Regensburger Centrum für
Interventionelle Immunologie

TRUCKs
the next generation of adoptive T cell therapy

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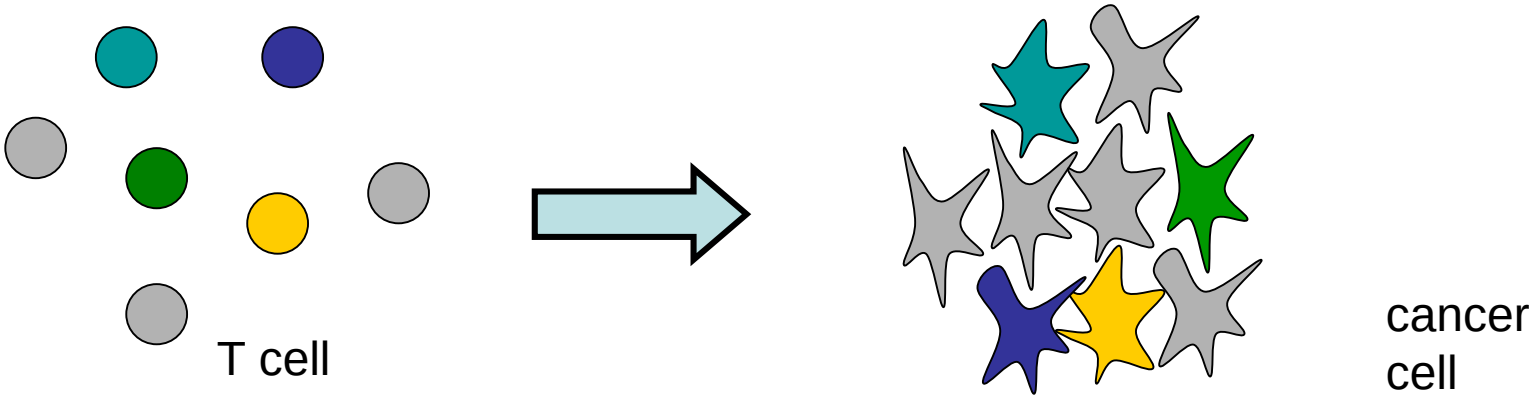
T cells with engineered specificity

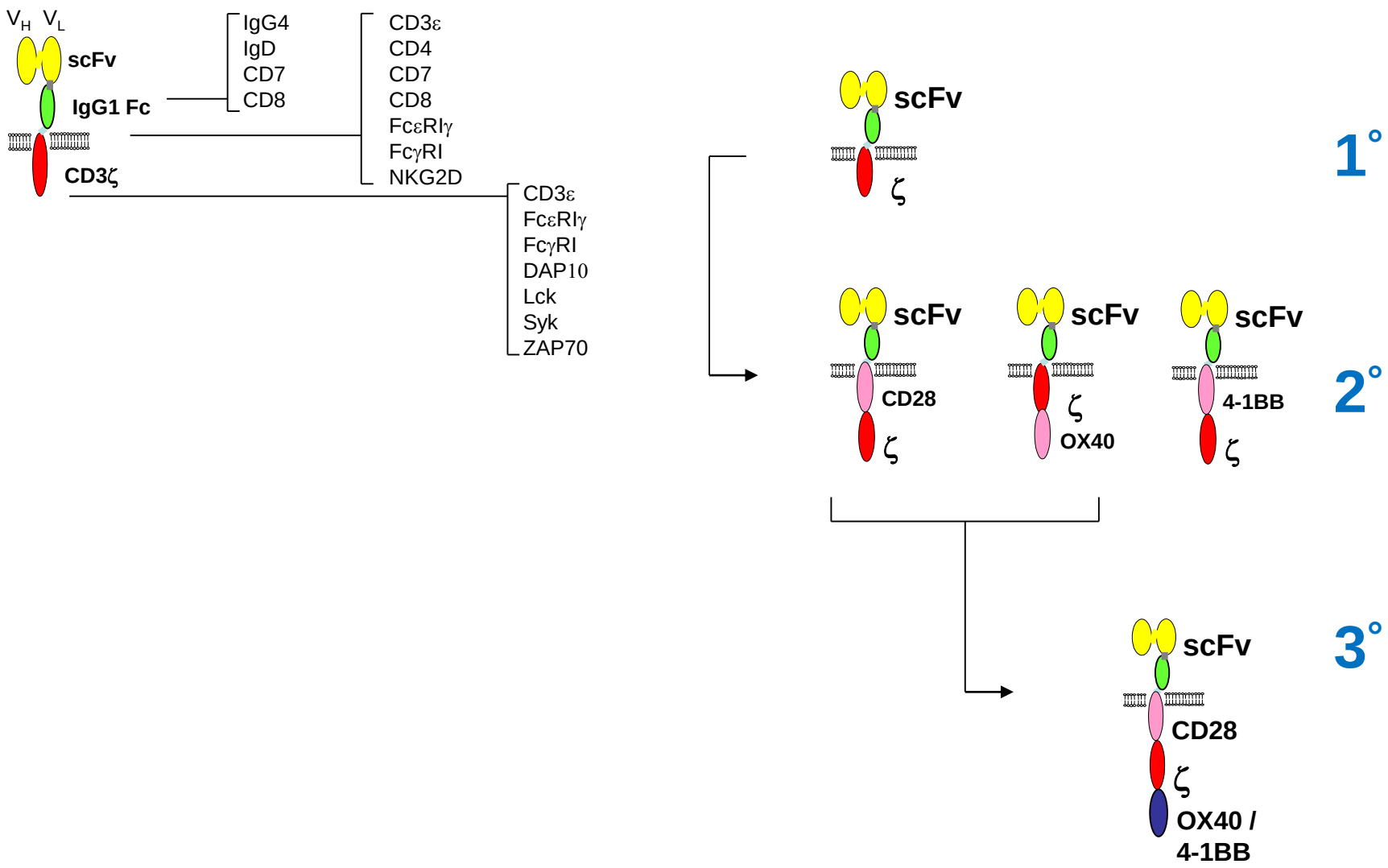


The aim:

To give patient´s immune cells specificity

for targeting autologous cancer cells.

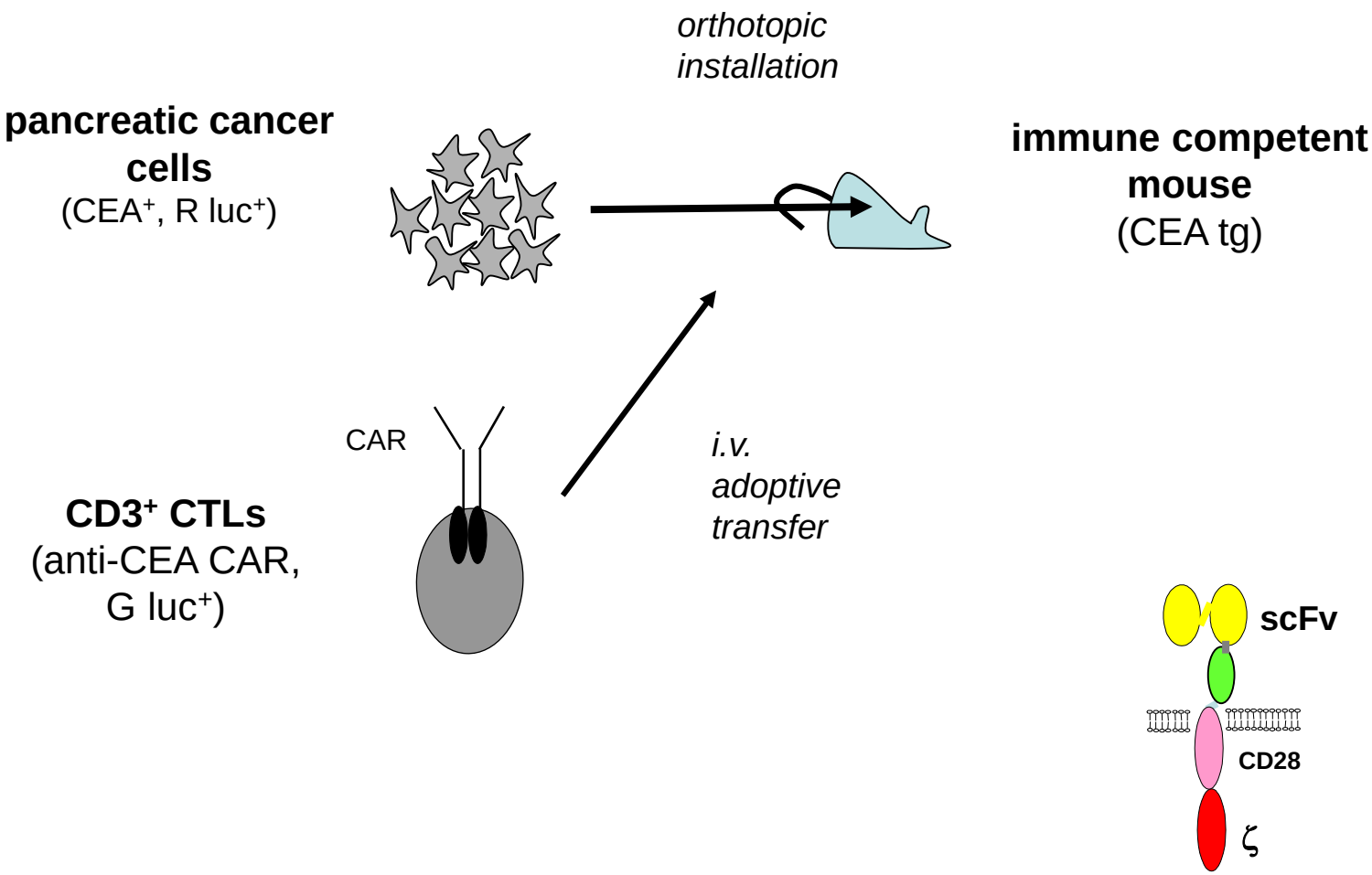
The zoo of chimeric antigen receptors (CARs)



- **Tumor lesions are heterogenous with respect to the expression of targetable antigens**

- **„Tumor associated antigens“ are not exclusively expressed by tumor cells.**

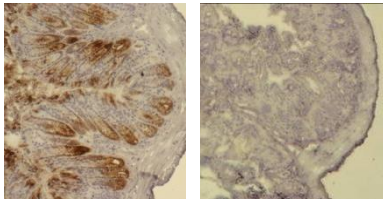
CAR T cells to target pancreatic cancer cells in the tolerant, immune competent mouse



The CEAtg mouse displays the human pattern in CEA expression

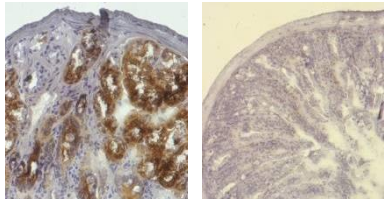
CEA tg **wt**

large intestine

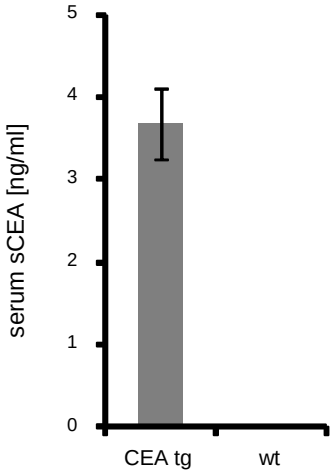


CEA

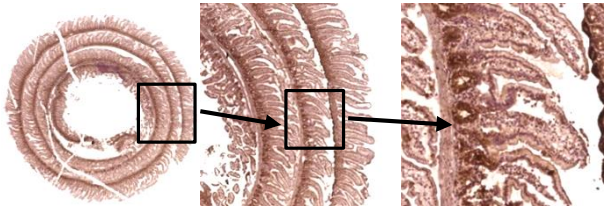
small intestine



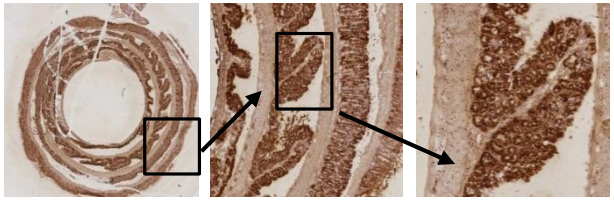
CEA



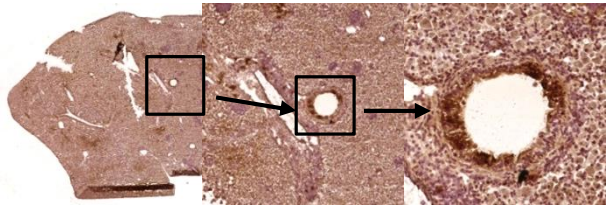
small intestine



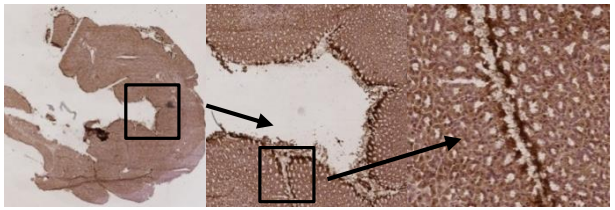
large intestine



lung



stomach



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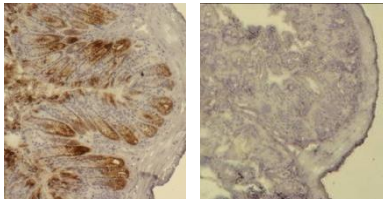
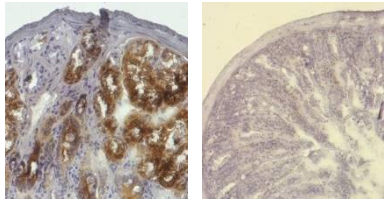


small intestine

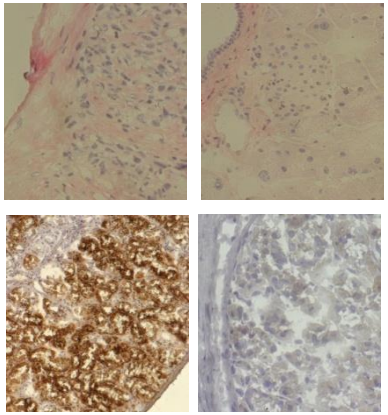


CEA

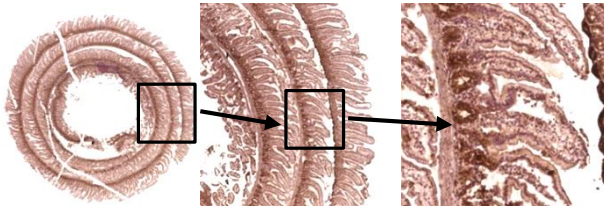
CEA

transplanted pancreatic carcinoma cells in the CEA tg mouse

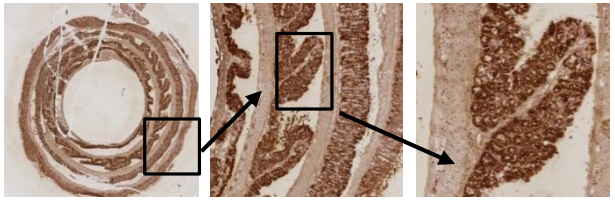
CEA^{+} tumor w/o tumor



small intestine

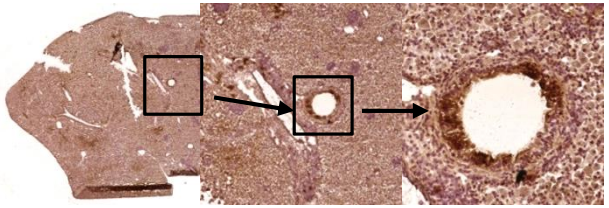


large intestine



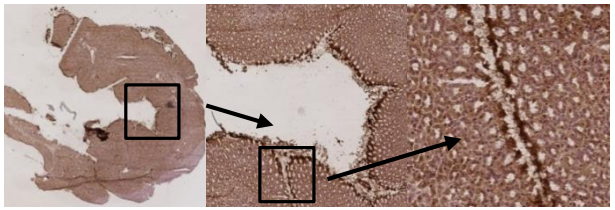
H&E

lung

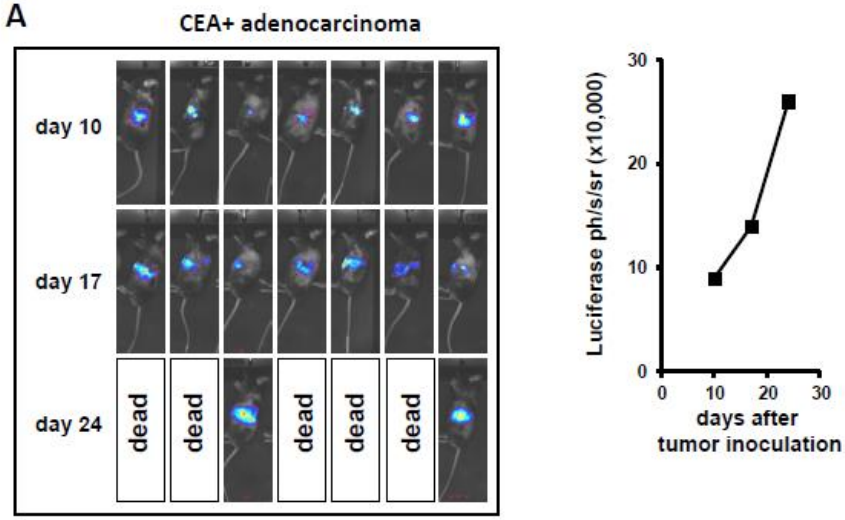


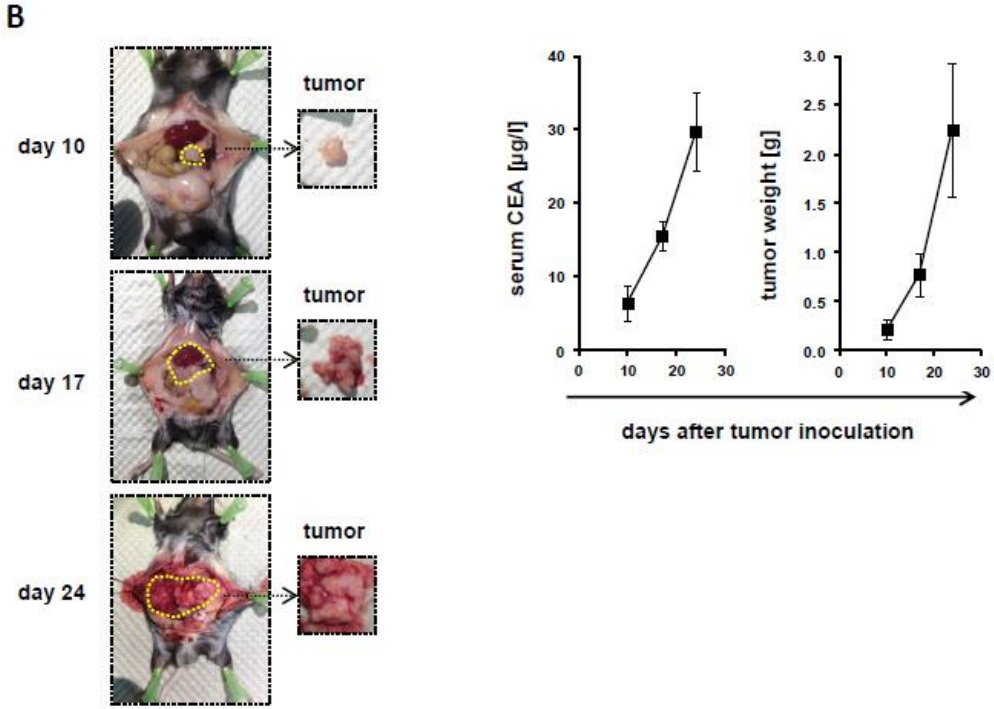
CEA

stomach



Growth of panc02 pancreatic cancer in the CEAtg mouse

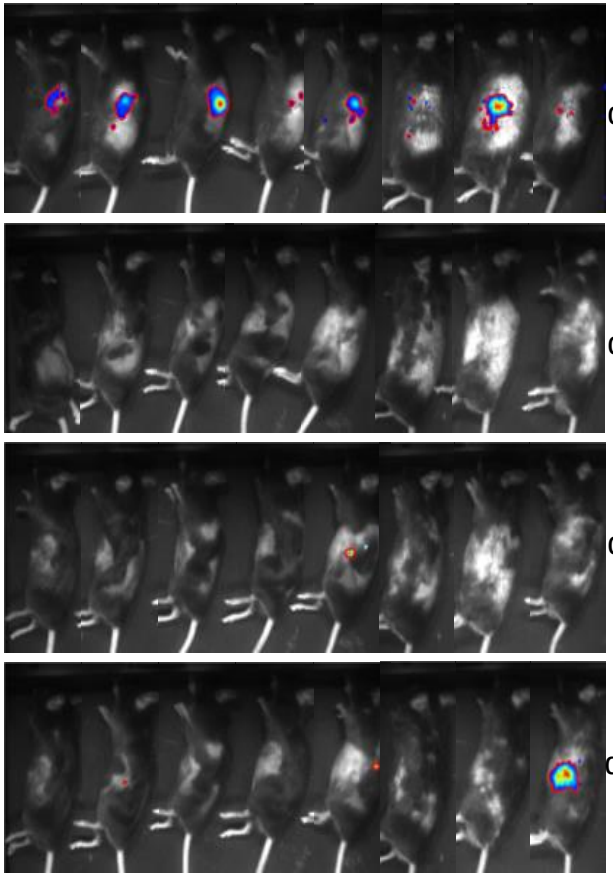




Imaging tumor and CAR engineered T cells

tumor imaging

T cells (CAR$^+$)
tumor (CEA$^+$)



day 0

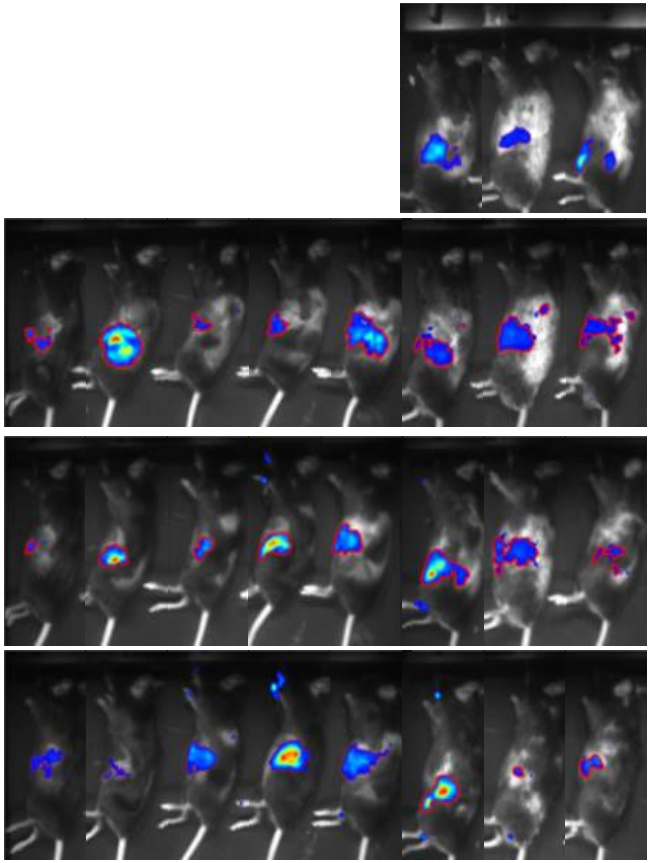
day +9

day +23

day +37

T cell imaging

T cells (CAR$^+$)
tumor (CEA$^+$)



day +3

day +7

day +21

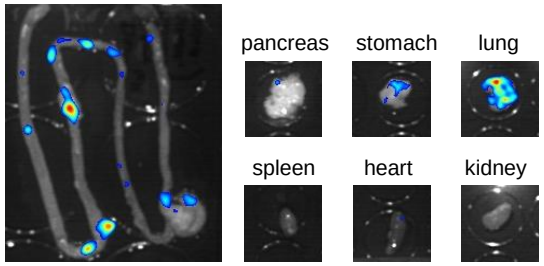
day +35

No severe auto-immunity by anti-CEA CAR T cells

T cell imaging

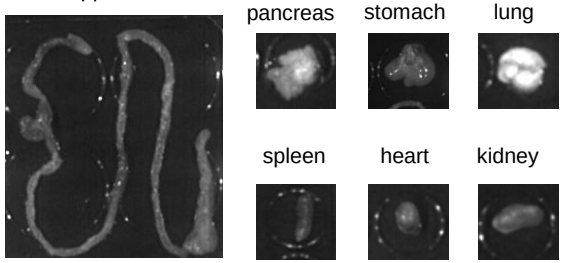
CEAtg mouse treated with anti-CEA CAR T cells

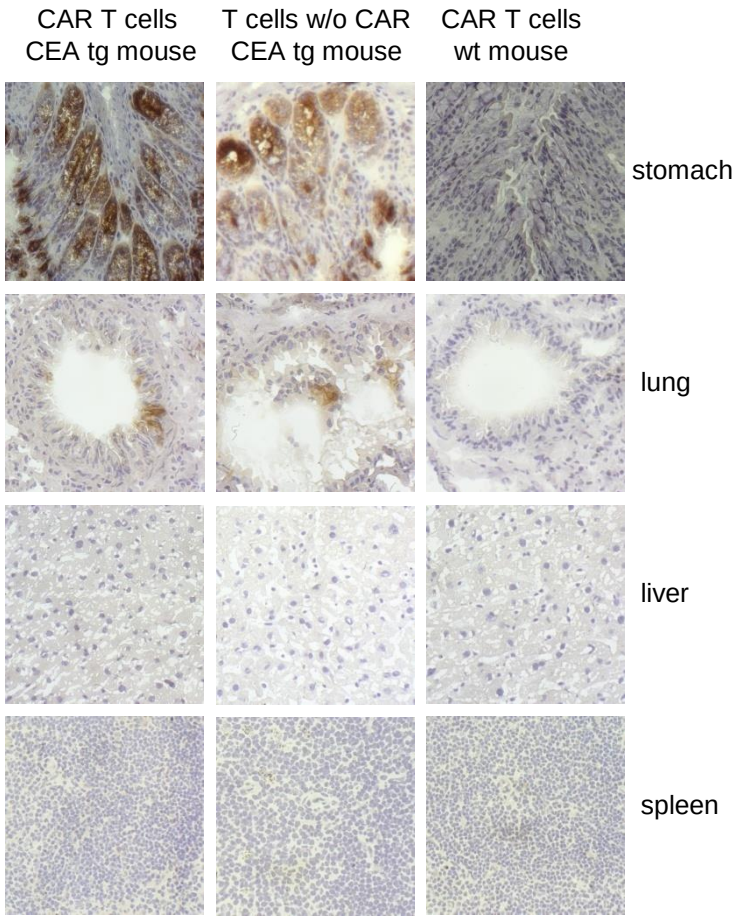
small & large intestine, appendix



CEAtg mouse treated with T cells w/o CAR

small & large intestine, appendix

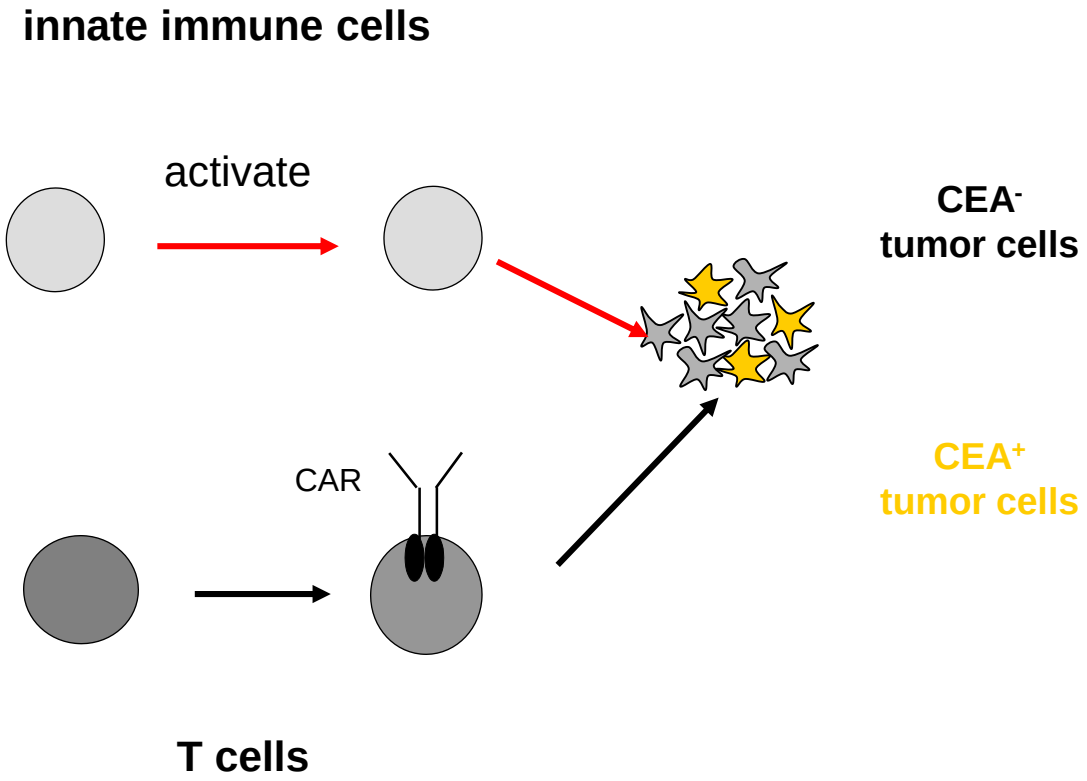




- Tumor lesions are heterogenous with respect to the expression of targetable antigens:

  there are always cancer cells which lack the targeted antigen

An innate immune cell attack together with a CAR T cell attack may help to eliminate a solid cancer lesion



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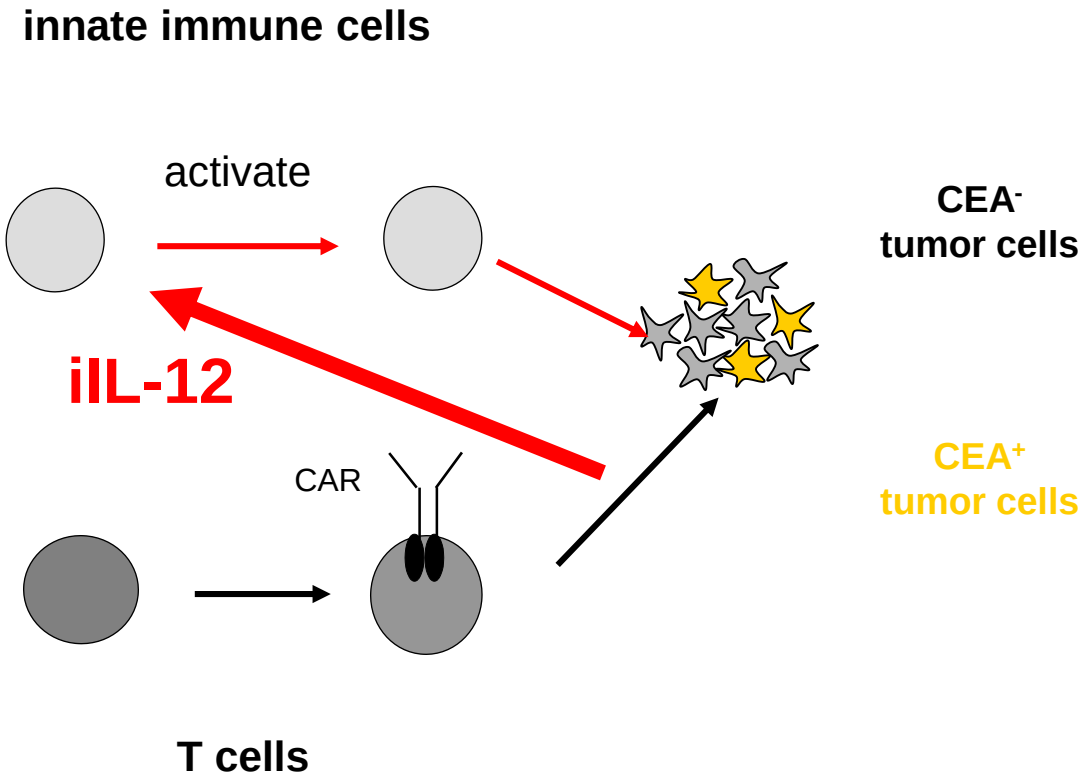
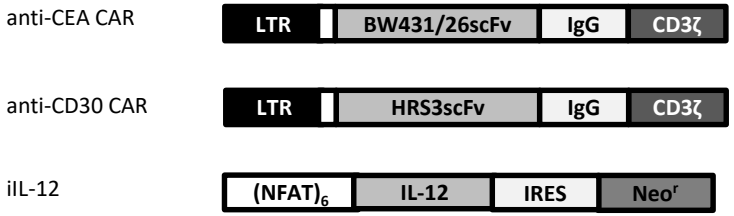
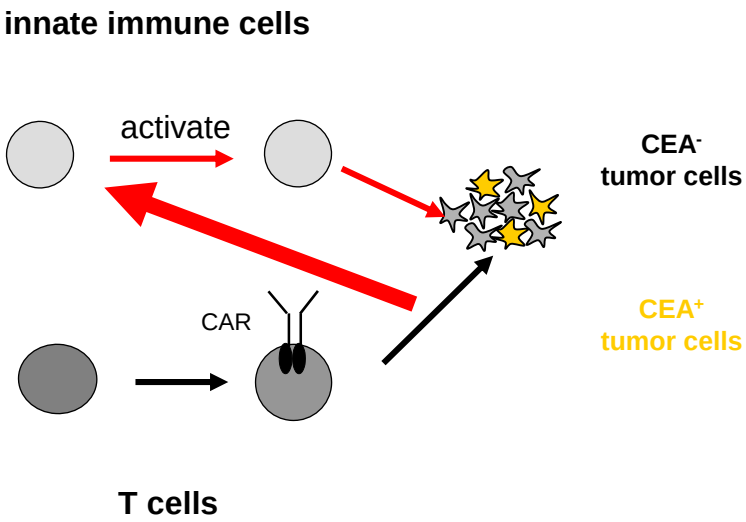
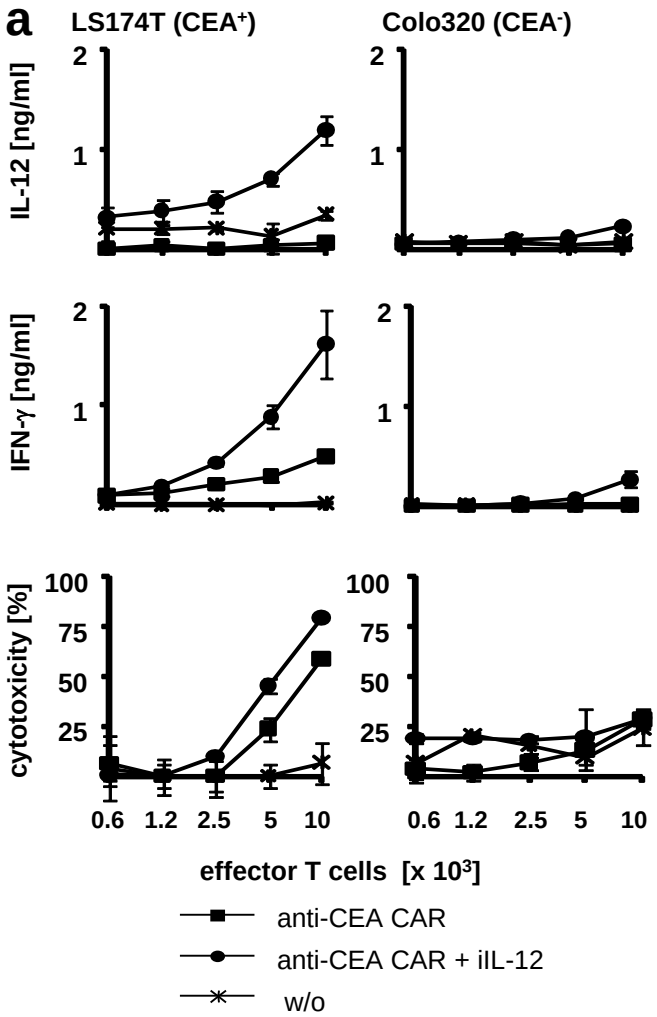


T cells engineered with CAR inducible IL-12







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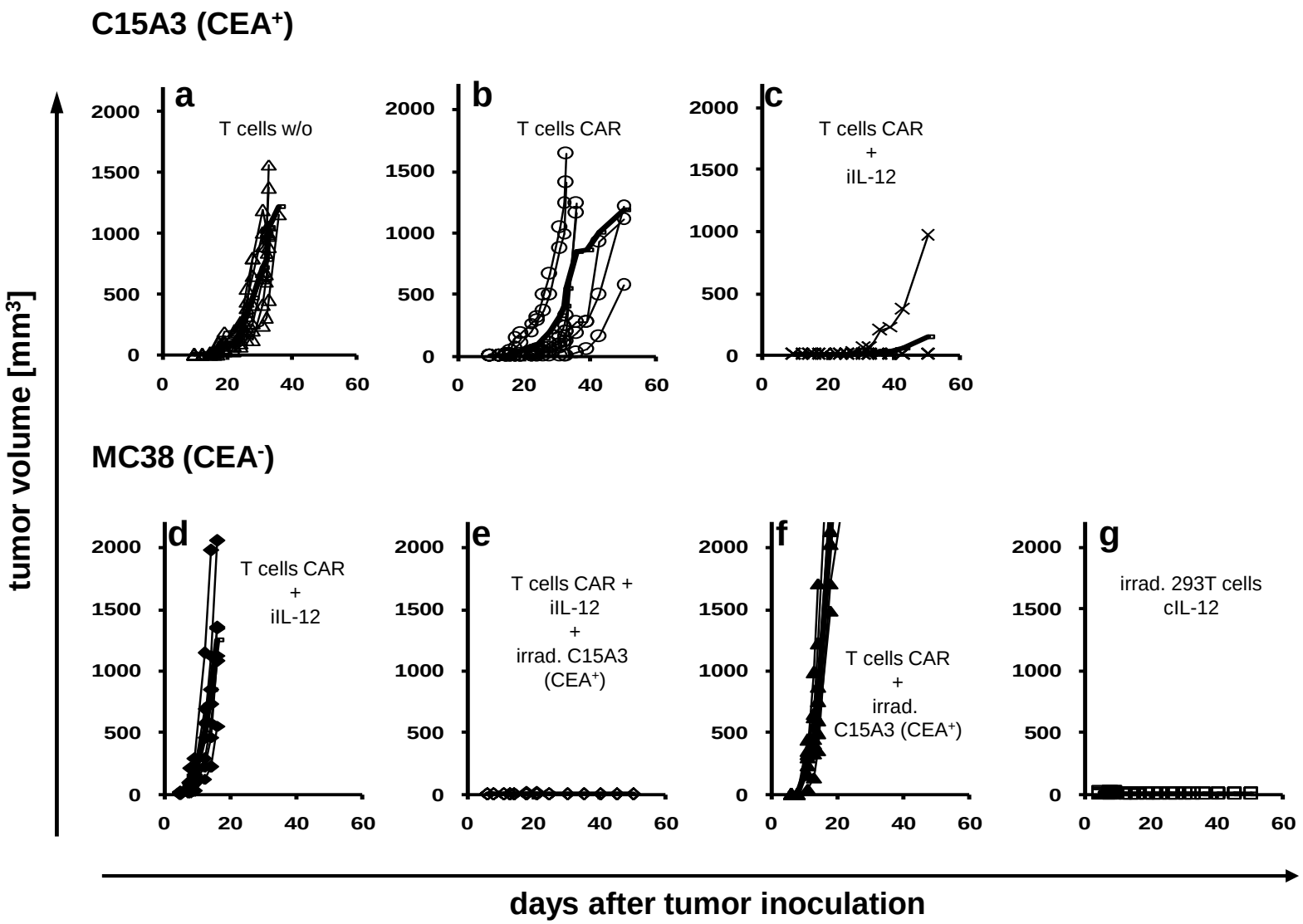
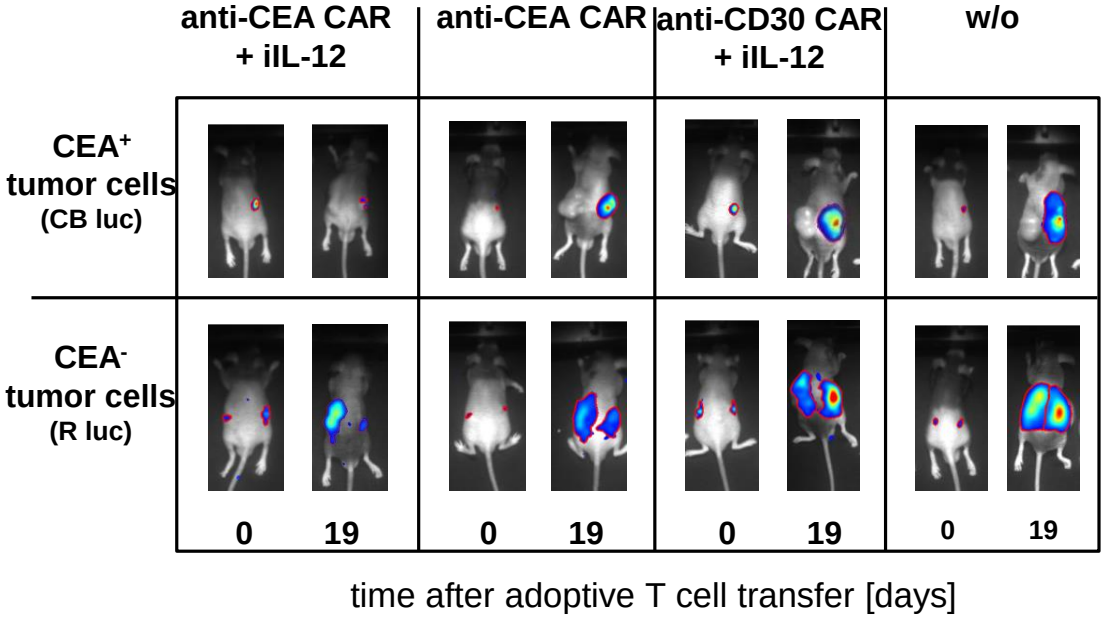
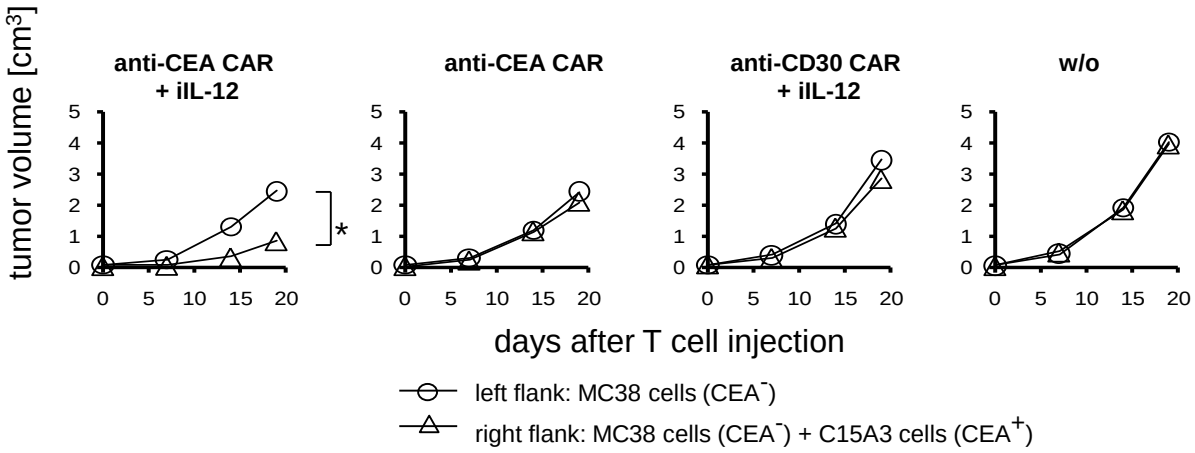
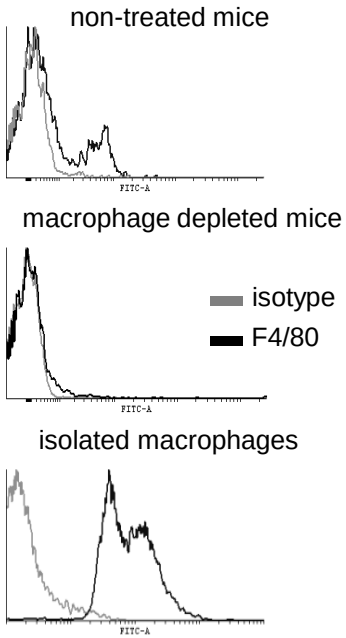


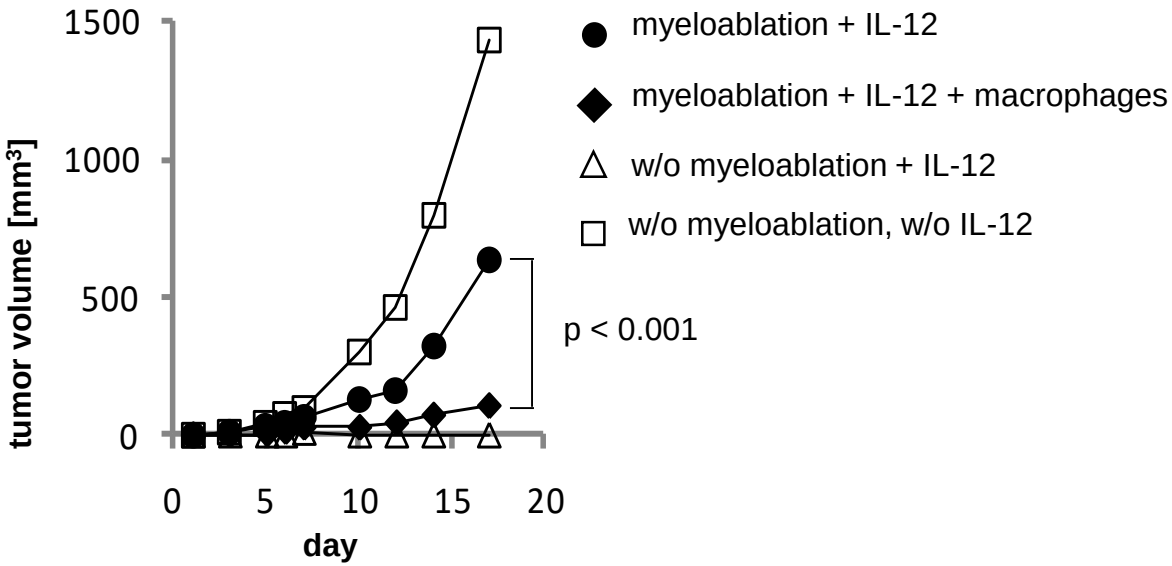
T cells engineered with CAR inducible IL-12 control of CEA$^-$ cancer cells in CEA$^+$ tumors



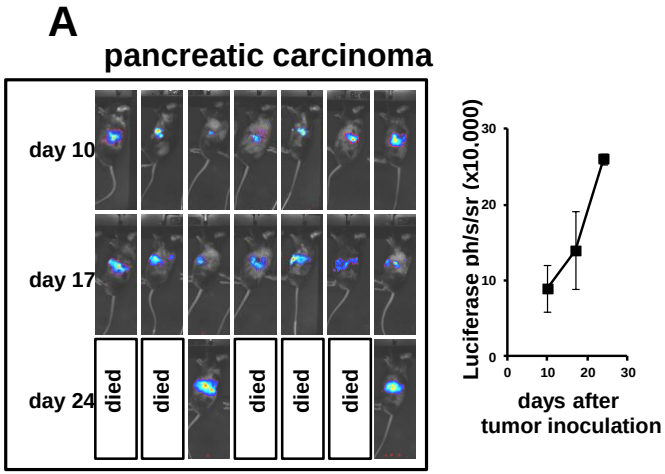


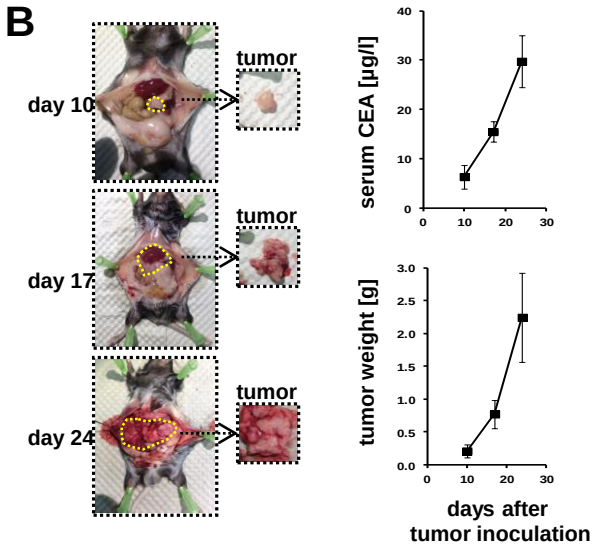
Activated macrophages are involved in killing CEA$^-$ tumor cells

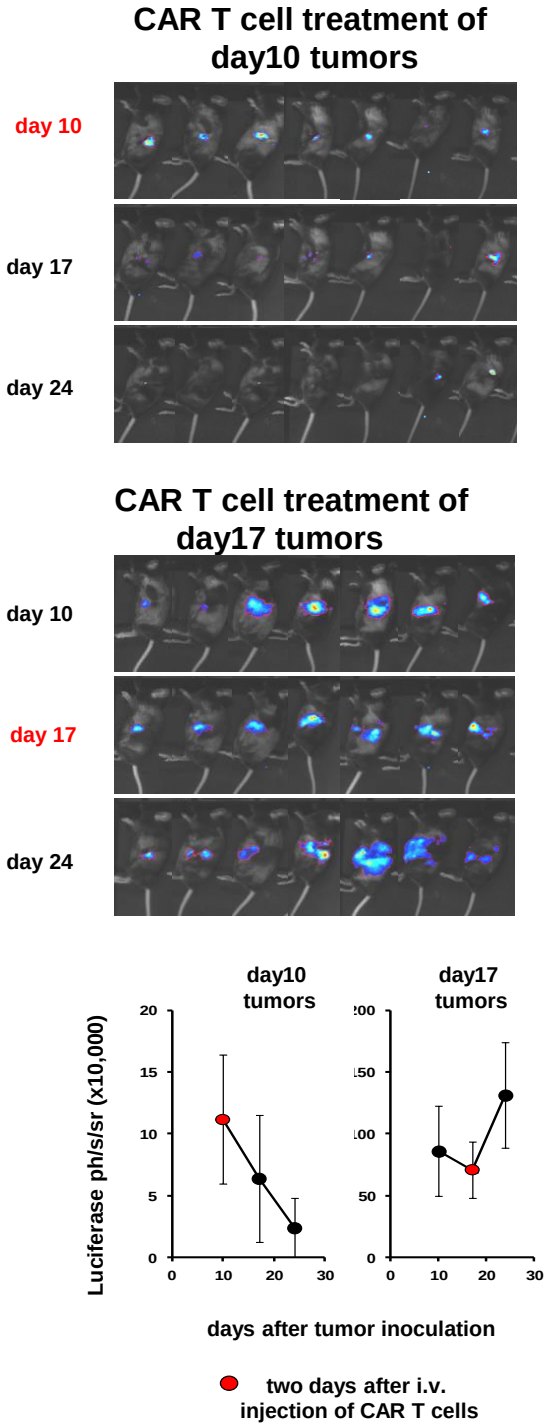




CAR T cell treatment of advanced tumors fails

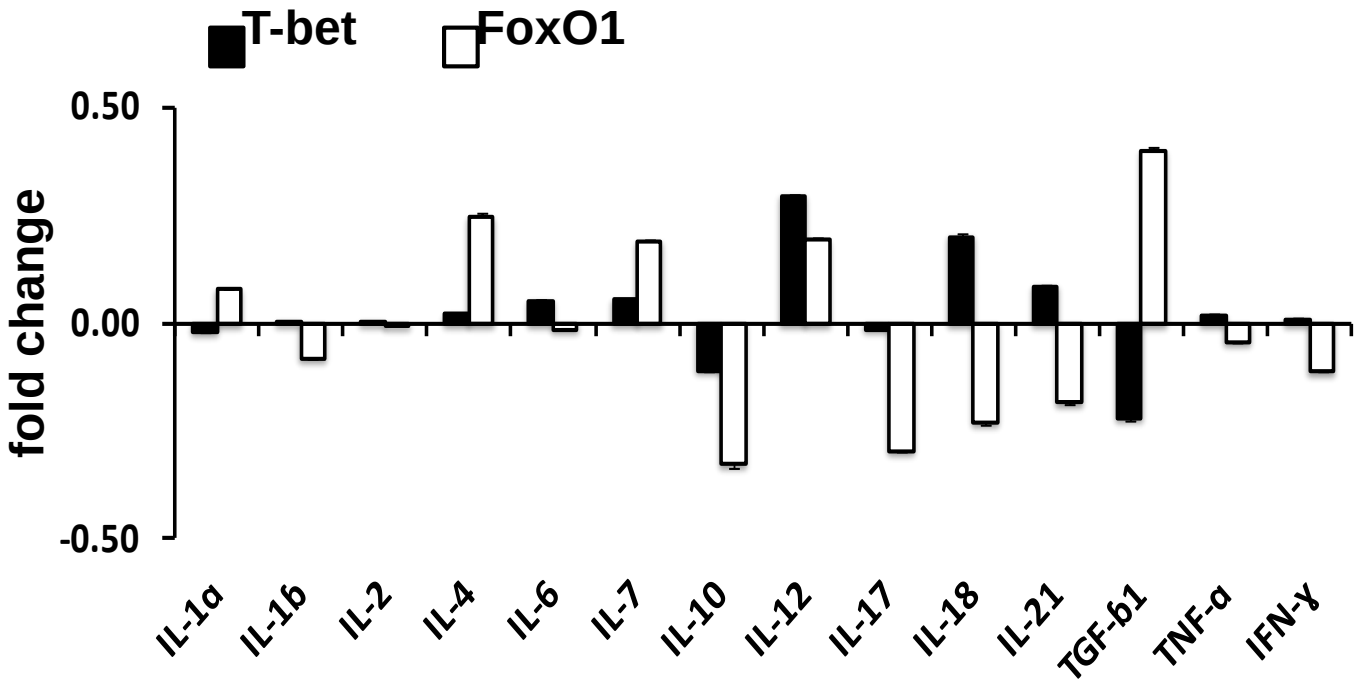






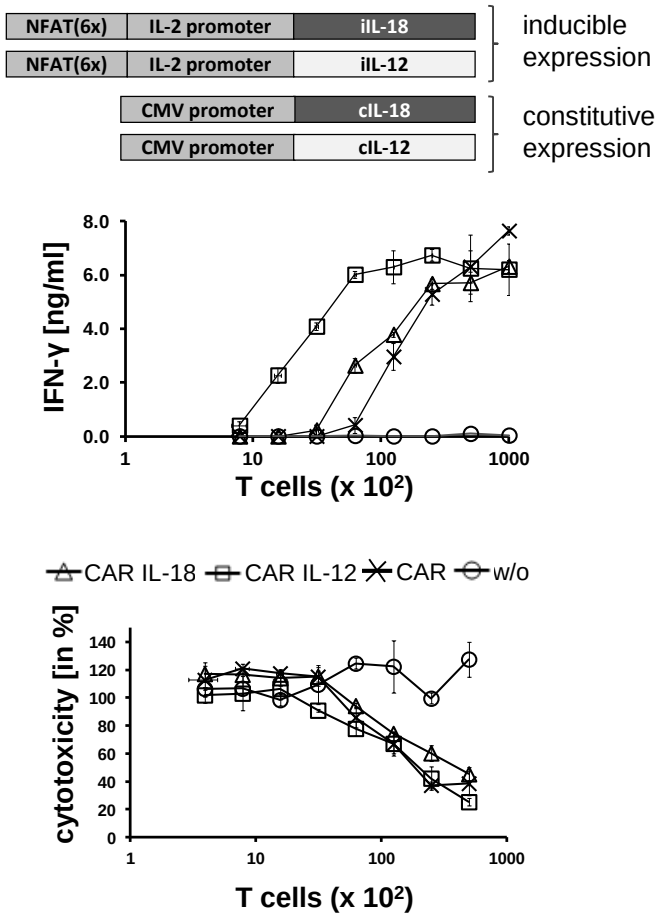
Chmielewski et al., Cell Reports 2017

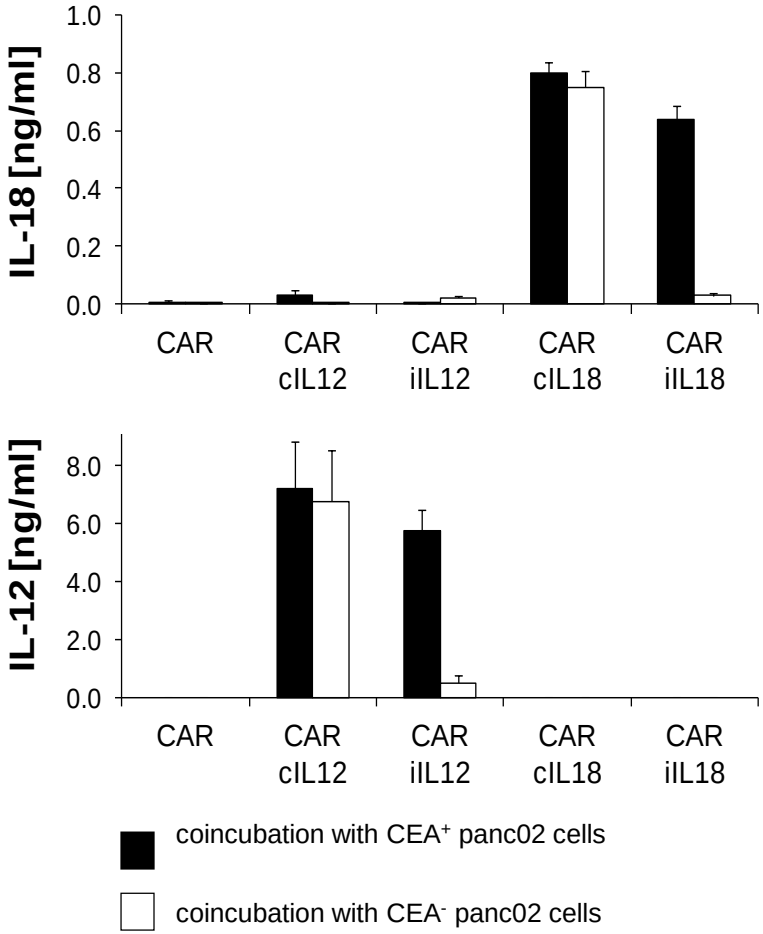
IL-18 induces T-bet^{high} FoxO1^{low} effector T cells



Chmielewski et al., Cell Reports 2017

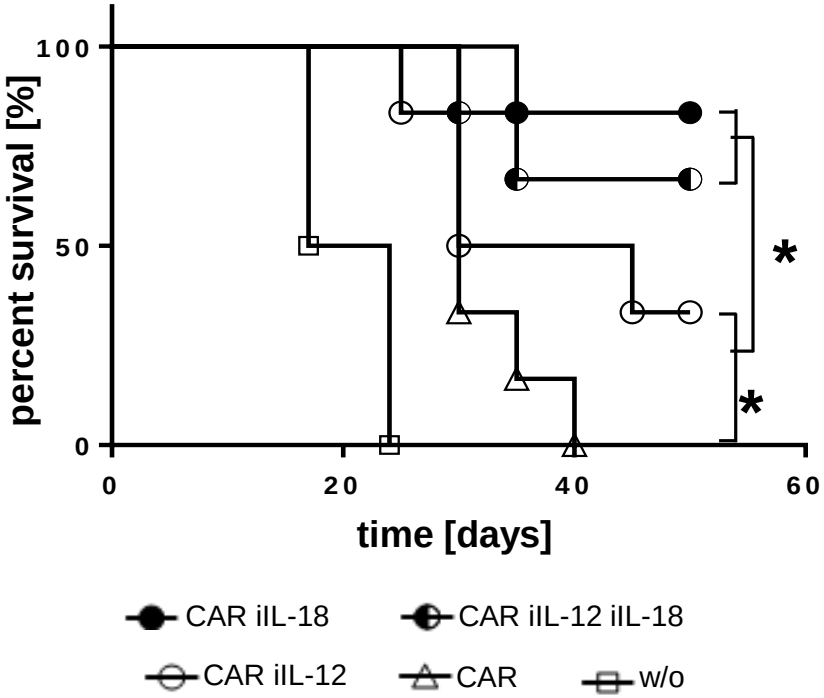
CAR T cells with inducible IL-18





Chmielewski et al., Cell Reports 2017

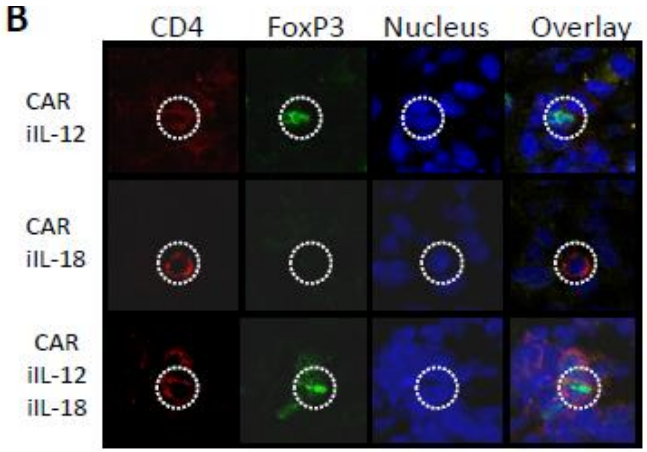
CAR T cells with inducible IL-18 improve survival of tumor bearing mice

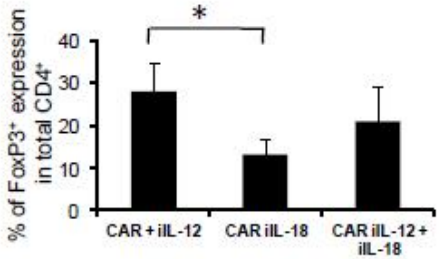


Chmielewski et al., Cell Reports 2017

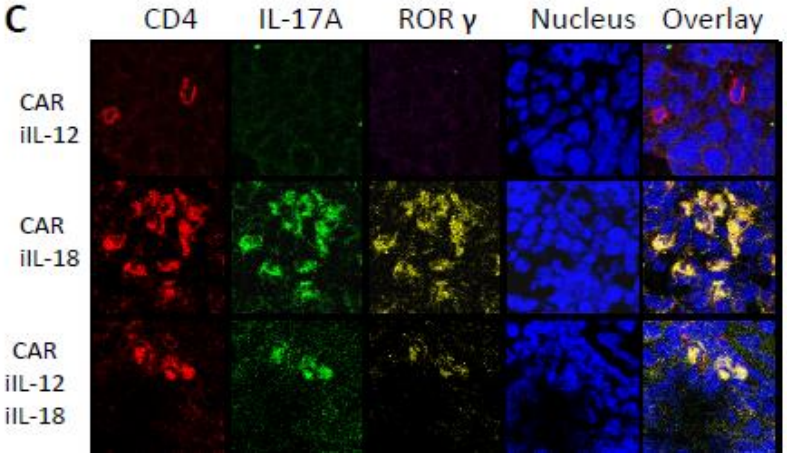
IL-18 CAR T cells modulate the immune environment

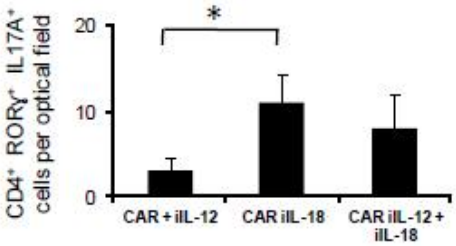
Decrease in Treg cells





Increase in Th17 cells





Chmielewski et al., Cell Reports 2017

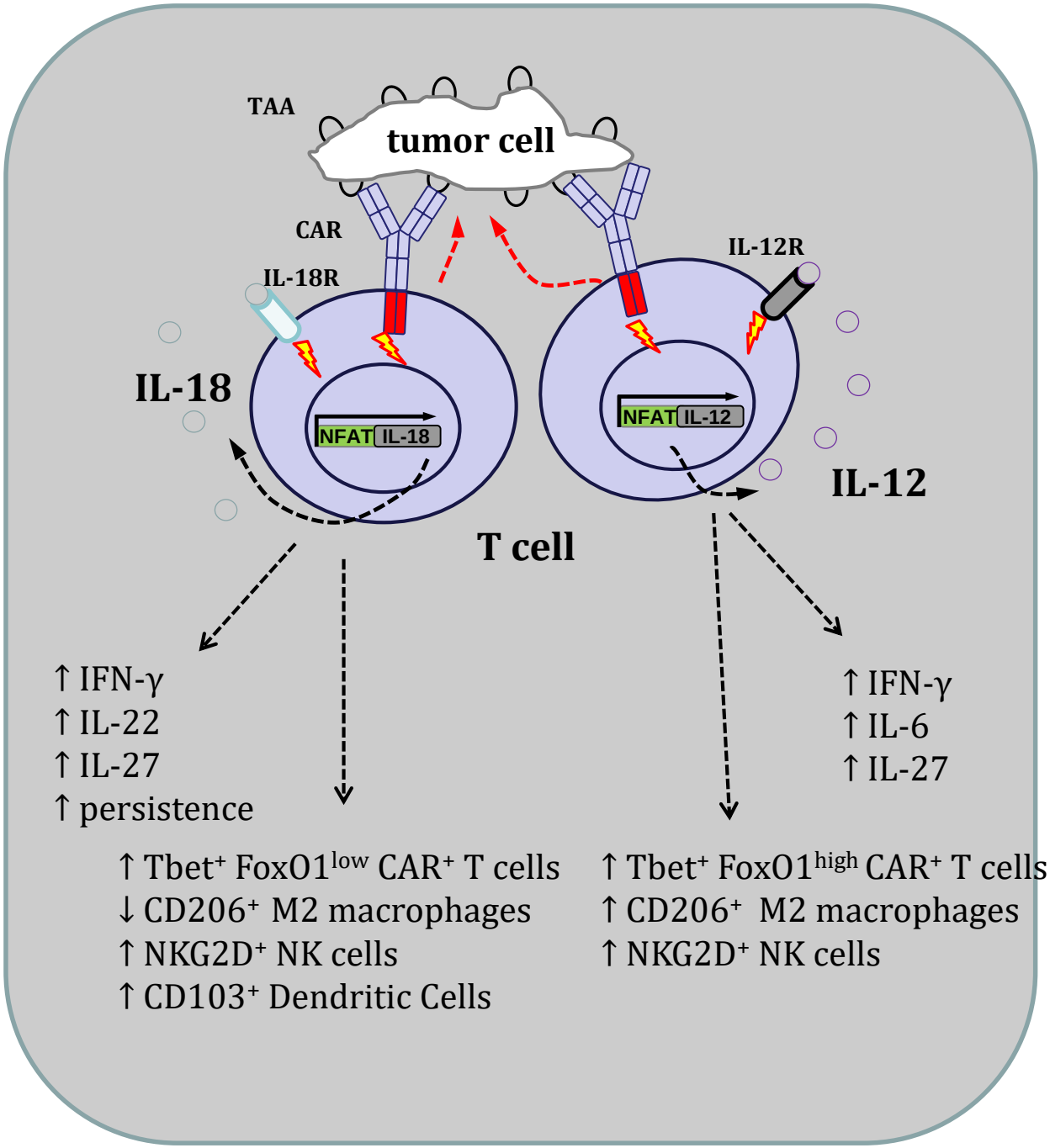
Therapy-related side-effects of T cells engineered with TCR and iIL-12 and/or iIL-18

treatment	maximum weight loss[a]	edema[b]	therapy-related death[c]	overall survival[d]
mock	57%	0%	0%	0%
TCR only	11%	0%	0%	29%
TCR+iIL-12	78%	29%	43%	14%
TCR+iIL-18	0%	0%	0%	57%
TCR+iIL-12+iIL-18	56%	29%	29%	43%

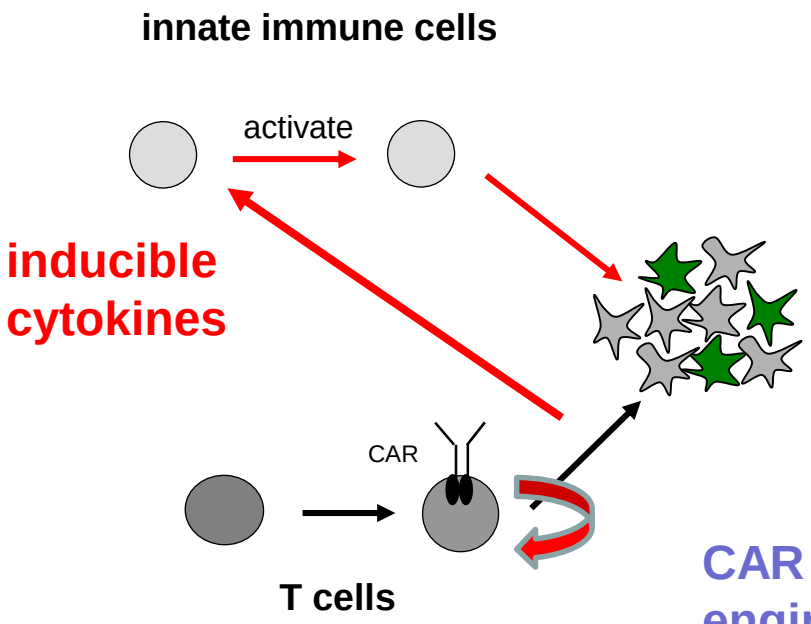
[a] percentage of mice showing a loss of weight exceeding 10% of starting weight (day -15)
[b] percentage of mice developing edema; mice were categorized positive for edema based on visual evaluation by a pathologist and increase in body weight exceeding 3.0% per day over a period of 7 or more days
[c] percentage of mice dying within the first 10 days after T cell administration while no tumor growth was detected
[d] percentage of mice alive at day 45

Kunert et al., Oncoimmunol. 7, e1378842 (2018)

CAR T cells releasing IL-12 or IL-18



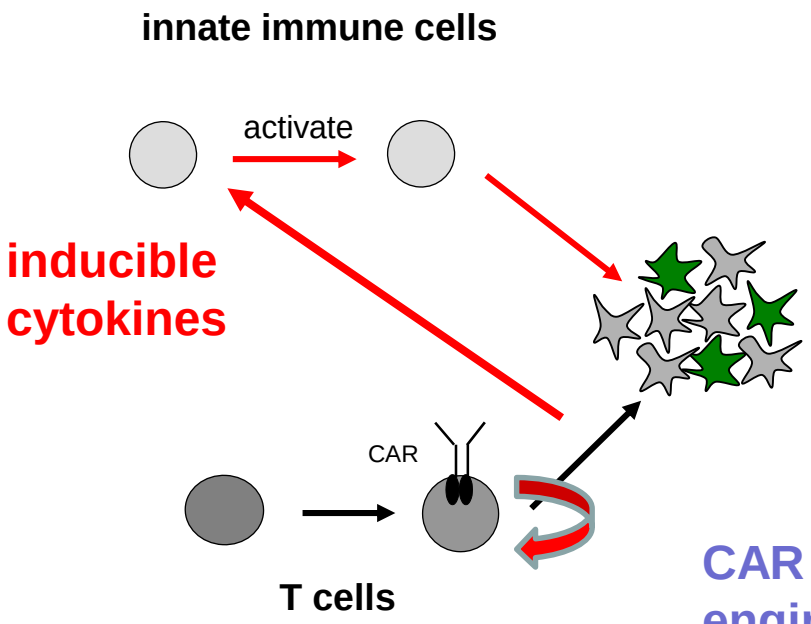
Chmielewski & Abken, 2018



CAR redirected T cells
engineered to secrete (combi-)cytokines
which activate innate cells
to attack those cancer cells
which are not recognized by the CAR.

TRUCKs

T cells **r**edirected for antigen-**u**nrestricted **c**ytokine-initiated **k**illing



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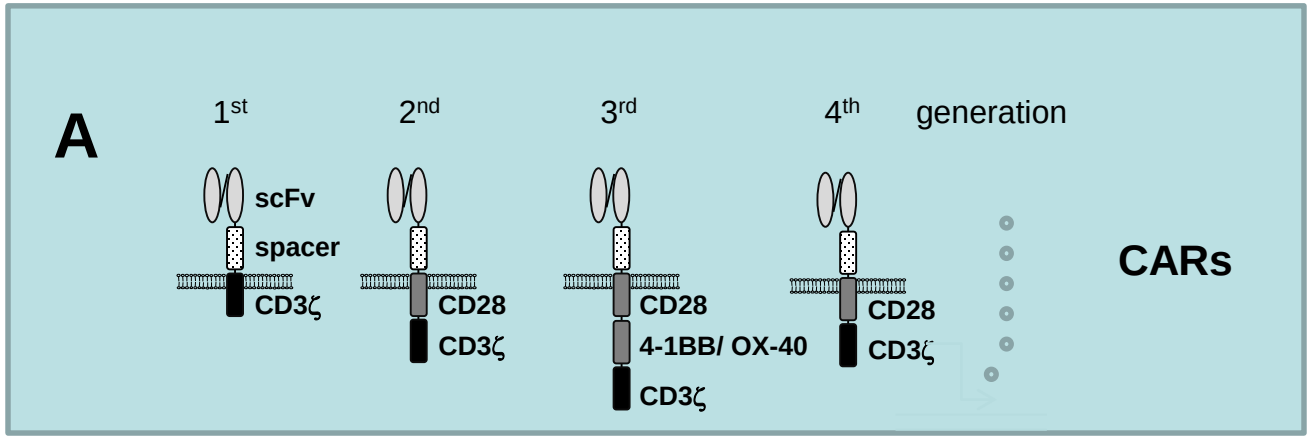
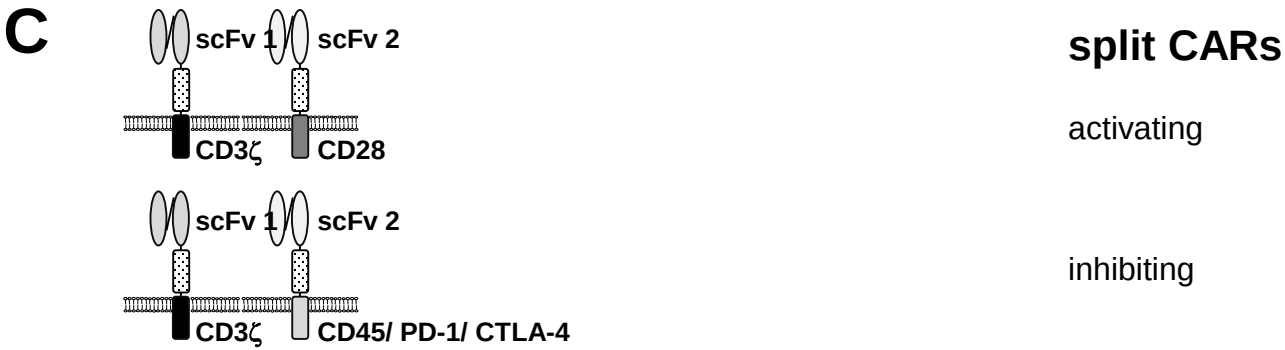

A
1st
2nd
3rd
4th
generation
scFv
spacer
CD3ζ
CD28
CD3ζ
CD28
4-1BB/ OX-40
CD3ζ
CD28
CD3ζ
CARs


B
CD45/ PD-1/ CTLA-4
iCAR

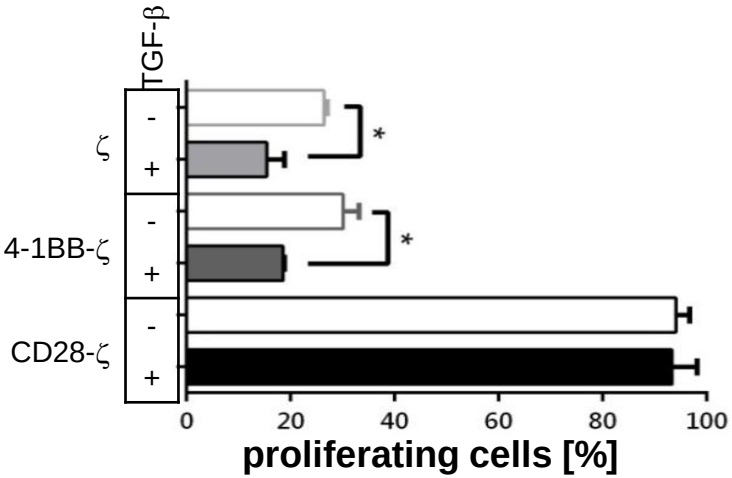

C
scFv 1
scFv 2
CD3ζ
CD28
split CARs
activating
scFv 1
scFv 2
CD3ζ
CD45/ PD-1/ CTLA-4
inhibiting


D
PD-1
CD28
switch receptor

Next generation TRUCKs:

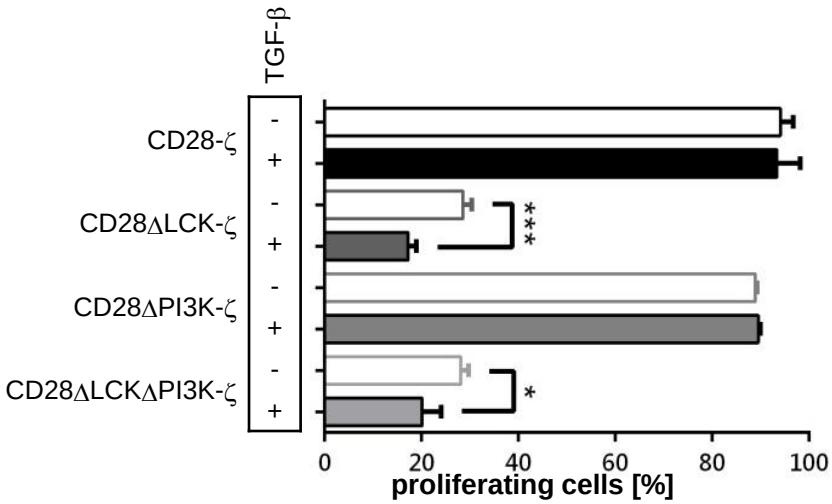
How to overcome TGF-β repression of CAR T cells in solid tumor lesions?

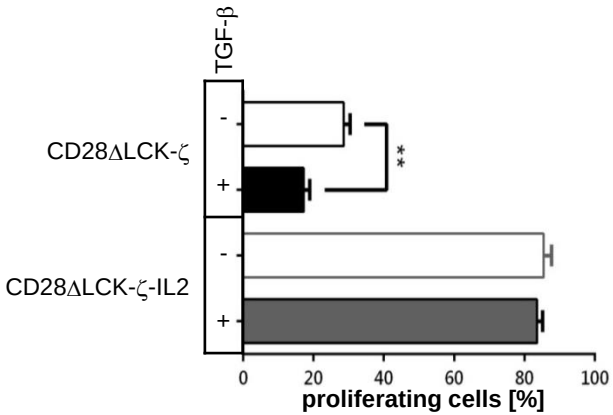
CD28-ζ CAR, but not 4-1BB-ζ CAR, counteracts TGF-β1 repression

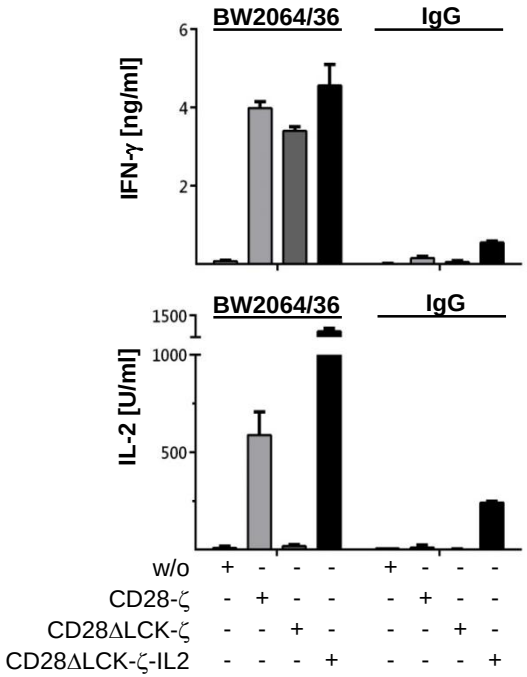


Golumba-Nagy et al., Mol. Ther., 2018

TGF-β1 resistance is mediated by IL-2

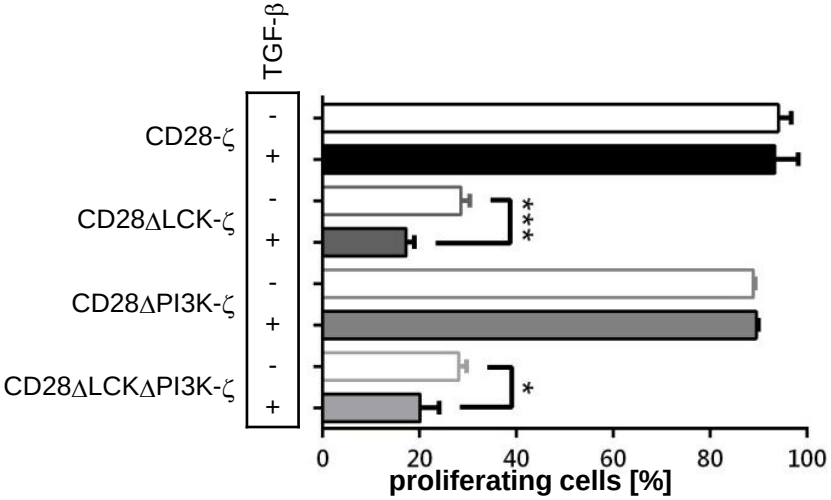


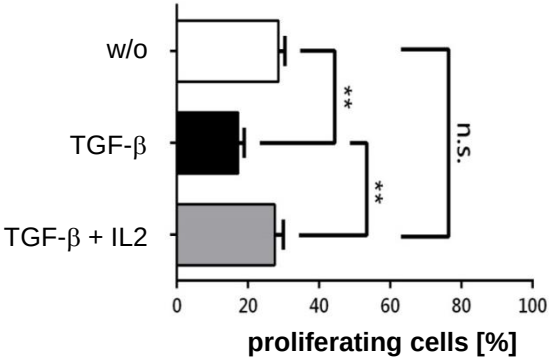


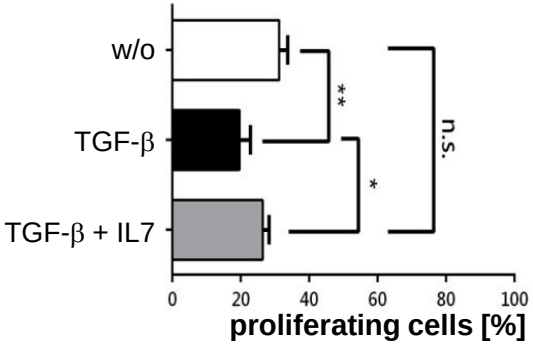


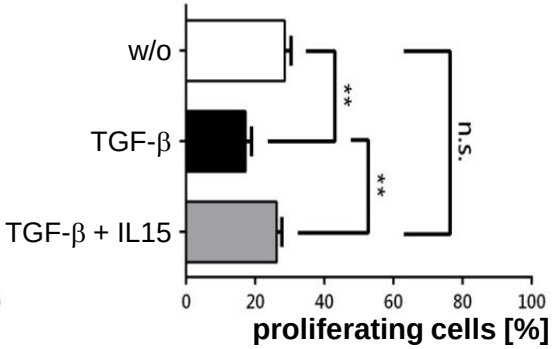
Golumba-Nagy et al., Mol. Ther., 2018

TGF-β1 resistance is mediated by IL-2 which can be replaced by IL-7



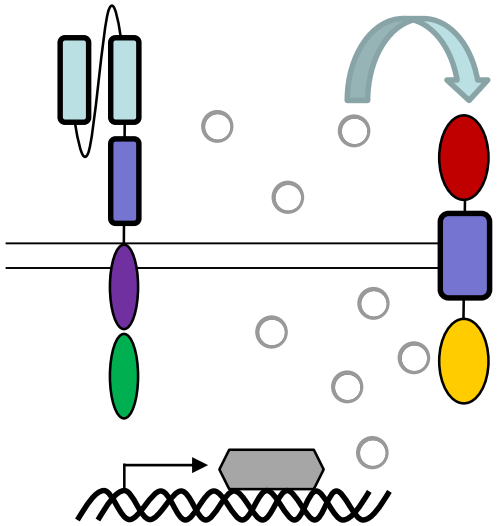






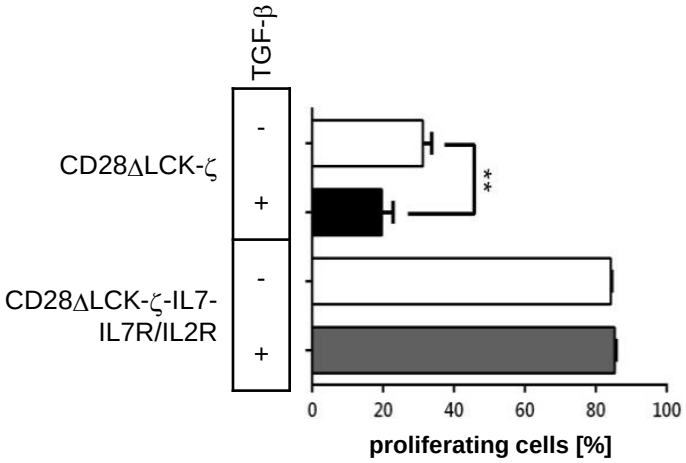
Golumba-Nagy et al., Mol. Ther., 2018

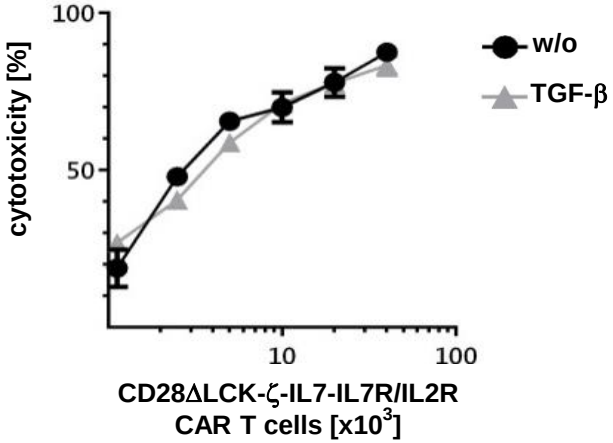
A TRUCK with inducible release of IL-7 and an artificial IL-7R/IL-2Rβ receptor provides resistance to TGF-β1



Golumba-Nagy et al., Mol. Ther., 2018

A TRUCK with inducible release of IL-7 and an artificial IL-7R/IL-2Rβ receptor provides resistance to TGF-β1





Golumba-Nagy et al., Mol. Ther., 2018

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