



*Reimagined*  
**2020**   
NOVEMBER 9-14



Society for Immunotherapy of Cancer



# Disclosures

Immatics US, Inc (*Co-Founder, SAB*)

Achelois Oncology (*SAB*)

Genome Frontiers (*SAB*)



Society for Immunotherapy of Cancer

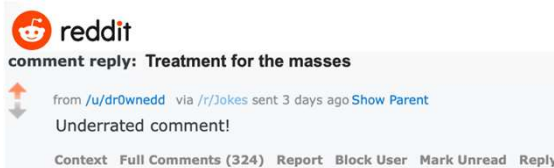
#SITC2020



# Endogenous T Cell Therapy

*Treatment for the masses<sup>1</sup>*

<sup>1</sup>Blattman and Greenberg, Science, 2004



Society for Immunotherapy of Cancer

#SITC2020

**Cassian Yee MD**

*Professor*

**Melanoma Medical Oncology**

**Immunology**

*Director*

**Solid Tumor Cell Therapy**

*Co-Director*

**ACT Platform**

*Member*

**Parker Institute for Cancer Immunotherapy**

[cjee@mdanderson.org](mailto:cjee@mdanderson.org)

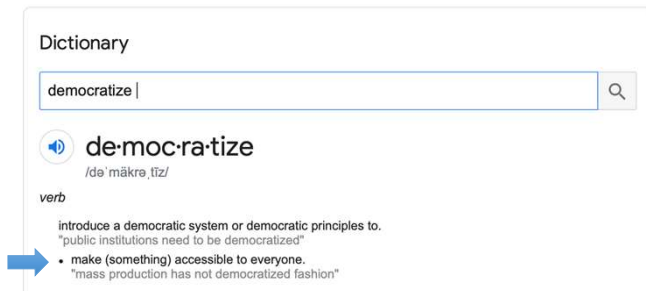
[www.tcellsrus.com](http://www.tcellsrus.com)

Wechat ID: cassianyee



# Endogenous T Cell Therapy

*<sup>2</sup>Democratization of cell therapy*



**Cassian Yee MD**

*Professor*

**Melanoma Medical Oncology**

**Immunology**

*Director*

**Solid Tumor Cell Therapy**

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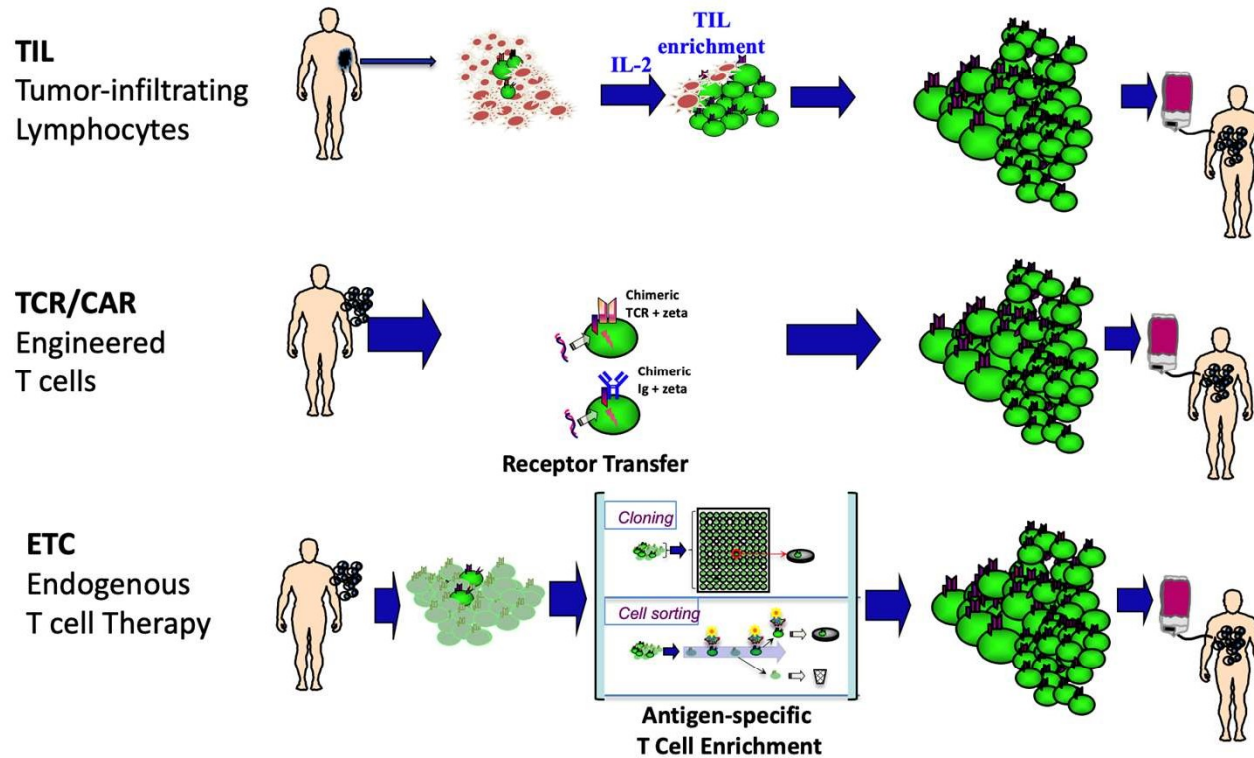
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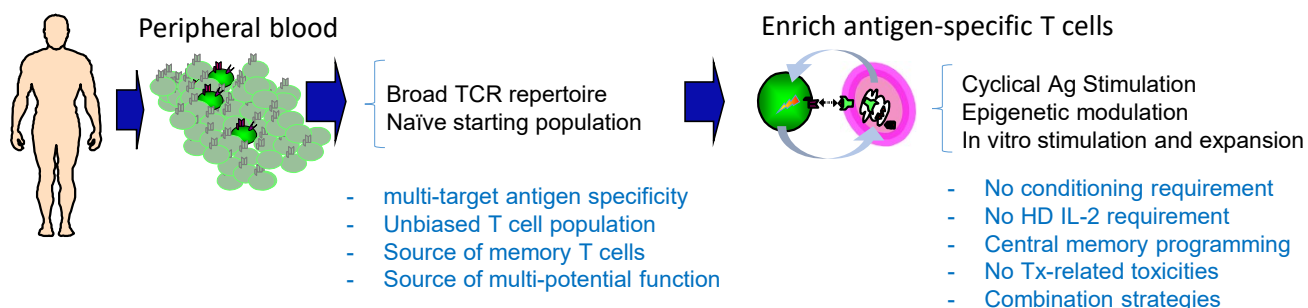
Society for Immunotherapy of Cancer

#SITC2020

## How to make T cells?

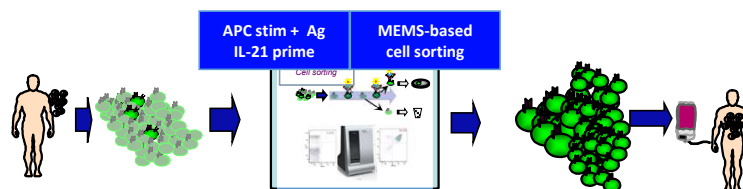


# Endogenous T Cell (ETC) Therapy:



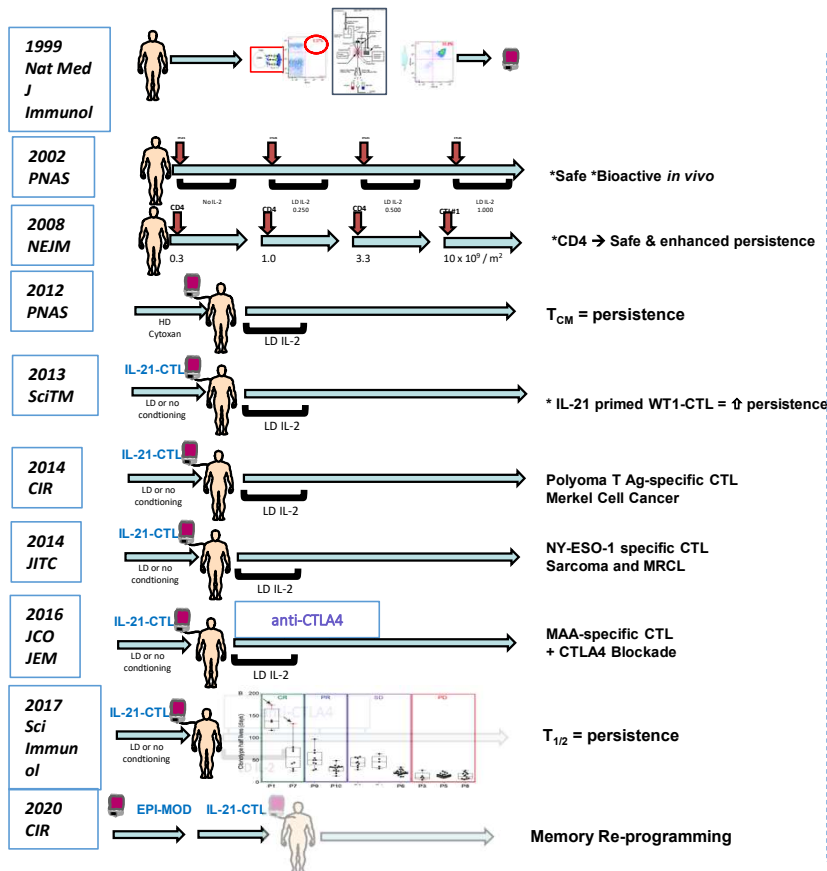
**Why has this not be done before?**

< 1:1,000,000 Tumor antigen-specific  $T_{CM}$  cells > 80 %  $10^{10}$



# Endogenous T Cell Therapy

(a brief one-slide trip down memory lane)



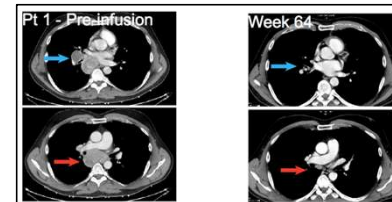
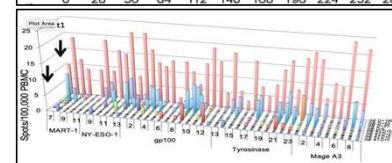
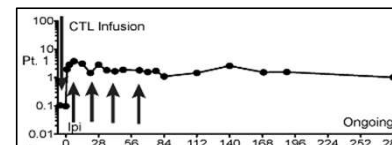
Persistence

Ag Spreading

Durable Responses

Multiple Tumors

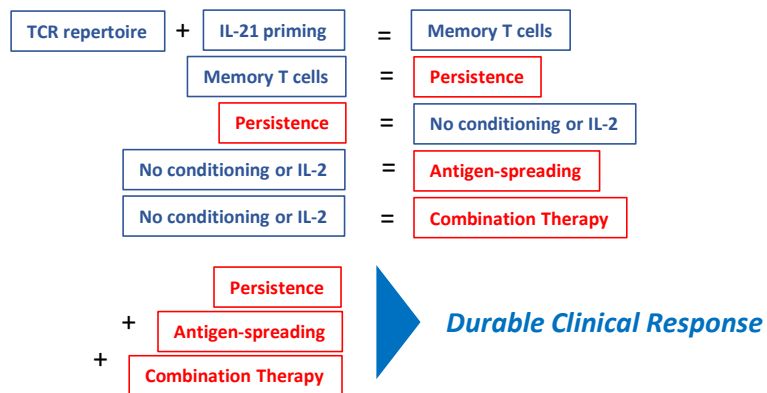
Combination Tx



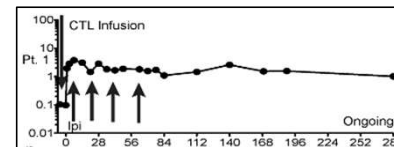
| Endogenous T Cell Therapy                                                                 |              |            |            |               |           |
|-------------------------------------------------------------------------------------------|--------------|------------|------------|---------------|-----------|
| Disease                                                                                   | Antigen      | Design     | Year       | IRRC          | PR/CR     |
| Melanoma                                                                                  | MART-1       | Alone      | 2002 - 10  | 4             | 1/0       |
|                                                                                           | gp100        | CTLA4      | 2012 - 10  | 3             | 1/1       |
|                                                                                           | tyrosinase   |            | 2016 - 10  | 7             | 2/2       |
| Leukemia                                                                                  | NY-ESO-1     | CD4        | 2008 - 9   | 4             | 1/1       |
|                                                                                           | WT1          |            | 2013 - 6/6 | 0/6           | 6/6       |
| Merkel                                                                                    | T antigen    |            | 2014 - 10  | 8             | 3/2       |
| Breast                                                                                    | NY-ESO       |            | 2007 - 1   | 0             |           |
| Ovarian                                                                                   | Col6A3/PRAME | anti-CD137 | 2019 - 3   | Pending       |           |
| Sarcoma                                                                                   | NY-ESO       | Vaccine    | 2019 - 1   |               |           |
| Uveal Melanoma                                                                            | SLC45A2      | CTLA4      | 2018 - 3   | Pending       |           |
| <b>TOTALS</b>                                                                             |              |            |            | <b>66 pts</b> | <b>34</b> |
| 66 patients treated (does not include highlighted: ovarian, sarcoma, uveal melanoma) TETC |              |            |            |               |           |
| IRRC = 34 patients / 66                                                                   |              |            |            |               |           |
| PR = 8                                                                                    |              |            |            |               |           |
| CR = 7 (> 18 months)                                                                      |              |            |            |               |           |

# Endogenous T Cell Therapy

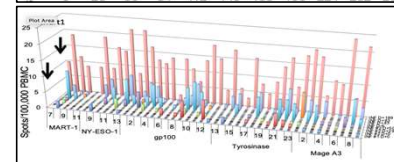
(a new math)



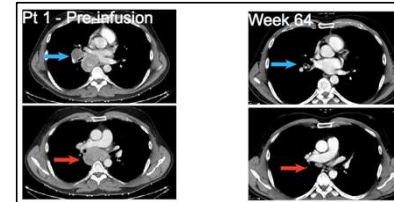
Persistence



Ag Spreading



Durable Responses



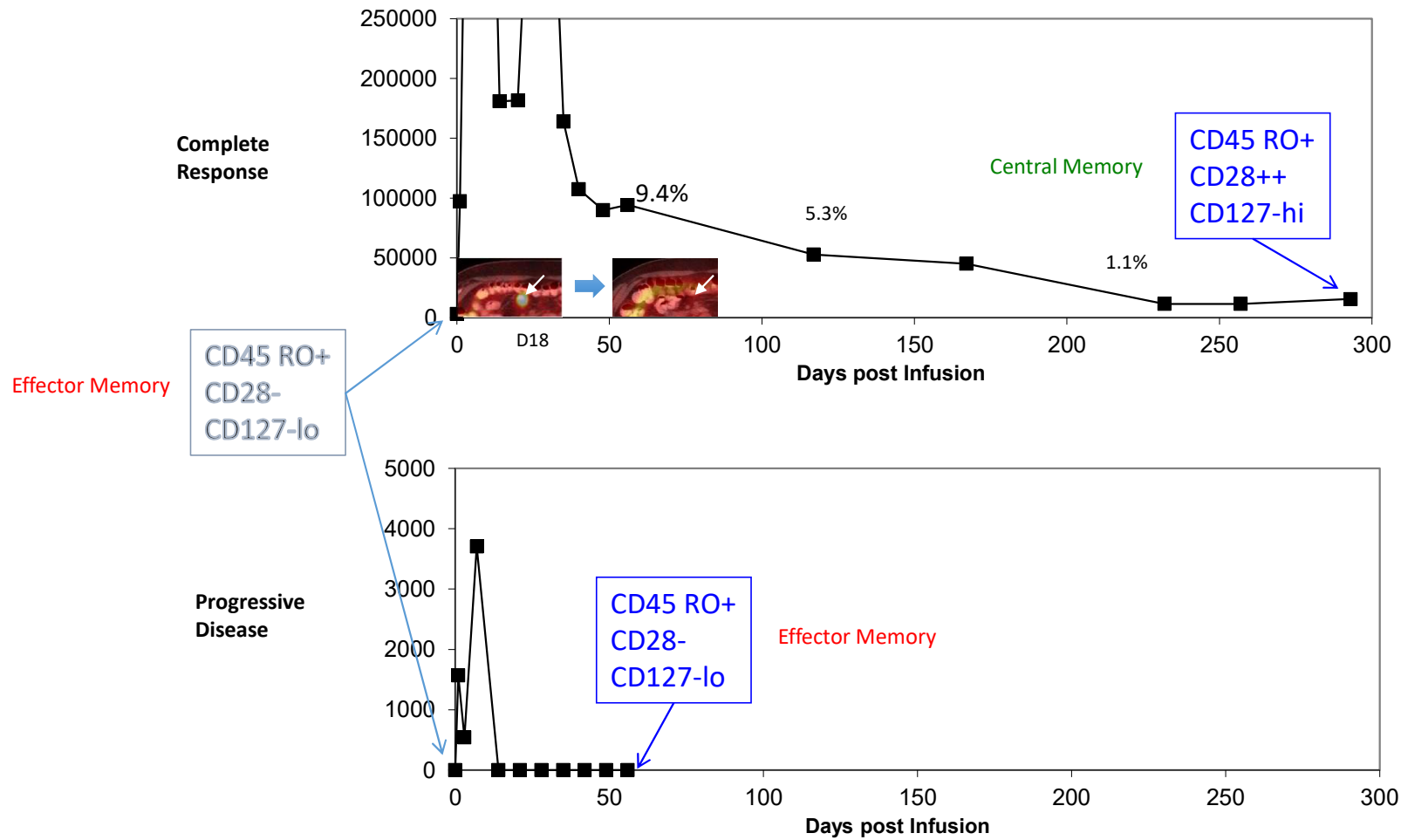
Multiple Tumors

| Disease        | Antigen                   | Design       | Year       | n             | IRRC      | PR/CR      |
|----------------|---------------------------|--------------|------------|---------------|-----------|------------|
| Melanoma       | MART-1, gp100, tyrosinase | Alone, CTLA4 | 2002 - 10  | 4             | 4         | 1/0        |
|                |                           |              | 2012 - 10  | 3             | 3         | 1/1        |
|                |                           |              | 2016 - 10  | 7             | 7         | 2/5        |
|                |                           |              | 2019 - 4   | 2             | 2         | 0/1        |
| Leukemia       | NY-ESO/ Tyr               | CD4          | 2008 - 9   | 4             | 4         | 1/1        |
|                |                           |              | 2013 - 6/6 | 0/6           | 6/6       |            |
| Merkel         | T antigen                 |              | 2014 - 10  | 8             | 8         | 3/2        |
| Breast         | NY-ESO                    |              | 2007-1     | 0             |           |            |
| Ovarian        | Col6A3/PRAME              | anti-CD137   | 2019 - 3   | Pending       |           |            |
| Sarcoma        | NY-ESO                    | Vaccine      | 2019 - 1   | Pending       |           |            |
| Uveal Melanoma | SLC45A2                   | CTLA4        | 2018 - 3   | Pending       |           |            |
| <b>TOTALS</b>  |                           |              |            | <b>66 pts</b> | <b>34</b> | <b>8/7</b> |

66 patients treated (does not include highlighted : ovarian, sarcoma, uveal melanoma TETC)  
 IRRC = 34 patients / 66  
 PR = 8  
 CR = 7 (> 18 months)

Combination Tx

# Persistence



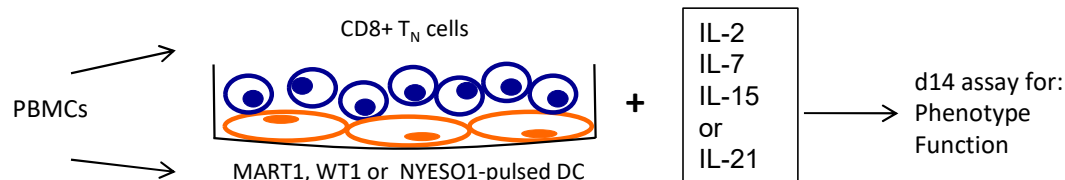
# Persistence

*“All T cells are equal,*

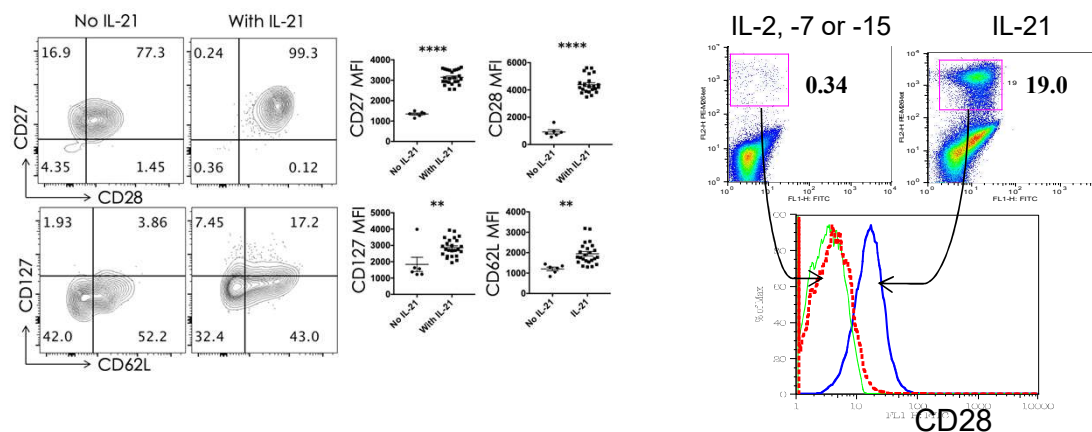
*but some are more equal than others...”*

Apologies to G. Orwell

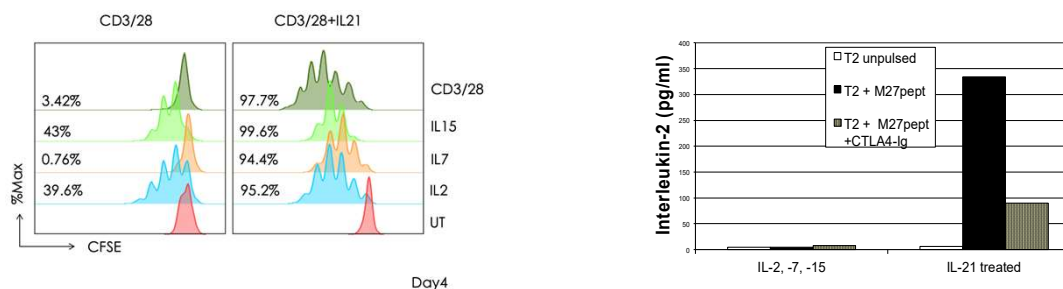
# IL-21 exposure during priming leads to generation of T<sub>CM</sub>



Phenotype

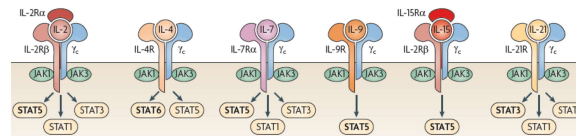


Function

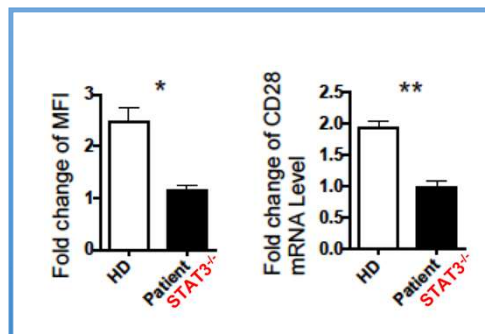
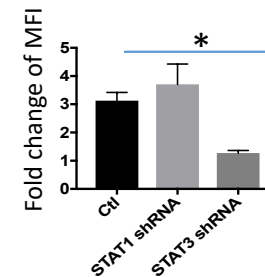
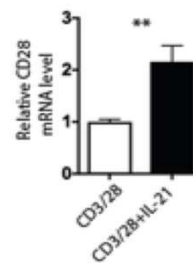
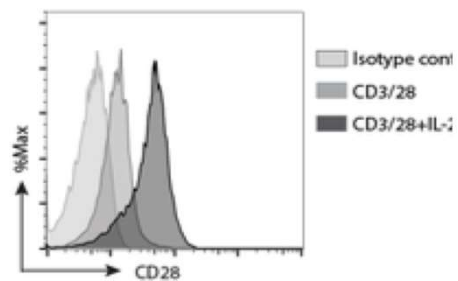


*J Immunol* 2005  
*Blood* 2008  
*CIR* 2020

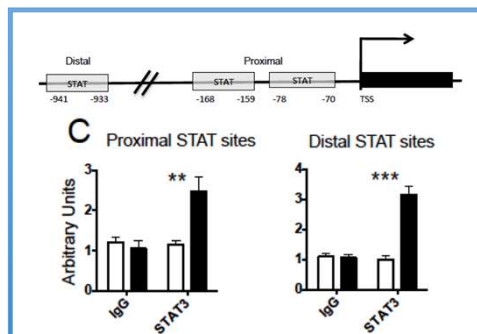
# Upregulation of CD28 by IL-21 in T<sub>CM</sub> is transcriptionally-mediated and STAT3-dependent



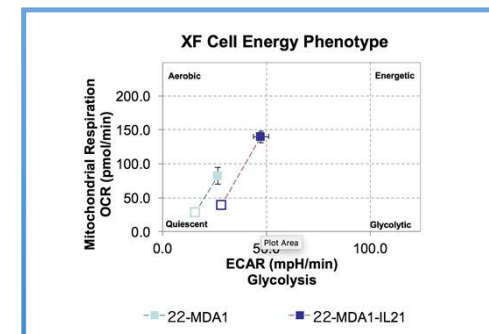
*Nat Rev Immunol* 2009; 9: 480



**STAT3<sup>-/-</sup> human**



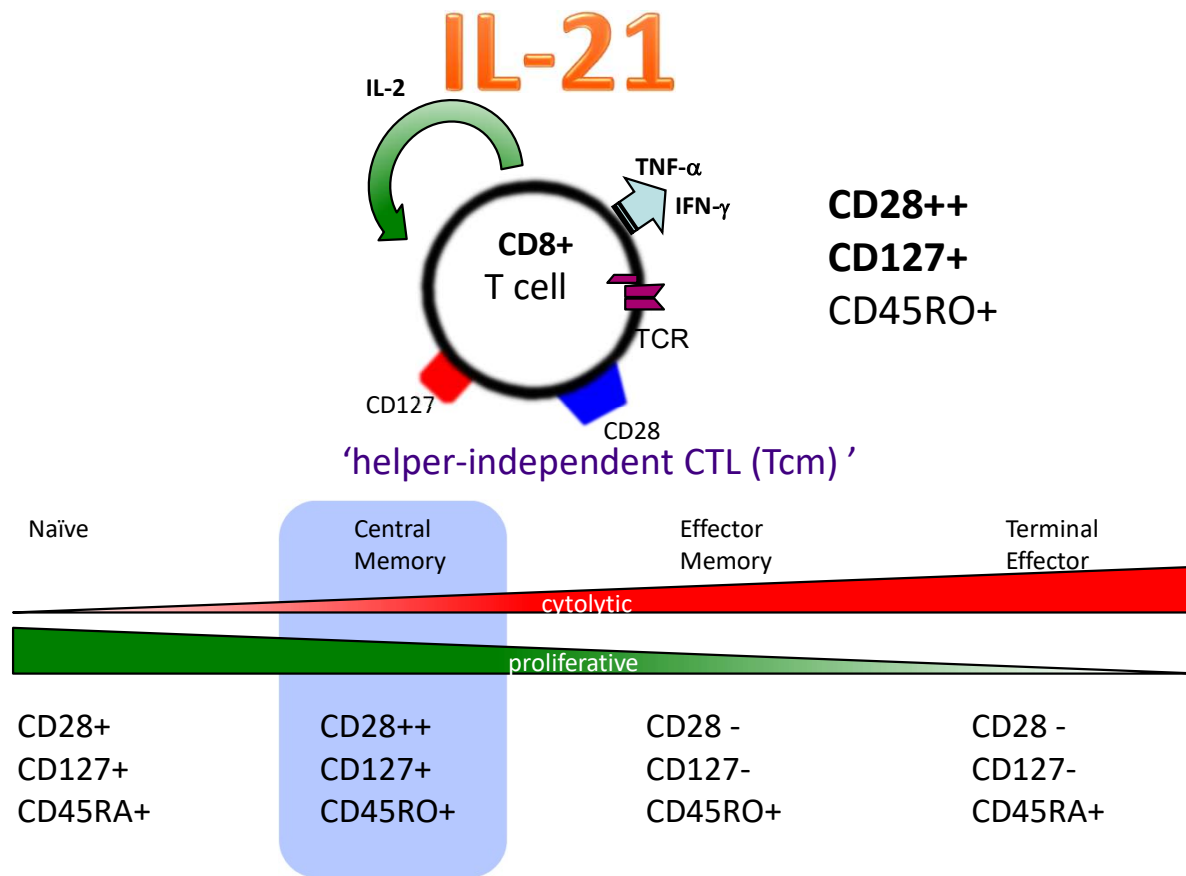
**ChIP-seq pSTAT3 binding**



**Metabolic fitness**

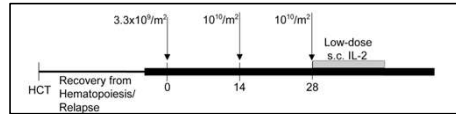
*J Immunol* 2005  
*Blood* 2008  
*CIR* 2020

# Priming with IL-21 Generates Central Memory-type T cell

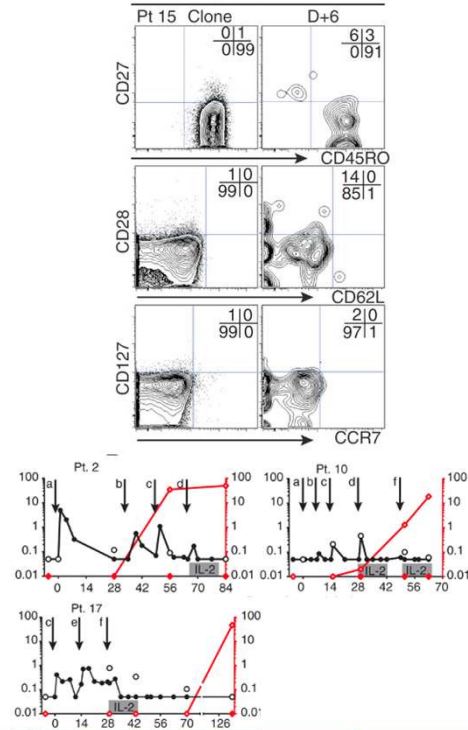


*J Immunol* 2005  
*Blood* 2008

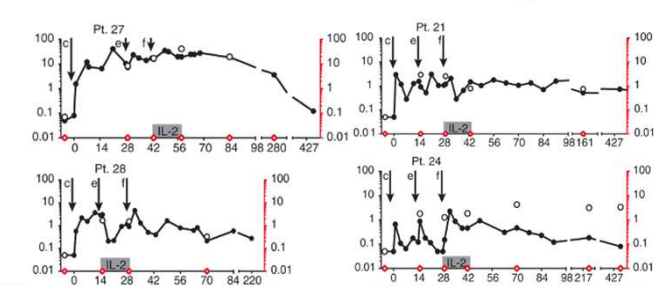
# Central memory phenotype of transferred IL-21-primed WT1-specific CTLs



**Generated without IL-21**  
A Gated on multimer<sup>+</sup> CD8<sup>+</sup> T cells

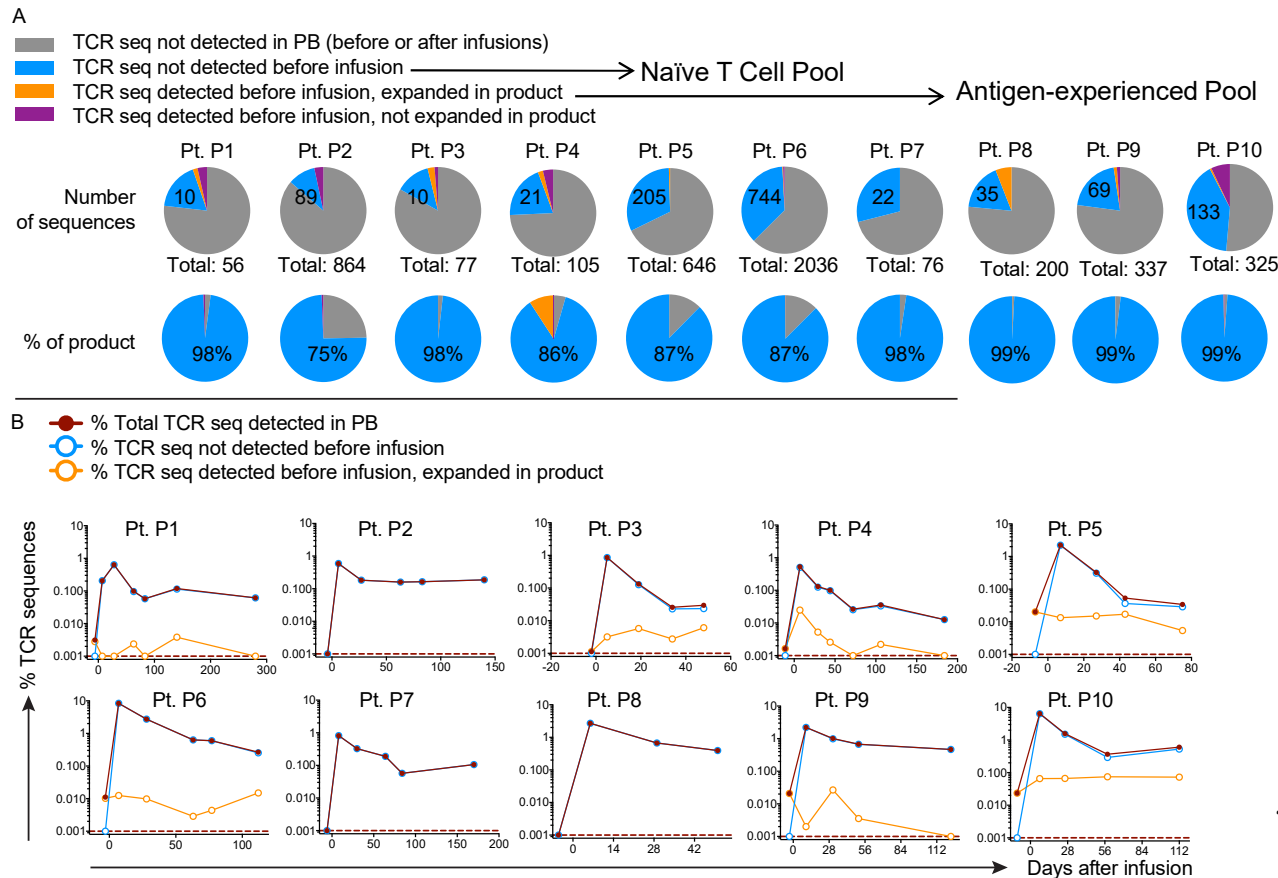


**Generated with IL-21**  
B Gated on multimer<sup>+</sup> CD8<sup>+</sup> T cells



Sci Transl Med 2013

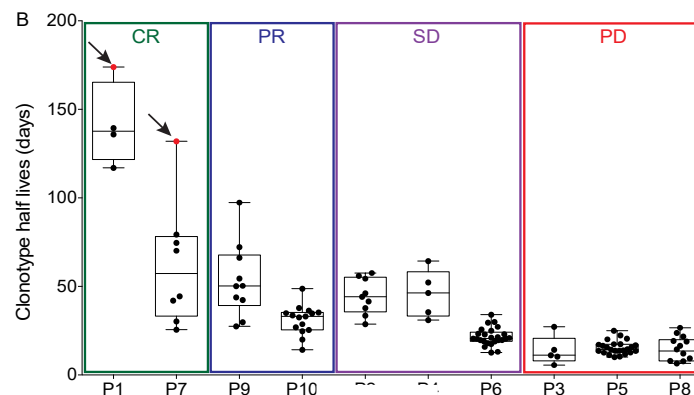
## Source of IL-21 primed T<sub>CM</sub> for ETC are Naïve early T cell precursors in peripheral blood



Science Immunology 2017

## In Vivo Persistence Of Transferred T Cell Clonotype(s) Correlates With Clinical Response

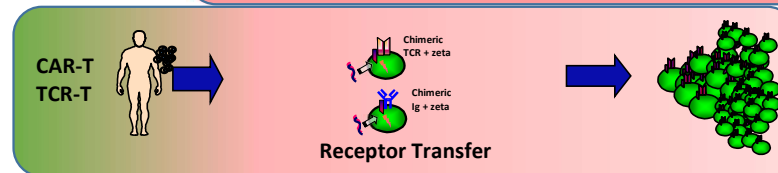
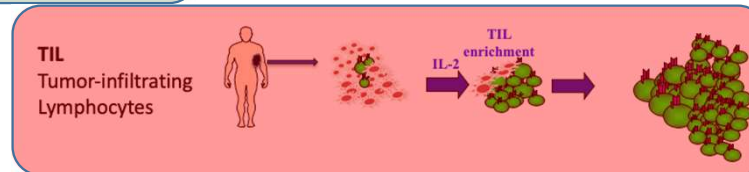
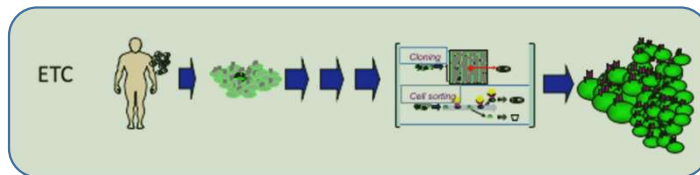
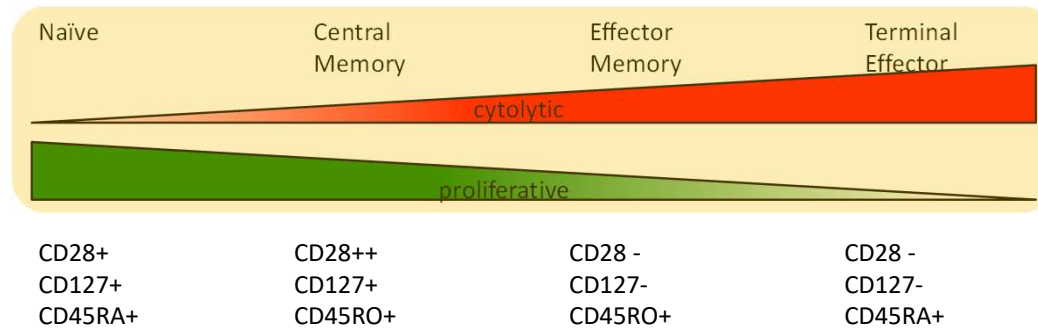
| Patient | Prior<br>Ipilimumab<br>treatment<br>failure | 6<br>weeks  | 12<br>weeks | 16/19<br>weeks | 28<br>weeks  | 40<br>weeks | 84<br>weeks  |
|---------|---------------------------------------------|-------------|-------------|----------------|--------------|-------------|--------------|
| 1       | YES                                         | SD<br>(-2)  | SD<br>(-34) |                | PR<br>(-80)  | PR<br>(-90) | CR<br>(-100) |
| 2       | YES                                         | SD<br>(-2)  | SD<br>(-6)  | SD<br>(-7)     |              |             |              |
| 3       | NO                                          | SD<br>(0)   | SD<br>(+19) |                | PD<br>(+25)  |             |              |
| 4       | YES                                         | PD<br>(69)  |             |                |              |             |              |
| 5       | NO                                          | PD<br>(+30) |             |                |              |             |              |
| 6       | NO                                          | PD<br>(+31) | SD<br>(+17) |                |              |             |              |
| 7       | NO                                          | SD<br>(-45) | PR<br>(-90) |                | CR<br>(-100) |             |              |
| 8       | NO                                          | SD<br>(+8)  | SD<br>(+21) | PD<br>(+27)    |              |             |              |
| 9       | NO                                          | SD<br>(-41) |             | PR<br>(-71)    |              |             |              |
| 10      | NO                                          | PR<br>(-76) | PR<br>(-79) |                |              |             |              |



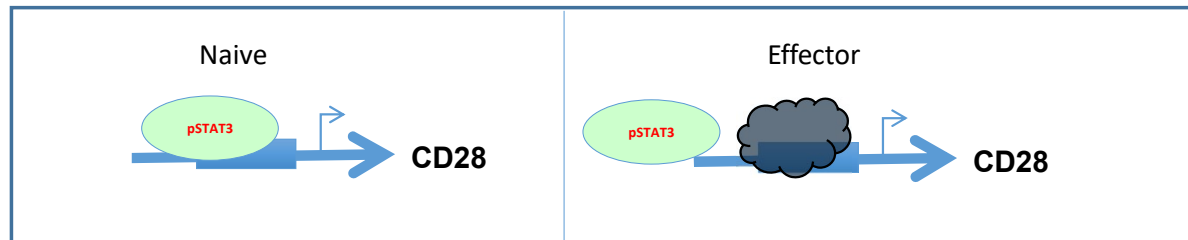
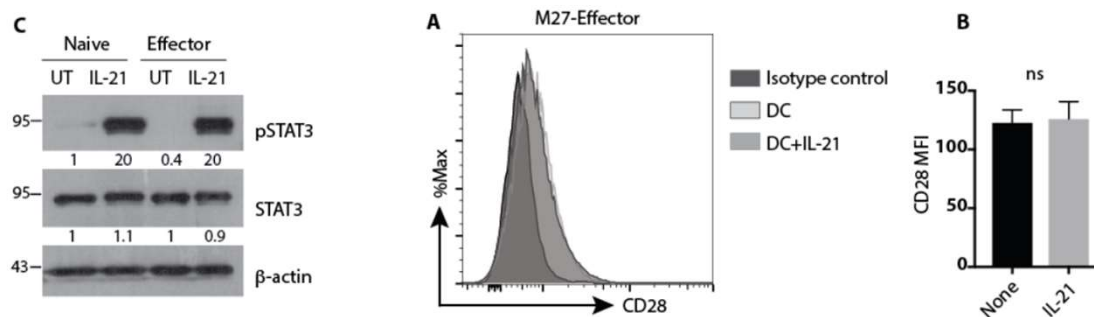
*Science Immunology 2017*

$T_{1/2}$  Half-life in vivo  $\approx$  Clinical Response

# 'Democratize'

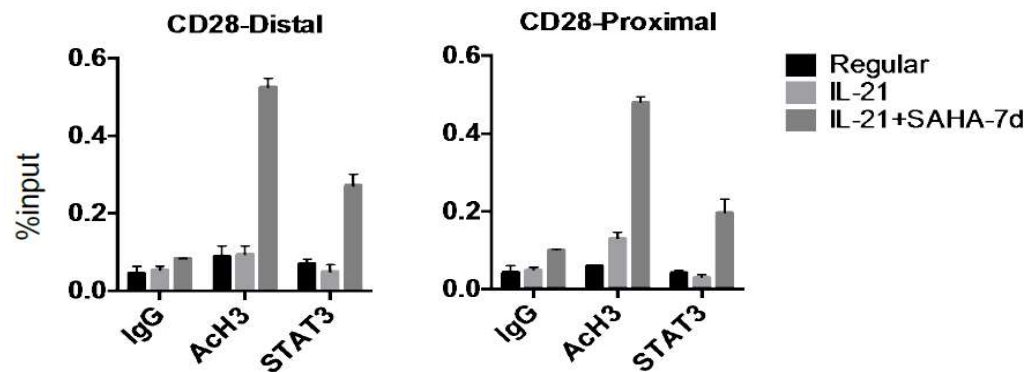
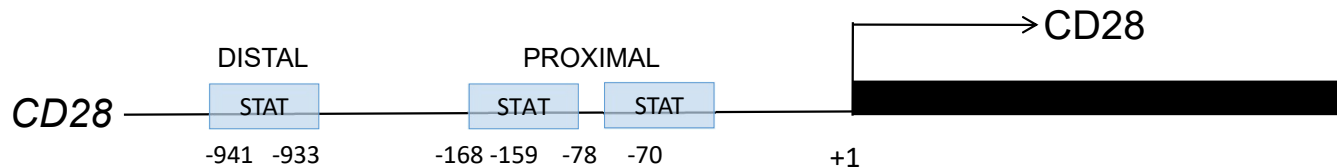
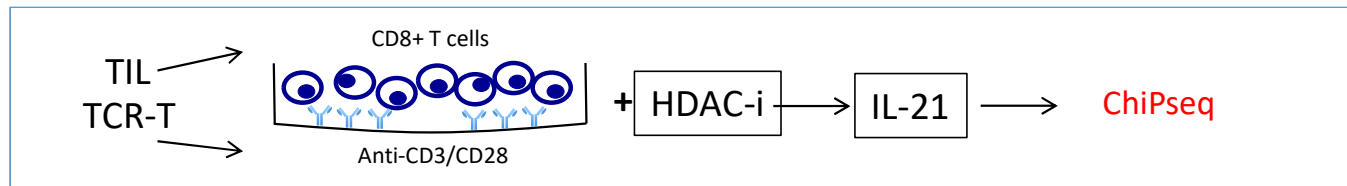


## IL-21 upregulates pSTAT3 levels but does not induce CD28 in T<sub>EFF</sub>



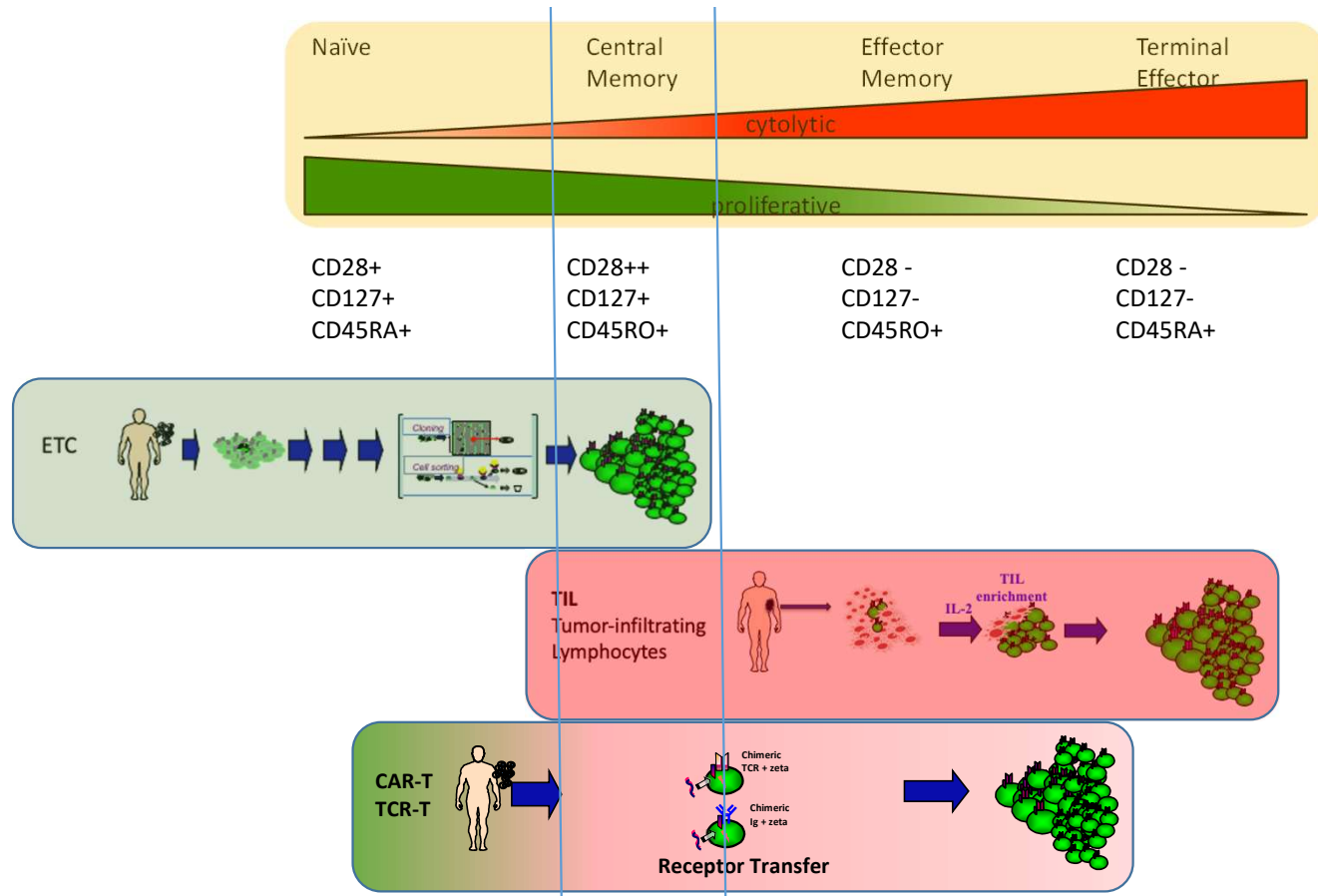
Wang et al, CIR 2020

# HDACi permits IL-21-induced pSTAT3 binding to CD28 promoter of Effector T cells



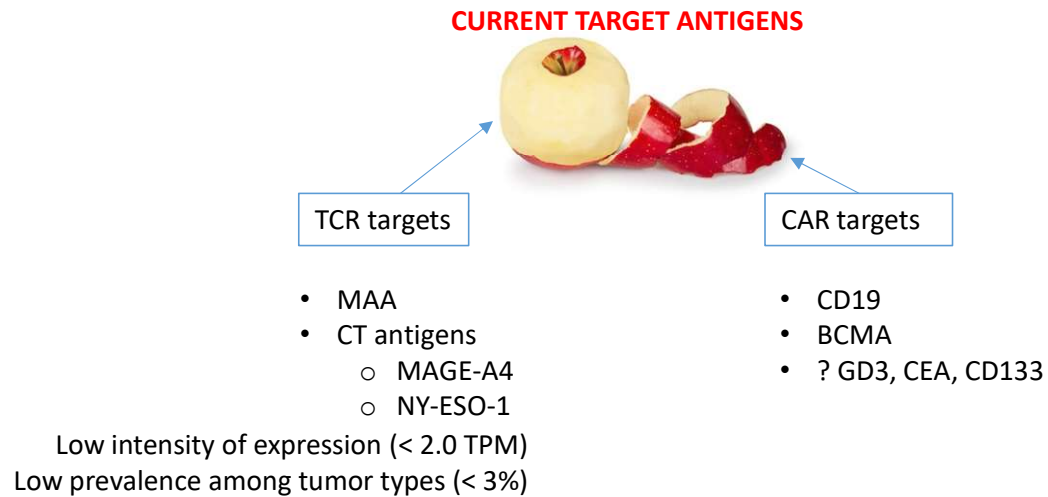
Wang et al, CIR 2020

# 'Operationalize'



## *<sup>2</sup>Democratization of cell therapy*

### ETC Provides Opportunity for Antigen Discovery and Epitope validation



# Antigen Discovery Pipeline: Identification of TCR Targets by in silico methods

*in silico*

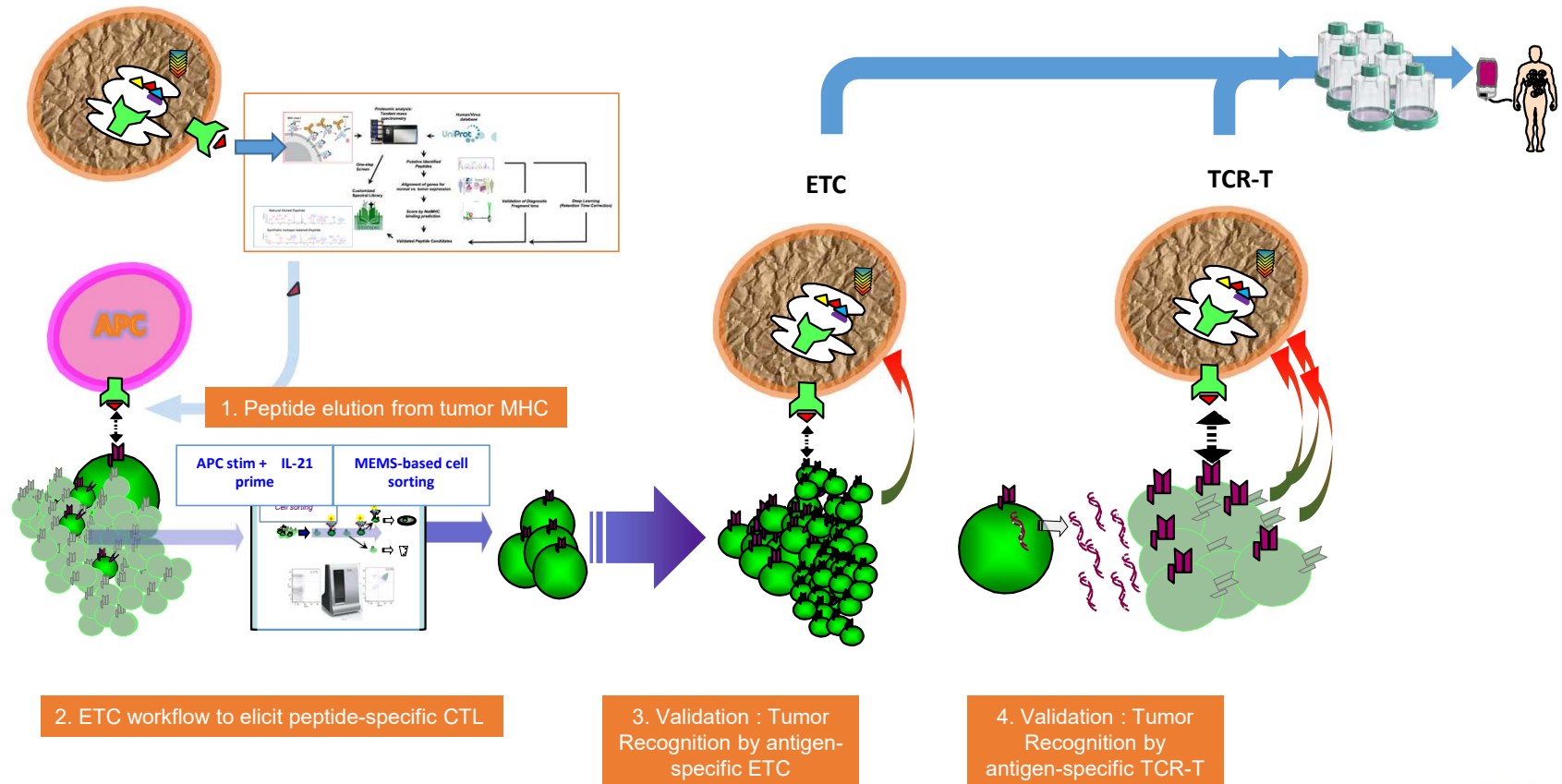


Tumor Cell

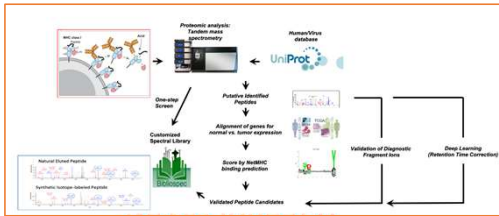
- Prediction algorithms / Reverse Immunology
- Neo antigens
- Overlapping peptides

# Antigen Discovery Pipeline: Identification of **immunogenic** TCR Targets

*MS-defined epitopes followed by Empiric Validation*



## Antigen Discovery Pipeline: MS data from MHC-eluted peptides yields > 200 high value targets



## Tumor database

Normal

- **4-5 targets with median TPM < 3 across 4 tumor types < 2% of patients**

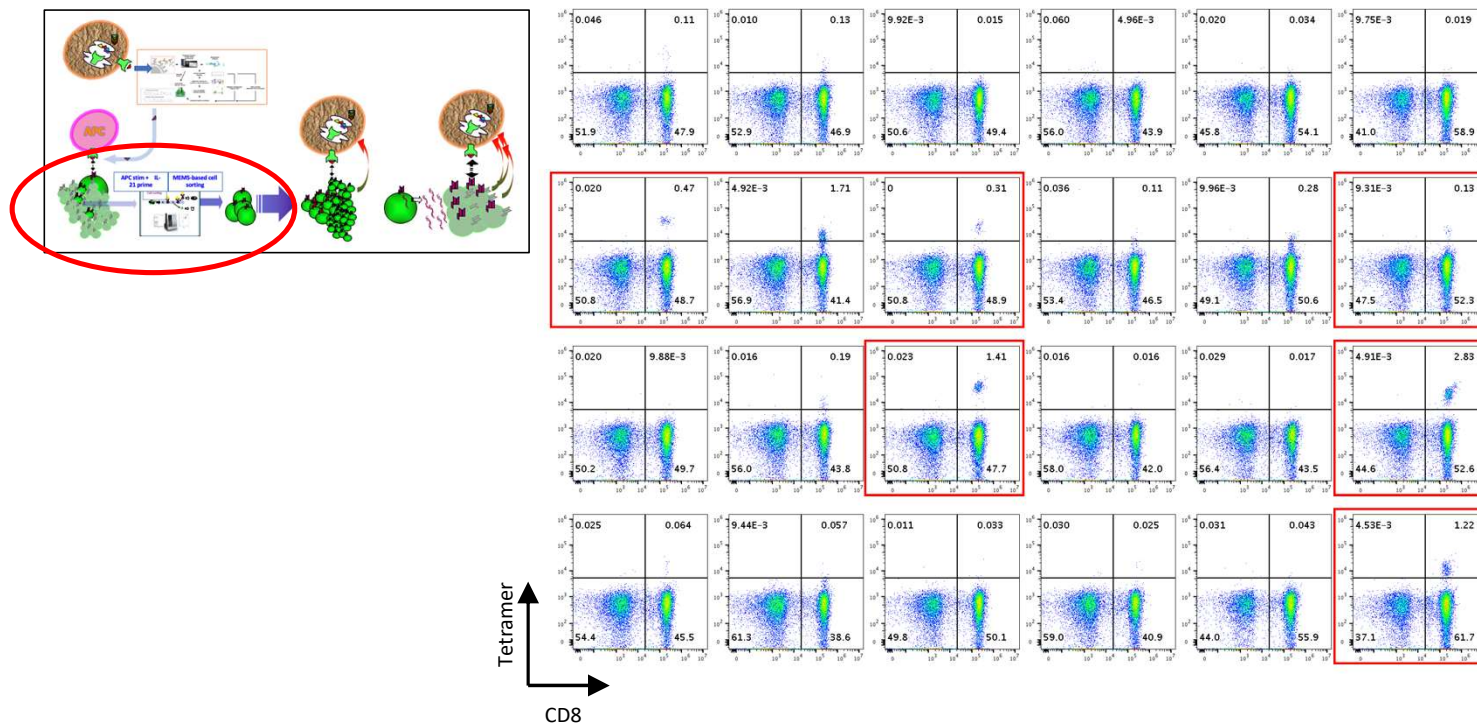
OLD

NEW

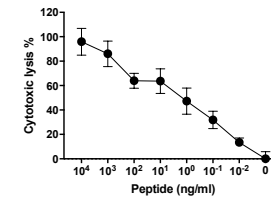
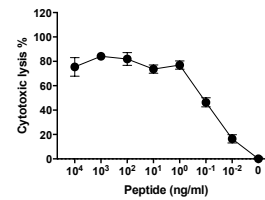
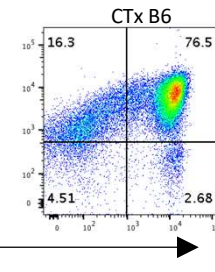
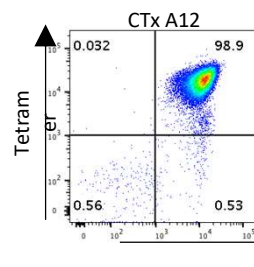
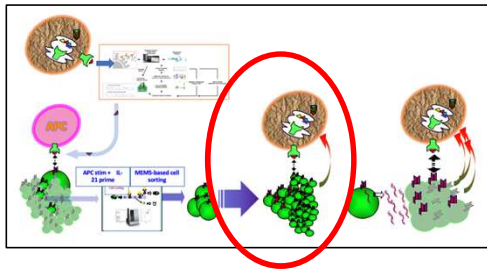
- **>200** high value targets  
**median TPM > 18**  
across **30 tumor types**  
**several HLA-Class I alleles**  
**(75% of Caucasian/Asian**  
pts)
- Tumor-selective (Testis or Prostate normal tissue restricted)

[illegible]

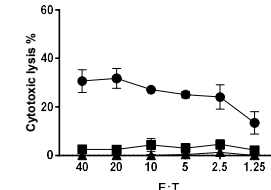
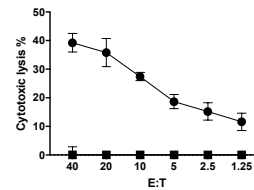
# Antigen Discovery Pipeline: TCR TARGET: CTx *in vitro* stimulation



# Antigen Discovery Pipeline: TCR TARGET: CTx *ETC* validation



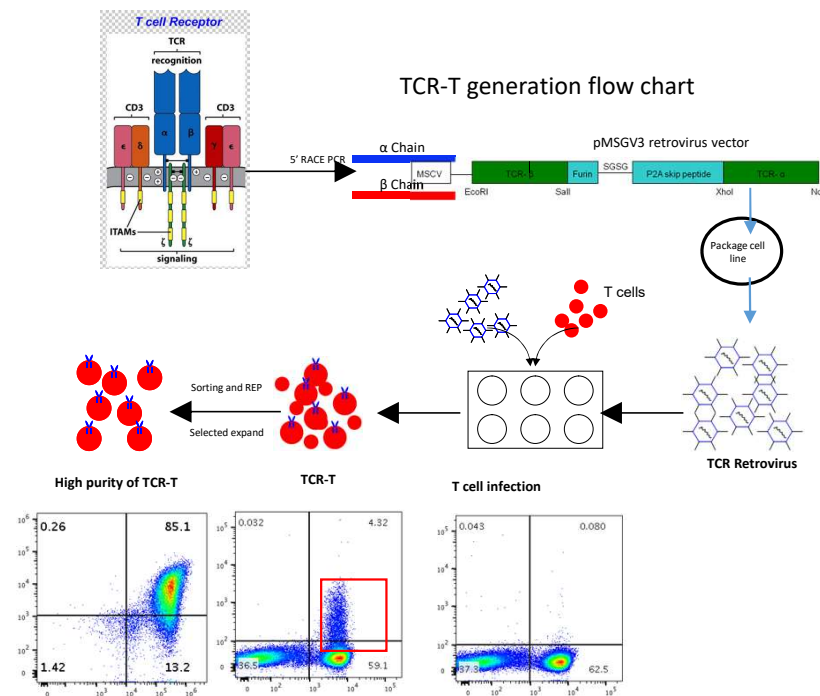
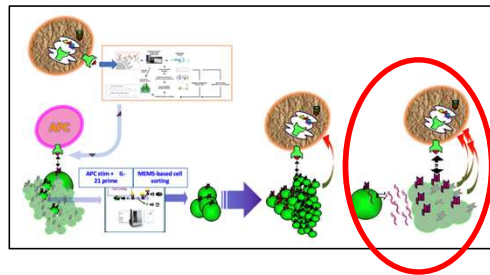
Peptide-pulsed T2



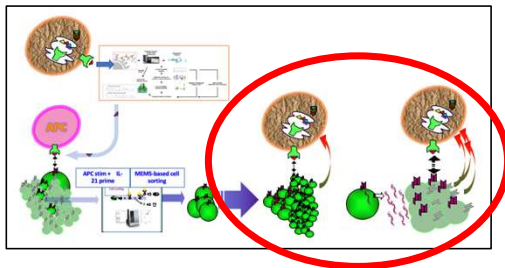
Tumor targets

● H1395  
■ H522

# Antigen Discovery Pipeline: TCR TARGET: CTx *TCR-T validation*

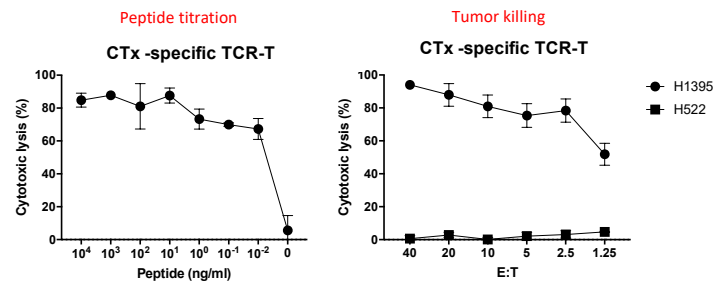


# Antigen Discovery Pipeline: TCR TARGET: CTx: *ETC* vs *TCR-T*

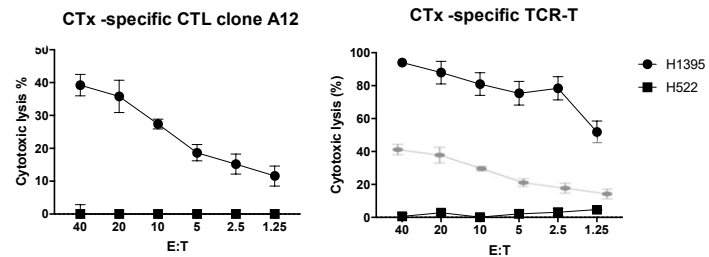


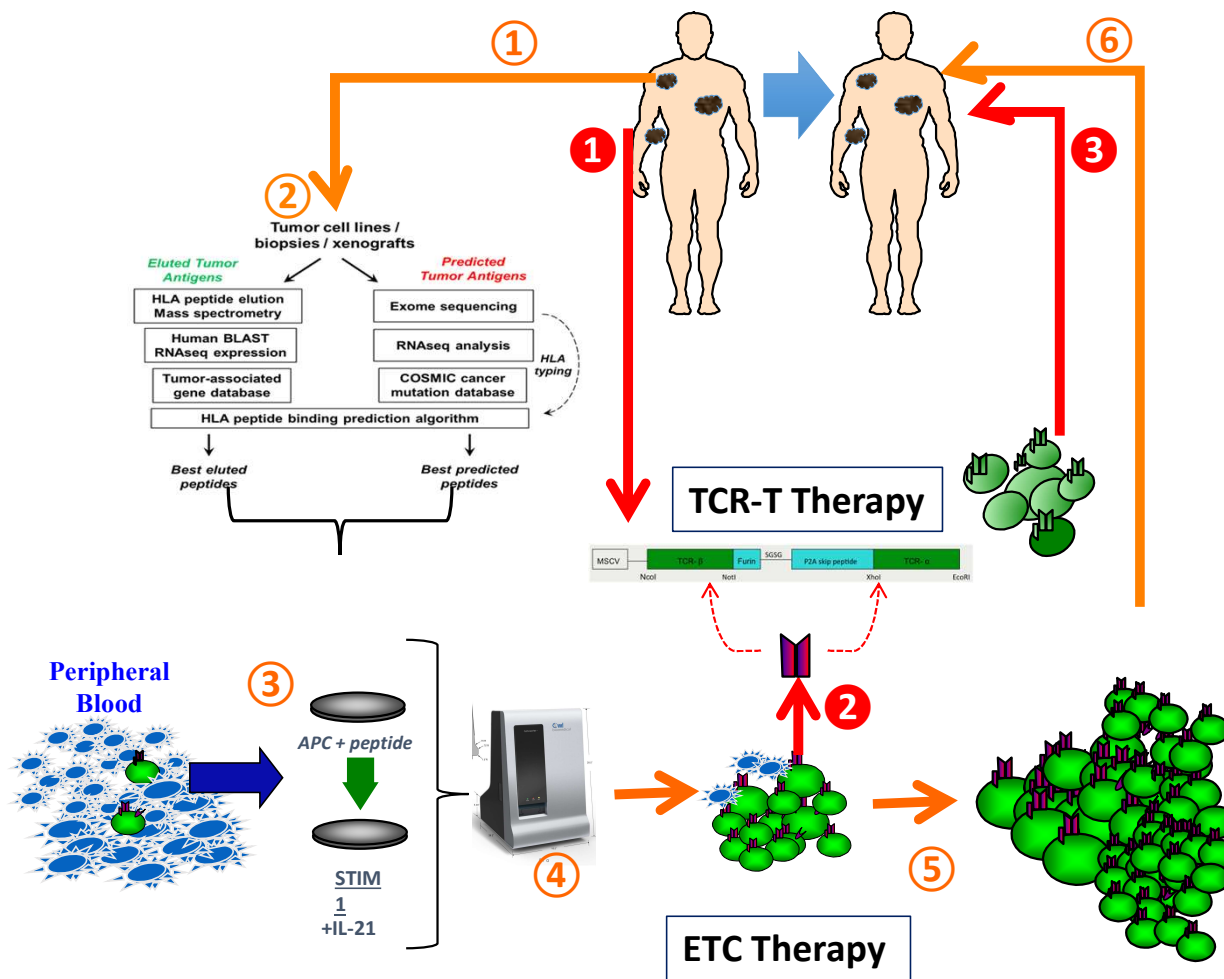
TCR-T

## Lung Cancer Cell Line Killing by TCR-T Engineered CTx-specific CTL

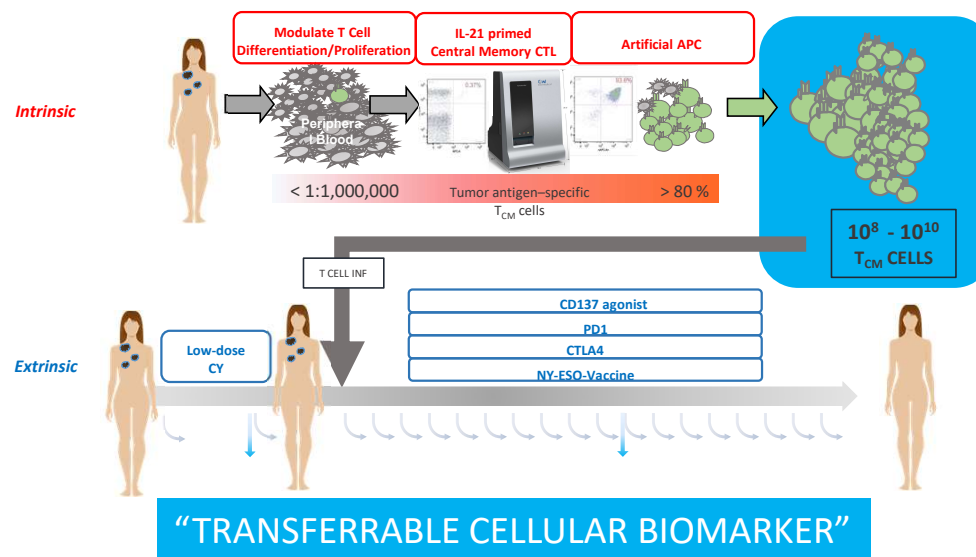
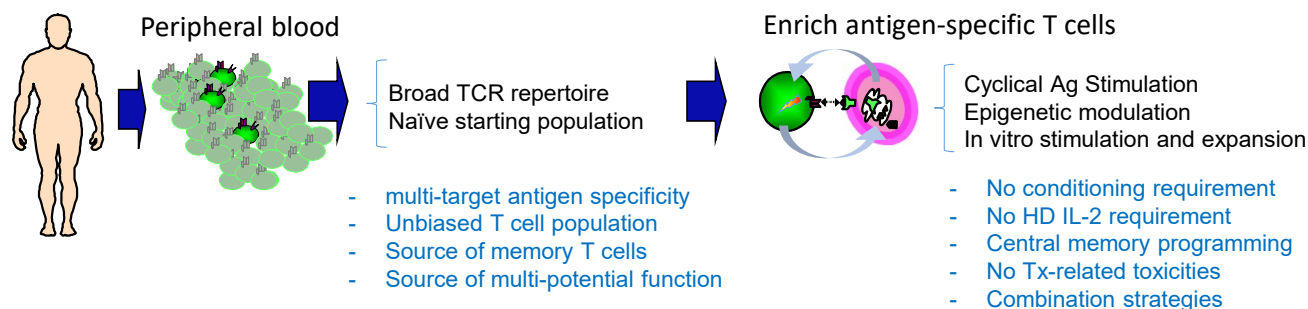


ETC vs TCR-T



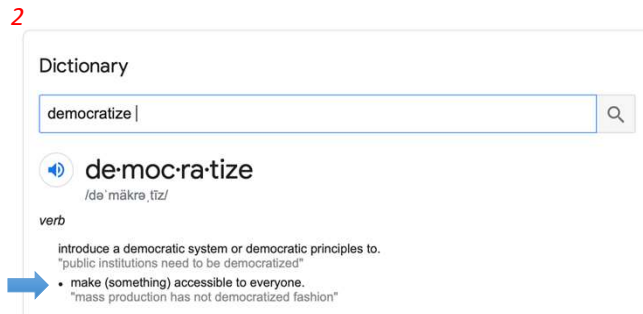


# Endogenous T Cell (ETC) Therapy:



# Endogenous T Cell Therapy

*<sup>2</sup>Democratization of cell therapy*



# Endogenous T Cell Therapy

*Make Cell Therapy Accessible to the Masses*



***The people who did all the work***

Ke Pan  
Yulun Chiu  
Natalia Miroballi

Ivy Lai  
Rebecca Shaw  
Macrina Melendrez  
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