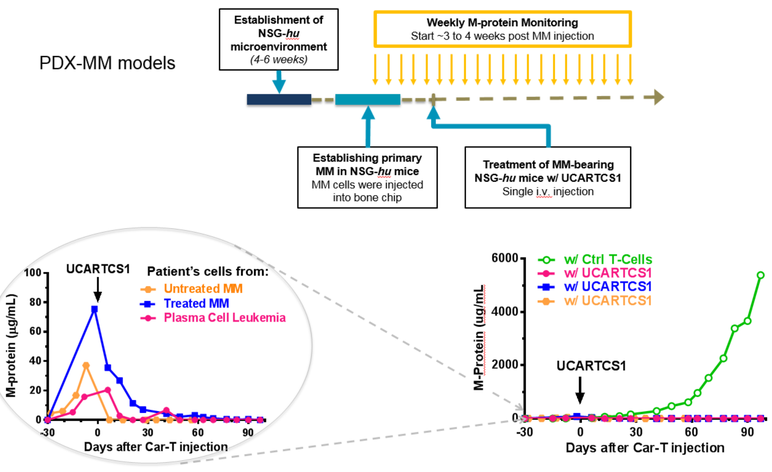
Activity is expressed as percentage of cell lysis (E:T ratio = 10:1). Mean and Standard Deviation is calculated from triplicate samples. Control T-cells are non-transduced dKO T-cells from the same donor. P value is calculated using standard T-test.

## #7 UCARTCS1-treated mice show durable control of tumor progression




- **All UCARTCS1-treated mice show durable control of the tumor progression and extended survival.**
- **Mice treated twice with 10 x $10^6$ UCARTCS1 show undetectable M protein levels in their serum at Day 67 and are alive up to 100 days post adoptive transfer.**

## #8 UCARTCS1 shows high activity against primary MM tumors in NSG-hu mice

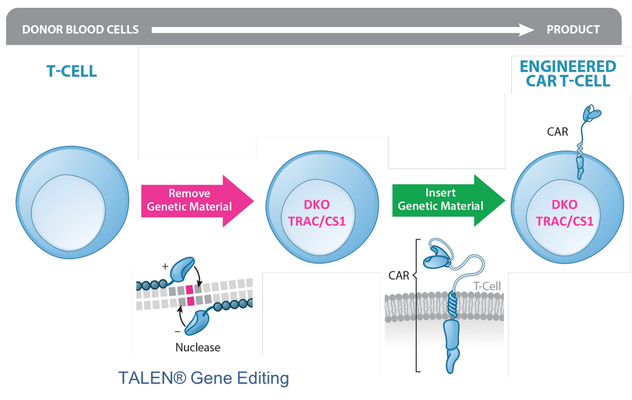



- **Tumor burden of UCARTCS1-treated mice was reduced to undetectable levels by 7 to 30 days post-treatment.**
- **The efficacy of UCARTCS1 was sustainable beyond 100 days after treatment.**

Right panel: The levels of serum M-protein of individual mouse (n=3) were shown before and after the injection of 10x$10^6$ UCARTCS1 cells. The control mouse in green received dKO T-cells.
Left panel: Zoom on the M-protein levels in UCARTCS1-treated mice (in yellow: NSG-hu mice engrafted with MM cells from an untreated patient; in blue: NSG-hu mice engrafted with MM cells from a treated patient; in pink: NSG-hu mice engrafted with MM cells from a patient with plasma cell leukemia).

## #9 UCARTCS1 manufacturing

- UCARTCS1 is manufactured from healthy donor cells.
- Manufacturing process of UCARTCS1 has been successfully adapted from previous UCARTs manufacturing in order to KO *CS1* prior to CAR transduction.
- As any off-the shelf product, UCARTCS1 will be controlled ahead of time.




TALEN® Gene Editing

- **Immediately available to the patient**
- **Patients do not have to provide raw materials**
- **Ease of use for physicians**
- **Shipped worldwide, ahead of time**
- **Competitive CoGs and logistics costs**

## #10 Conclusions

1) **CS1 gene inactivation using TALEN® allows a more efficient production of anti-CS1 CAR T-cells.**
2) **UCARTCS1 cells show high activity against MM cell line and primary MM samples *in vitro* and *in vivo.***
3) **UCARTCS1 does not induce significant lysis of normal donor peripheral blood mononuclear cells or CD34+ hematopoietic cells from bone marrow aspirates of healthy donors.**
4) **Cellectis has developed a GMP large scale process for the manufacturing of UCARTCS1.**

**Our results support further development and testing of this universal "off-the-shelf" allogeneic CS1-specific CAR-T product in MM patients with potential readministration.**

# CYNOMOLGUS MACAQUE GENE-EDITED CAR T-CELL PLATFORM: WORKING TOWARDS A RELIABLE IN VIVO ALLOGENEIC MODEL TO ASSESS SAFETY AND EFFICACY

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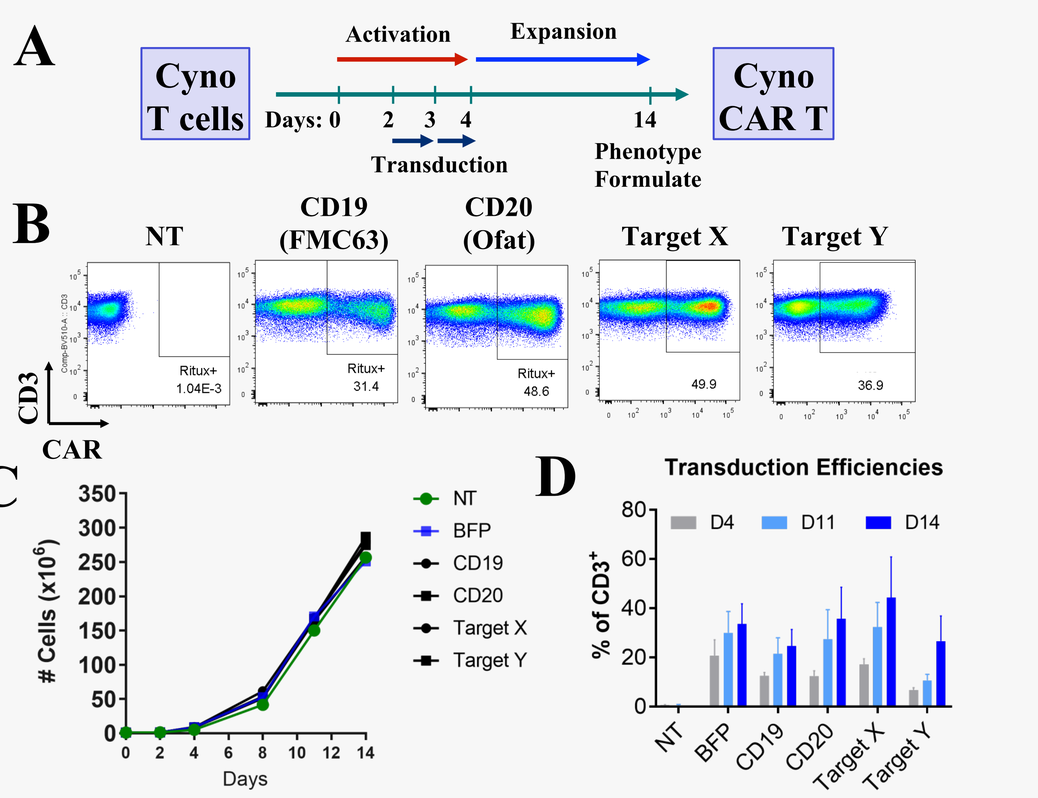
## ABSTRACT

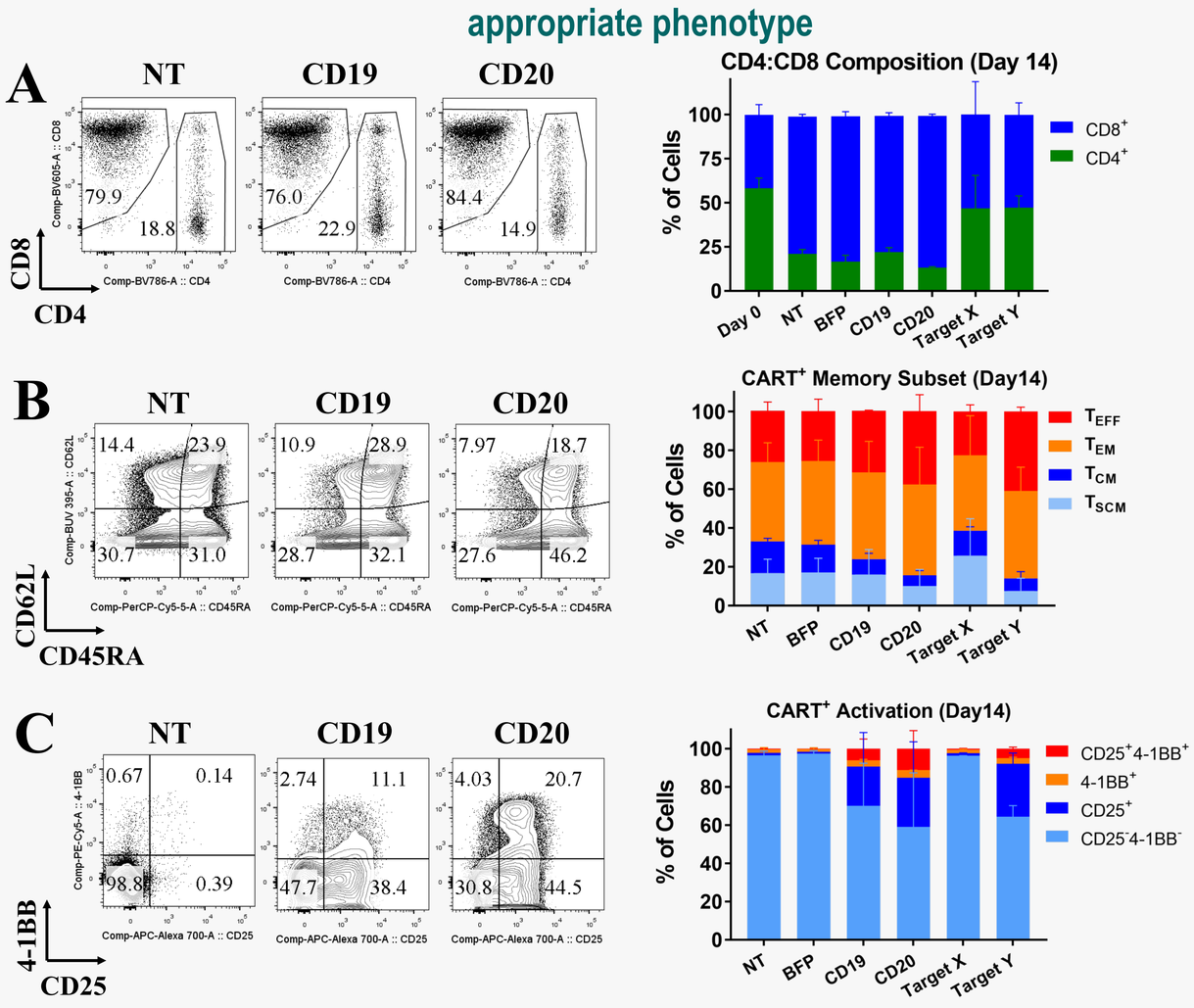
Chimeric antigen receptor (CAR) T cell therapies have recently been approved for commercialization and are proving to be transformative therapies in the fight against hematological malignancies. Allogeneic, or "off-the-shelf", CAR T cells generated from healthy donors allow for immediate treatment of large cohorts of patients, and may reduce the risk of manufacture failure associated with bespoke autologous therapies. As treatment modalities attempt to target other hematological and solid malignancies, there is a need for a robust and reliable pre-clinical animal model to validate the safety of novel targets potentially expressed on healthy tissues, as well as, to evaluate the potential graft-versus-host disease (GvHD) risk of an allogeneic CAR T cell therapy. Using cynomolgus macaques as an animal model, we have developed a reliable in vitro platform that allows for the generation and expansion of large numbers of cyno CAR T cells. First, by using an optimized cyno T cell activation and expansion protocol, followed by a retronectin-based gamma-retroviral dual transduction stage, optimal and stable expression of several CAR T constructs was achieved. Next, by optimizing CAR T cell expansion and formulating conditions, cyno CAR T cells were generated with improved CD4:CD8 ratios, minimal tonic signaling and enriched for early-differentiated CD62L+ T cells. Cyno CAR T cells manufactured with this optimized protocol display minimal activation in steady state conditions, and are readily activated by co-culture with target-bearing cells. An anti-CD19 CAR, based on FMC63 (human-specific), and an anti-CD20 CAR, based on Ofatumumab (Human/Cyno cross-reactive), were used to generate cyno 4-1BBz-based CAR T cells as proof-of-concept models. Large-scale batches of anti-CD19 and CD20 cyno CAR T cells were readily manufactured in our optimized process conditions and displayed optimal transduction and phenotype. Furthermore, these cyno CAR T cells displayed high post-thaw functionality against Raji and Daudi CD19+/CD20+ lymphoma target cells. Additionally, we have successfully achieved inactivation of the T cell receptor (TCR) complex through TALEN® induced gene-editing of the T Cell Receptor Alpha (TRAC) locus in cyno CAR T cells, with knock-out efficiencies up to 75% with minimal impact on cell viability and expansion capacity. After depletion of residual TCR+ cells, 97% of the CAR T cell culture was $CD3^-$ by flow cytometry. On-going efforts are directed at testing the in vivo efficacy of cyno CAR T cells in Raji-bearing NSG mice as a gate-keeping experiment that will endorse moving into autologous and allogeneic proof-of-concept studies in non-human primates. Overall these in vitro results demonstrate that cyno CAR T cells are a reliable in vitro platform to enable allogeneic CAR T cell safety studies in non-human primates.

## High efficiency transduction (30-50%) of cyno T cells was achieved with optimized protocol



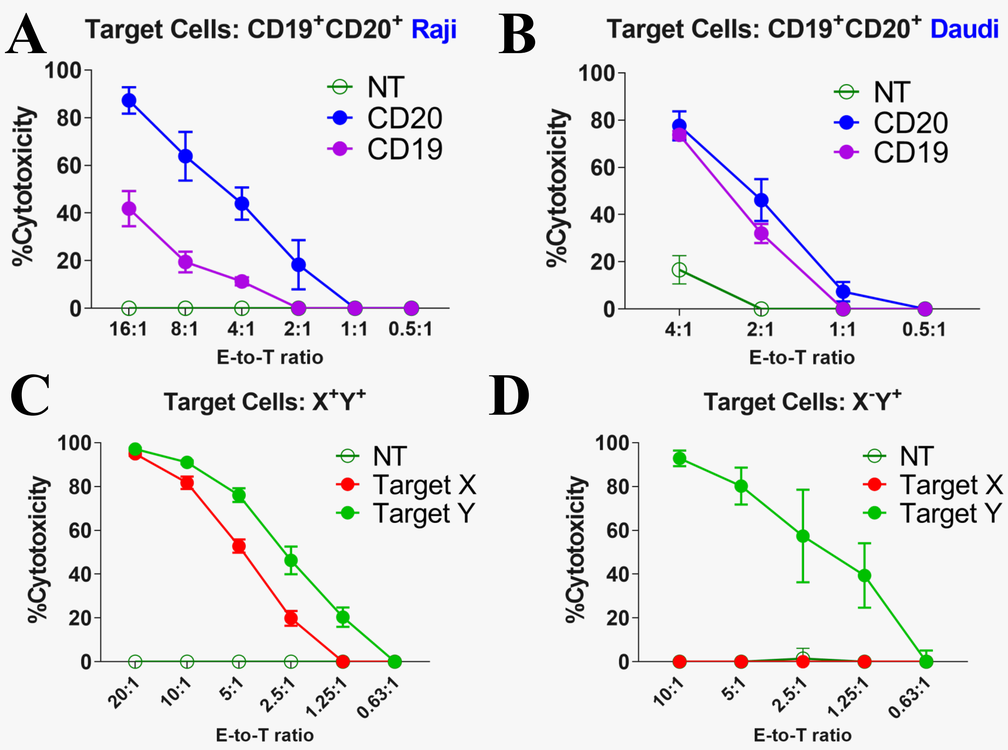

(A) Cyno Pan T cells were thawed and activated in the presence of anti-CD3/2/28 microbeads, IL-2 and IL-7 (Miltenyi Biotec) and Concavalin A (Sigma). Double retronectin-based transductions were performed on days 2 and 3 followed by expansion in G-Rex (Wilson Wolf) plates for 10 days. (B) Expression of different CAR constructs on Day 14 as determined by Flow Cytometry. (C-D) Expansion (C) and CAR expression levels (D) in cyno CAR T cells.

## Optimized protocol allows manufacture of cyno CAR T cells with appropriate phenotype



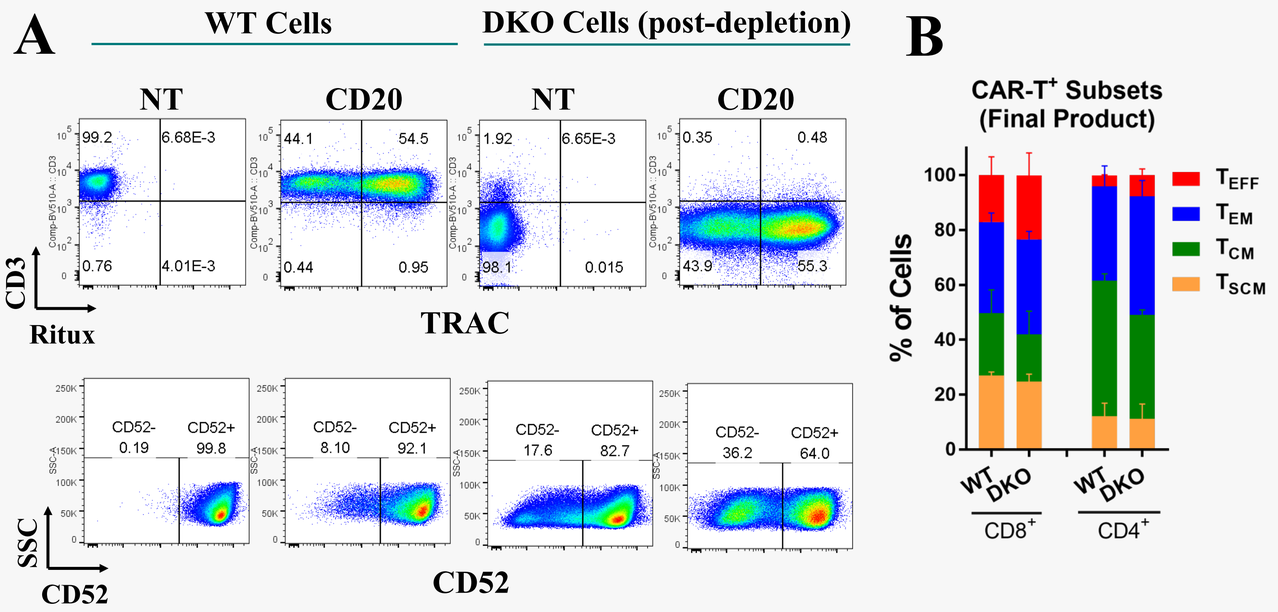

Cyno CAR T cells manufactured under our optimized process display improved CD4:CD8 composition (A), as well as, good retention of a high proportion of $T_{SCM}$ / $T_{CM}$ cells (B) and low levels of activation marker expression (C).

## Cyno CAR T cells display in vitro functionality against a variety of target cell lines



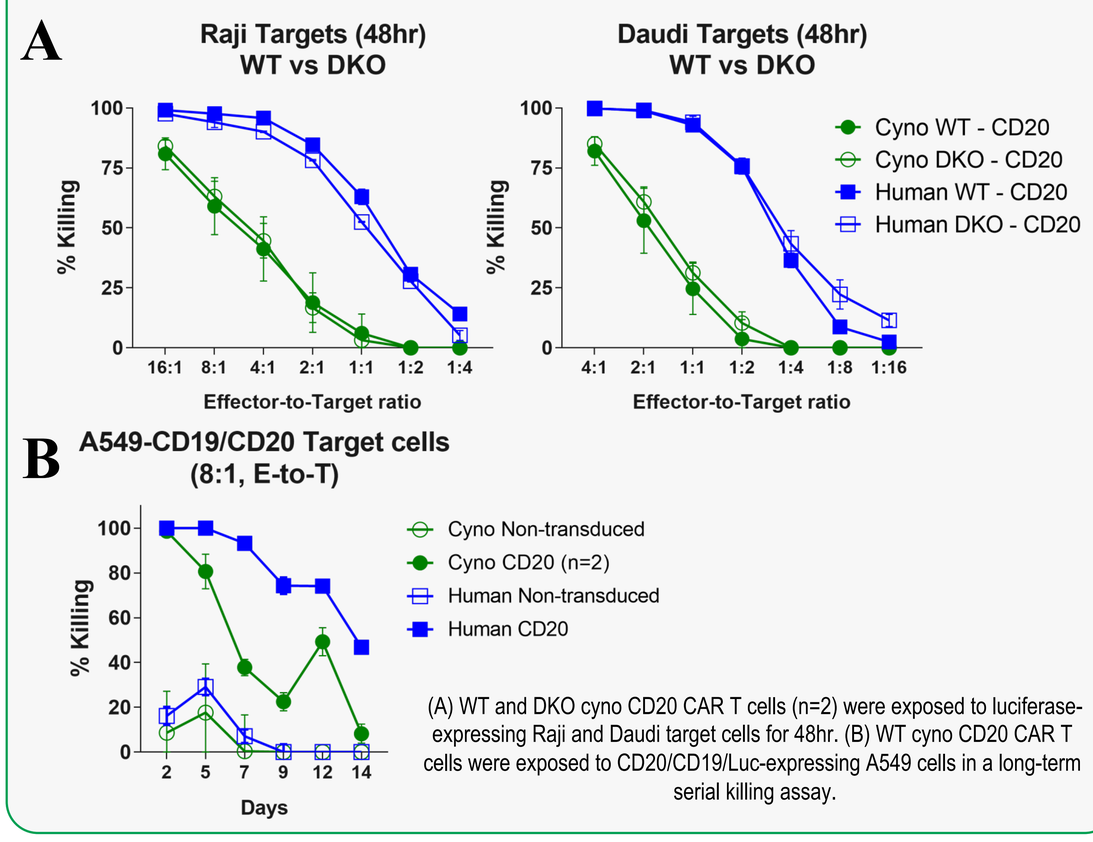

CD19-, CD20-, X- and Y-specific cyno CAR T cells were exposed to luciferase-expressing target-specific malignant cell lines for 48hr. After incubation viability of target cells was determined using a luciferase-specific substrate (Bright Glo).

## Efficient KO of TRAC/CD52 achieved with TALEN® technology




(A) TRAC and CD52 double knock-out in cyno CD20 CAR T cells using TALEN® technology. (B) Gene-editing step and posterior depletion of CD3/TRAC+ T cells does not affect the phenotype of cyno CD20 $CD4^+$ and $CD8^+$ CAR T cells.

## WT and DKO Cyno CAR T cells display comparable functionality




(A) WT and DKO cyno CD20 CAR T cells (n=2) were exposed to luciferase-expressing Raji and Daudi target cells for 48hr. (B) WT cyno CD20 CAR T cells were exposed to CD20/CD19/Luc-expressing A549 cells in a long-term serial killing assay.

## CONCLUSIONS

- Succesful development of a gene-edited cyno CAR T-cell platform
- The optimized cyno CAR T platform allows for efficient activation and transduction of cyno CAR T cells against several targets of clinical interest
- CAR-expressing cyno T cells expand efficiently and are functional against a variety of target cell lines
- *In vitro* efficacy of cyno CAR T cells appears to be slightly lower than similarly manufactured human CAR T cells
- TALEN®-mediated gene editing of cyno CAR T cells is efficient and allows for production of an allogeneic cyno CAR T cell product
- WT and DKO cyno CAR T cells display equal efficacy