



Society for Immunotherapy of Cancer

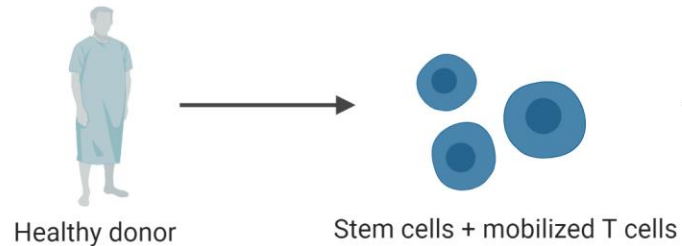
IL-18 and Adoptive Cell Therapies

Simone Minnie, PhD

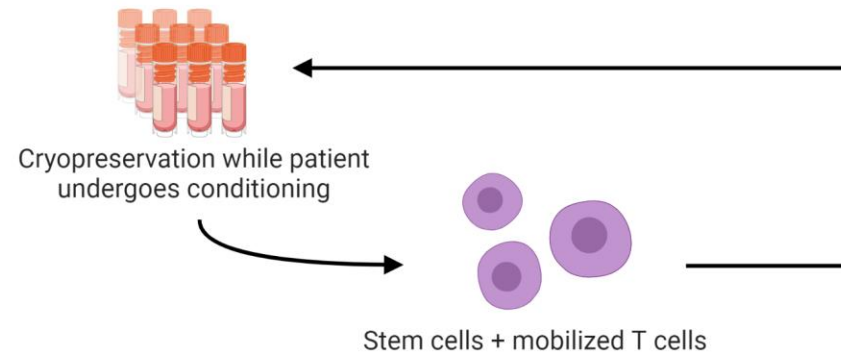
18th July 2022

Adoptive Cell Therapies

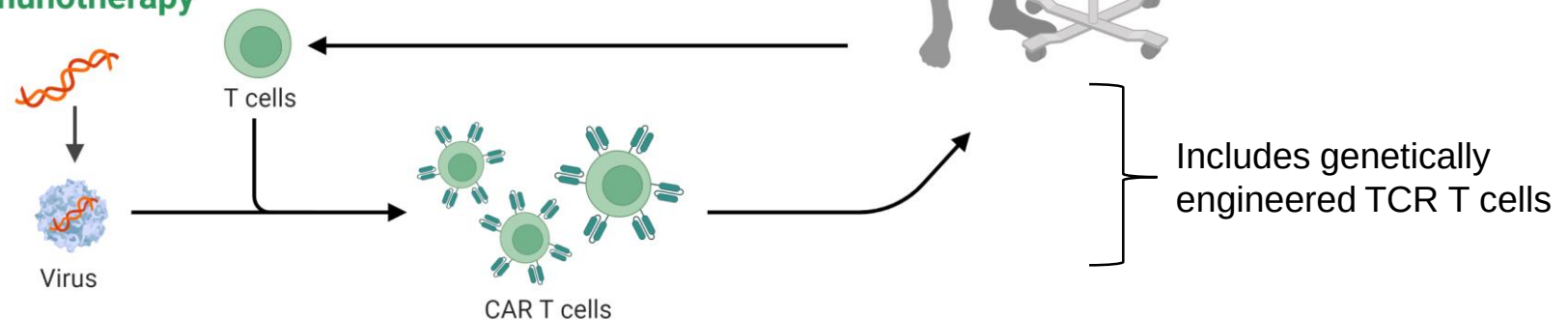
Allogeneic Stem Cell Transplantation



Autologous Stem Cell Transplantation / TIL harvest and infusion



Engineered Cell Immunotherapy

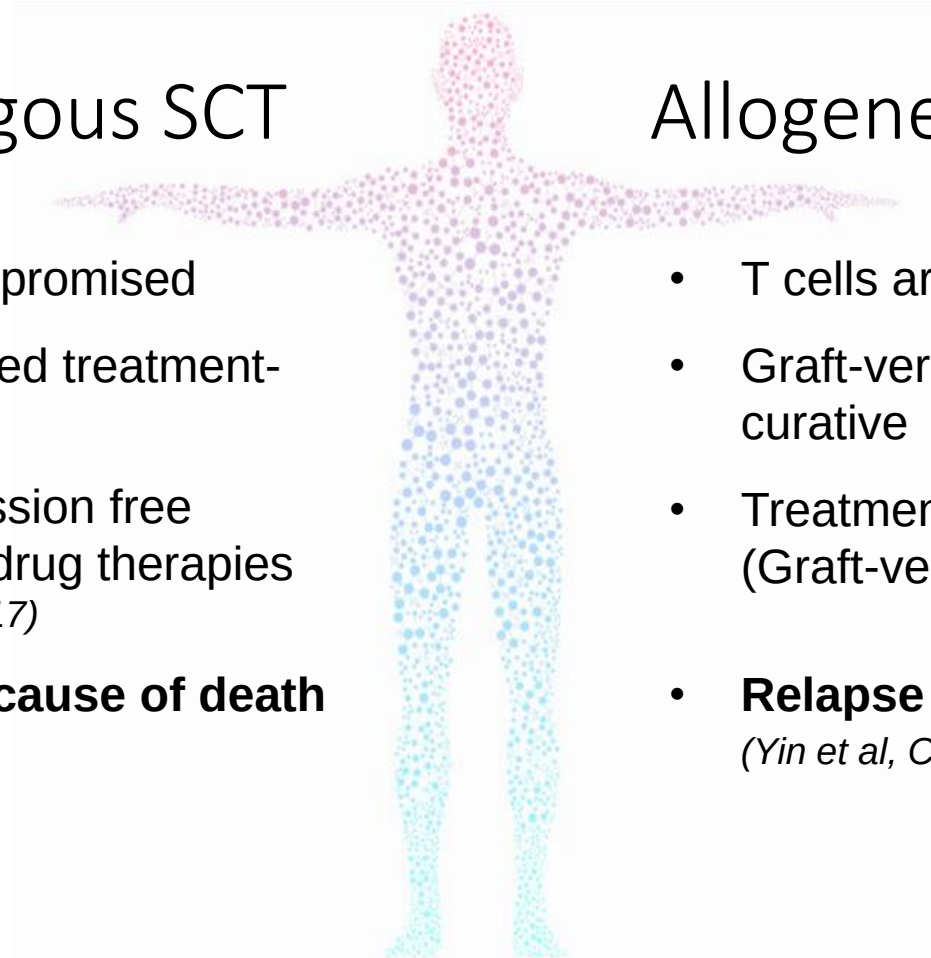


Autologous SCT

- T cell fitness likely compromised
- No HLA disparity - limited treatment-related mortality
- ASCT provides progression free survival benefit above drug therapies (*Attal et al. N Engl J Med, 2017*)
- **Relapse is the major cause of death**

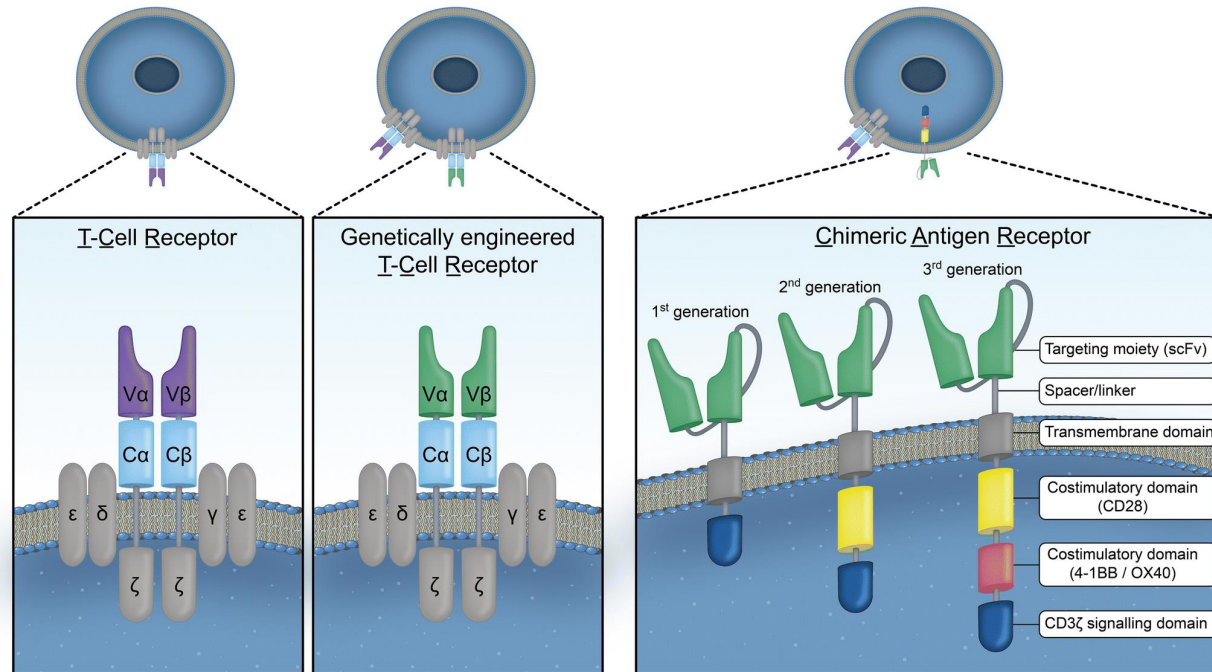
Allogeneic SCT

- T cells are from a healthy donor
- Graft-versus-tumor effect is potentially curative
- Treatment-related mortality often high (Graft-versus-host-disease)
- **Relapse is the major cause of death** (*Yin et al, Cancer Cell Int, 2018*)

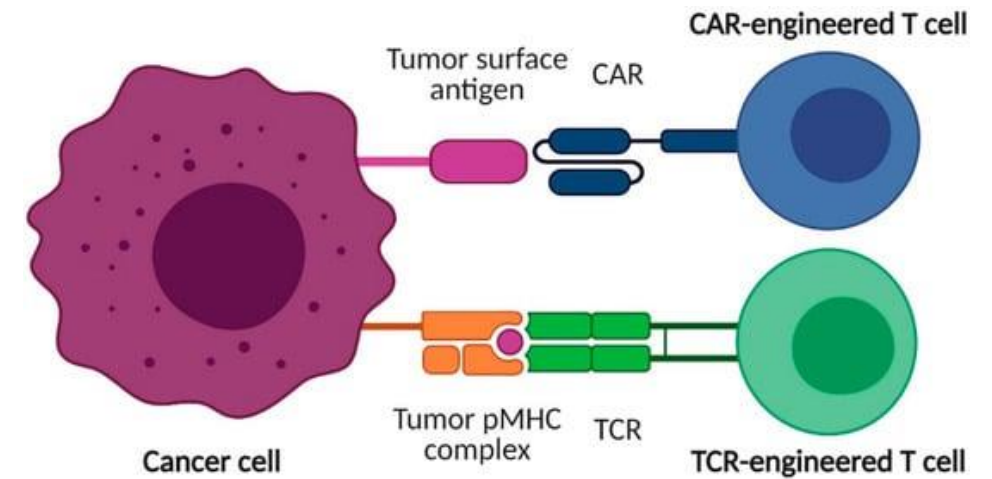


We need to improve anti-tumor efficacy of SCT for hematological malignancies

Engineered T Cell Immunotherapy



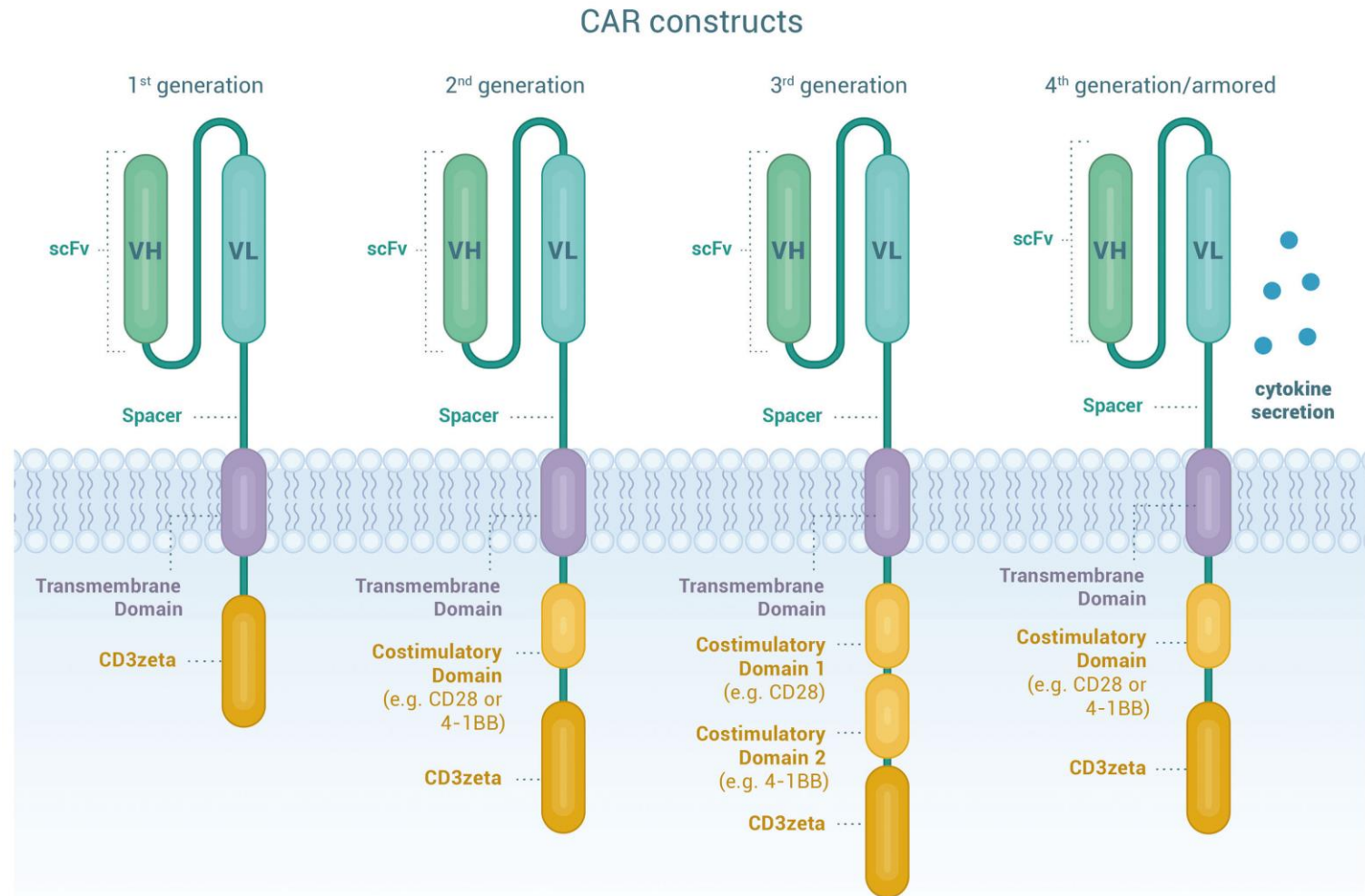
Met, Ö., Jensen, K.M., Chamberlain, C.A. *et al. Semin Immunopathol* **41**, 49–58 (2019).

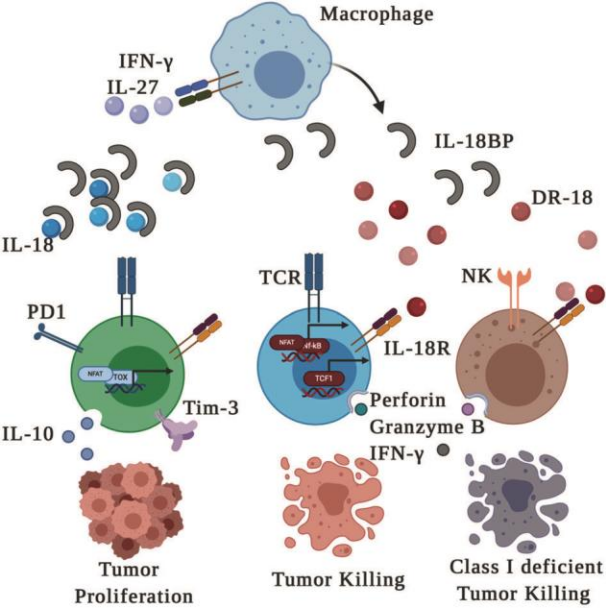


Campillo-Davo D, Anguille S, Lion E. *Cancers*. 2021; 13(18):4519.

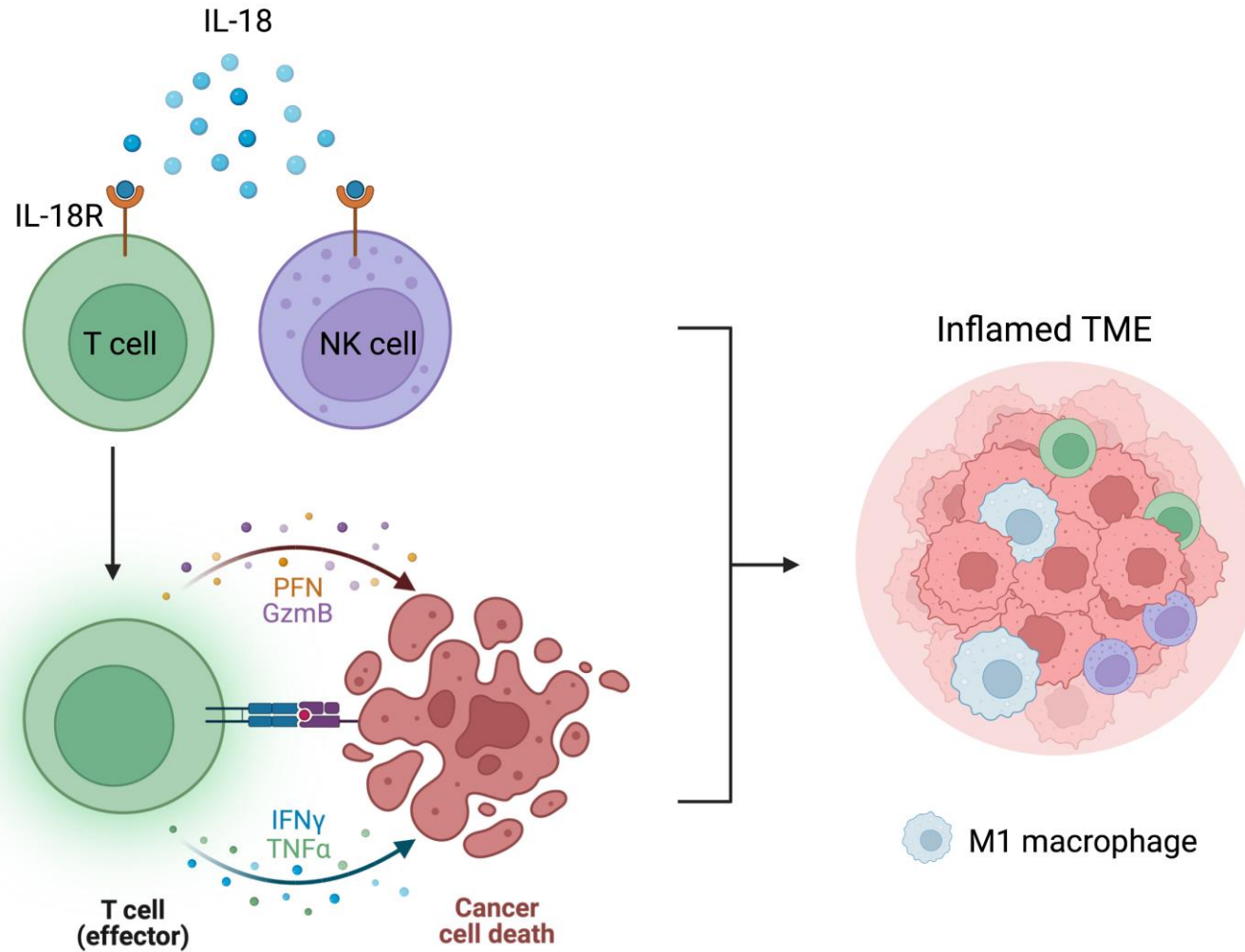
'Armored' CAR T cells

- Cytokine secretion can be constitutive or induced by CAR activation
- Cytokines include:
 - IL-12
 - ↑ IFN γ , granzyme B etc.
 - Pegram et al. *Blood* 2012
 - Yeku et.al *Sci. Rep.* 2017
 - Dose limiting toxicity in TILS
 - Zhang et al. *Clin. Cancer Res.* 2015
 - CAR T cell trials still ongoing
 - IL-15
 - Hoyos et al. *Leukemia* 2010
 - **IL-18**





lar Immunotherapy Partner

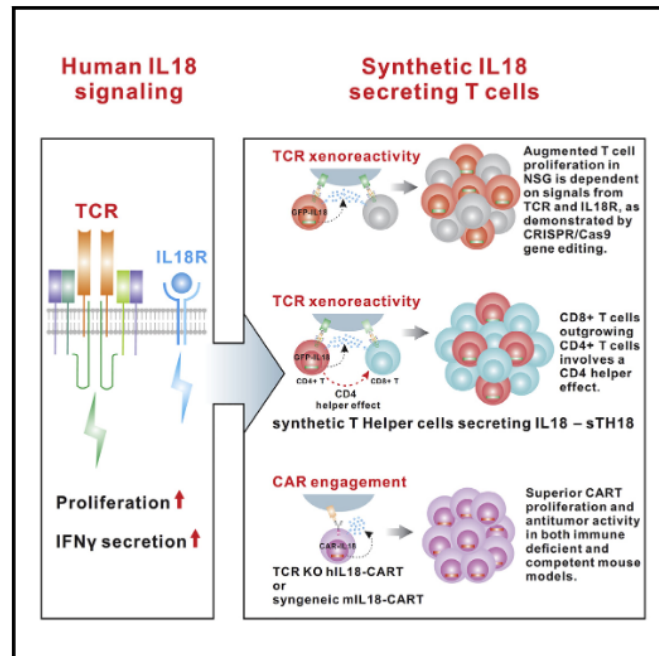


'Armored' CAR T cells expressing IL-18

Cell Reports

Augmentation of Antitumor Immunity by Human and Mouse CAR T Cells Secreting IL-18

Graphical Abstract



Report

Authors

Biliang Hu, Jiangtao Ren, Yanping Luo, ..., John Scholler, Yangbing Zhao, Carl H. June

Correspondence

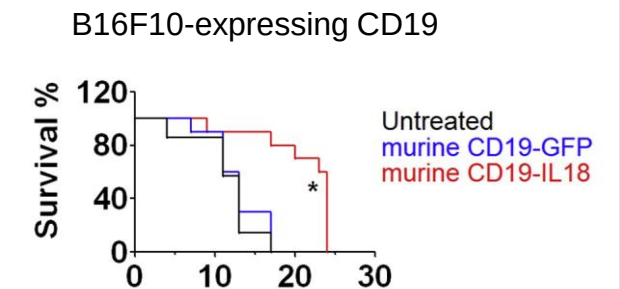
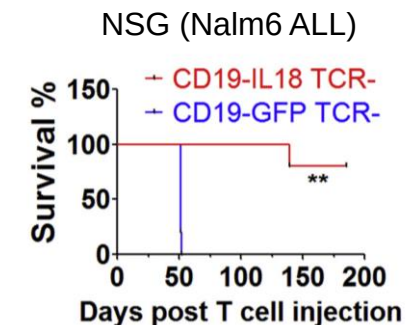
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In Brief

Hu et al. create IL-18-secreting chimeric antigen receptor T (IL-18-CAR T) cells to significantly boost CAR T cell proliferation and antitumor activity.

Highlights

- Augmented proliferation of synthetic IL-18-expressing human T cells
- rIL-18 augments IFN- γ secretion and proliferation of anti-CD3 activated T cells
- IL-18-secreting CD4 $^{+}$ T cells promote CD8 $^{+}$ T cells through a helper effect
- IL-18 CAR T cells have superior proliferation and antitumor activity in mouse models

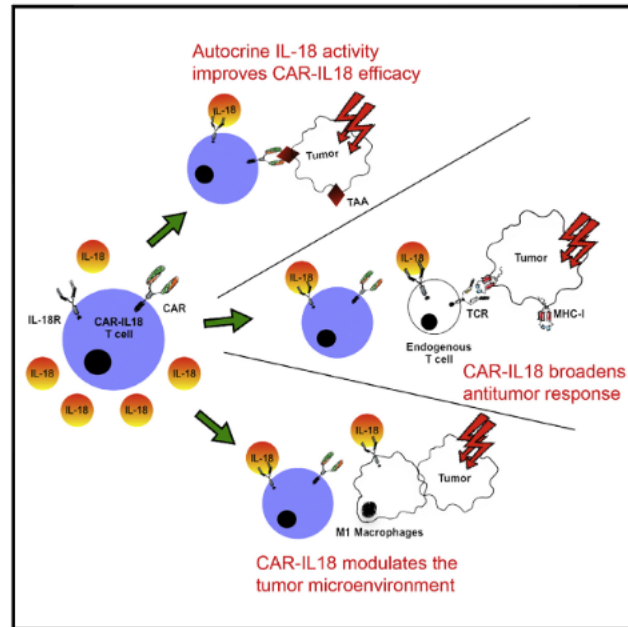


'Armored' CAR T cells expressing IL-18

Cell Reports

Engineered Tumor-Targeted T Cells Mediate Enhanced Anti-Tumor Efficacy Both Directly and through Activation of the Endogenous Immune System

Graphical Abstract



Authors

Mauro P. Avanzi, Oladapo Yeku, Xinghuo Li, ..., Anthony F. Daniyan, Matthew H. Spitzer, Renier J. Brentjens

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In Brief

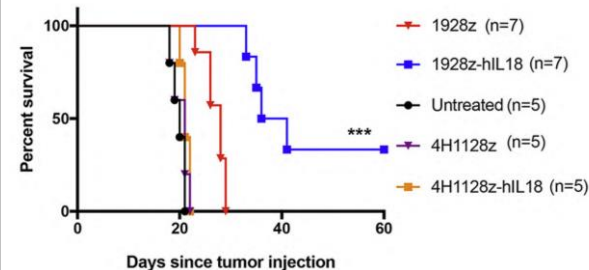
Avanzi et al. generate CAR T cells that secrete IL-18 and show improved activity in syngeneic hematologic and solid tumor models without prior preconditioning. They further show enhanced recruitment and anti-tumor activity of endogenous T cells.

Article

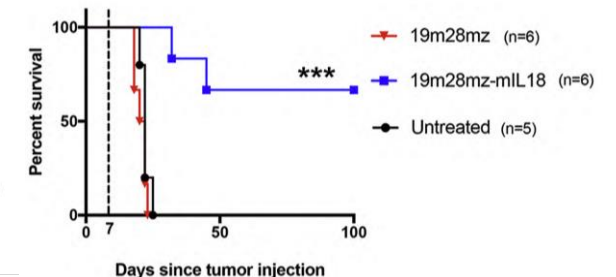
Highlights

- IL-18-secreting CAR T cells enhance anti-tumor efficacy via IL-18 autocrine stimulation
- IL-18-secreting CAR T cells favorably alter EL4 tumor microenvironment
- IL-18-secreting CAR T cells enhance the anti-tumor response of endogenous T cells
- IL-18-secreting CAR T cells are efficacious in syngeneic models without preconditioning

Xenograft (Nalm6 ALL)



C57BL/6 EL4hCD19+ tumors

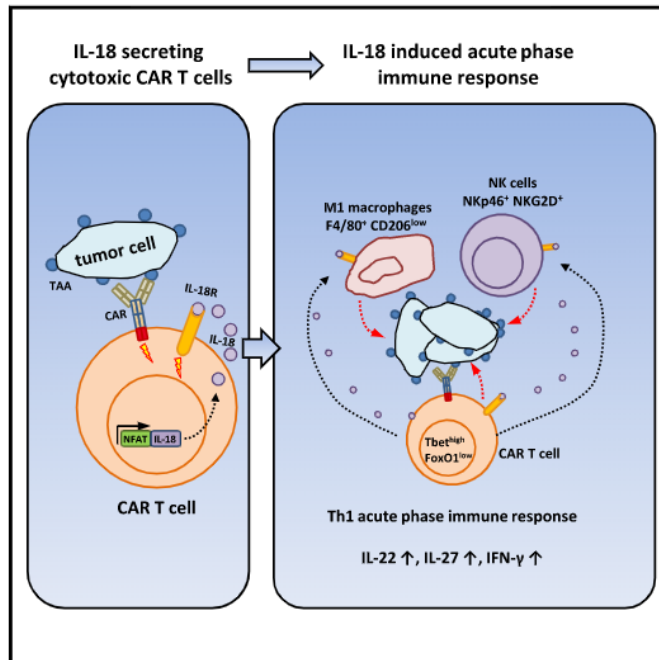


'Armored' CAR T cells expressing IL-18

Cell Reports

CAR T Cells Releasing IL-18 Convert to T-Bet^{high} FoxO1^{low} Effectors that Exhibit Augmented Activity against Advanced Solid Tumors

Graphical Abstract



Authors

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In Brief

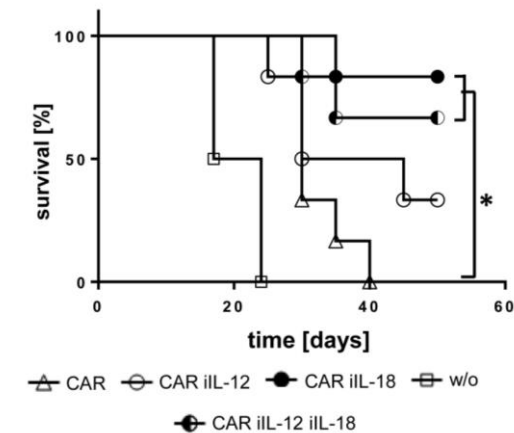
Chmielewski and Abken engineer IL-18-secreting CAR T cells (IL-18 TRUCKs) to convert cytotoxic T cells to Tbet^{high} FoxO1^{low} and shape a pro-inflammatory environment in advanced tumors.

Article

Highlights

- CAR T cells releasing IL-18 upon CAR stimulation convert to Tbet^{high} FoxO1^{low} T cells
- IL-18 TRUCK treatment induces a Th1 acute phase response in the tumor
- IL-18 TRUCK cells improve survival of mice with advanced pancreatic and lung tumors

Advanced pancreatic tumor model



NFAT-driven cytokine production

huCART19-IL18 in clinical trials

- Trial identifier: NCT04684563
- Phase 1 dose finding and safety trial (currently recruiting)
- Patients with chronic lymphocytic leukemia or non-hodgkin lymphoma
 - Relapsed/refractory disease
 - Ineligible for/relapsed after ASCT or commercial CAR T cell product

Possible pitfalls of 'armored' CAR T cells

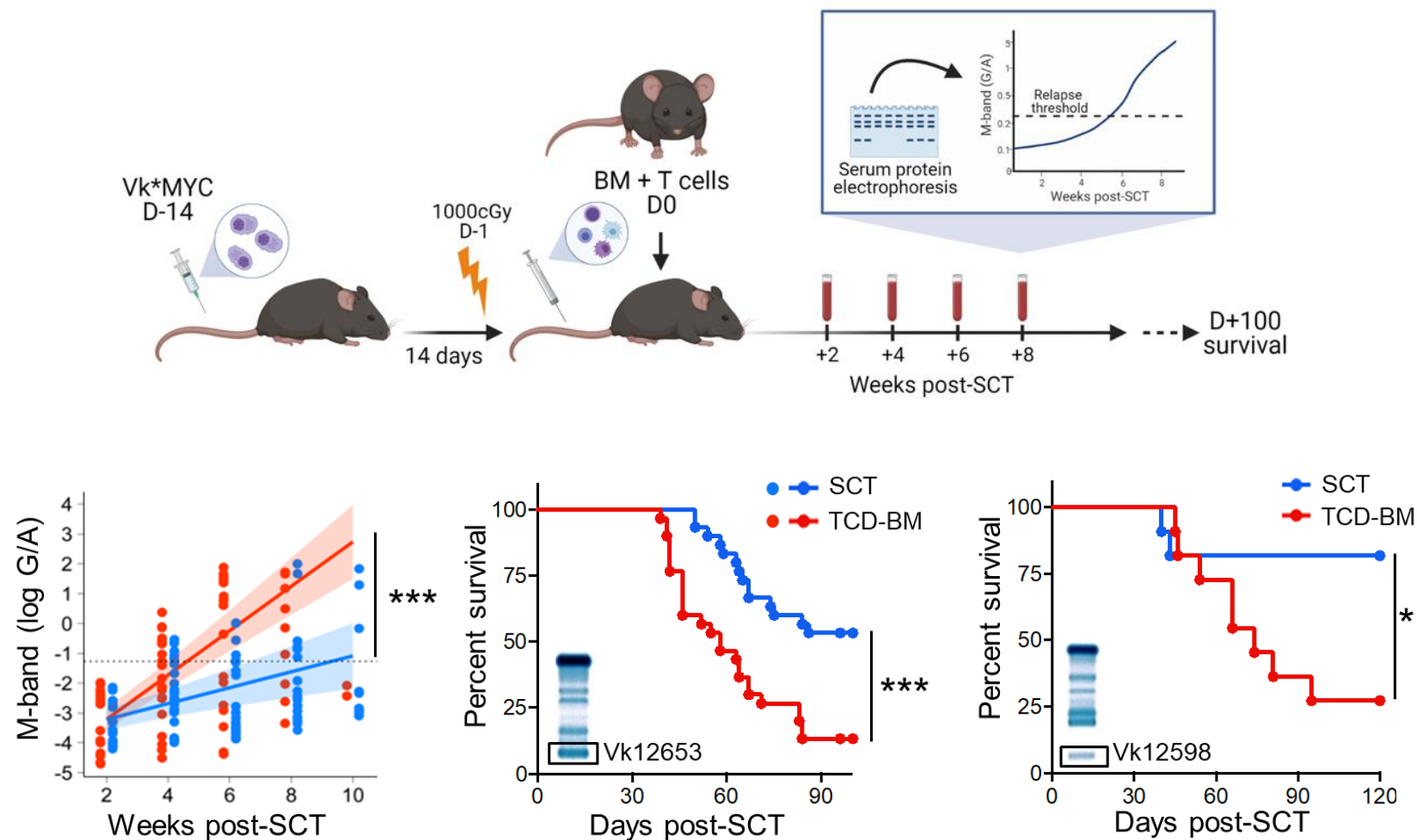
- 1) Toxicity related to constitutive cytokine production – particularly IL-12
- 2) Cytokine and T cell immunotherapies are permanently linked
 - To limit possible cytokine toxicity = eliminating T cells
- 3) IL-18-BP is induced in response to IL-18 as a negative feedback regulator, particularly in the TME!
- Using a dosable cytokine therapy to boost proliferation/function of adoptively transferred T cells addresses limitations #1 + #2
- Decoy-resistant IL-18 addresses limitation #3

Decoy-resistant IL-18 in hematological malignancies

Using preclinical murine models to (hopefully)
inform clinical translation

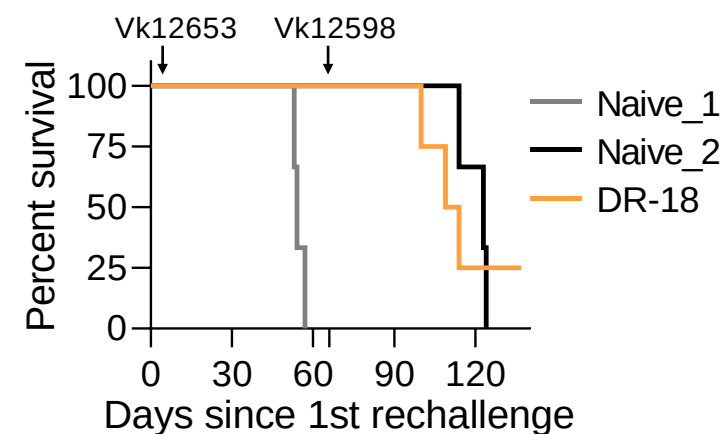
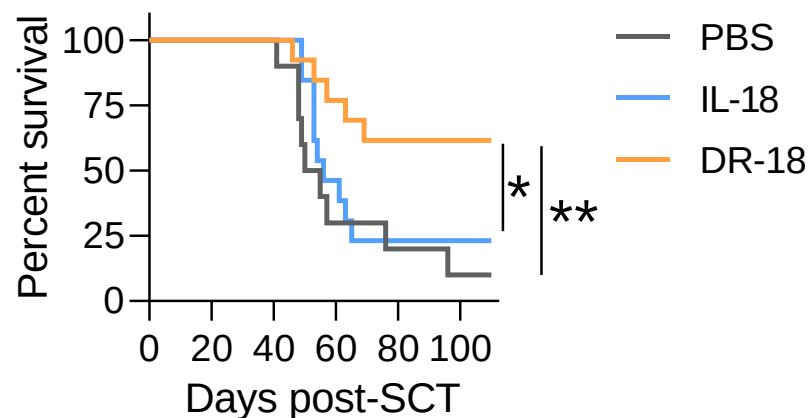
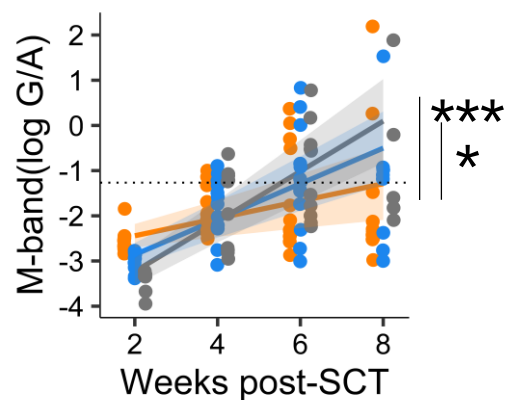
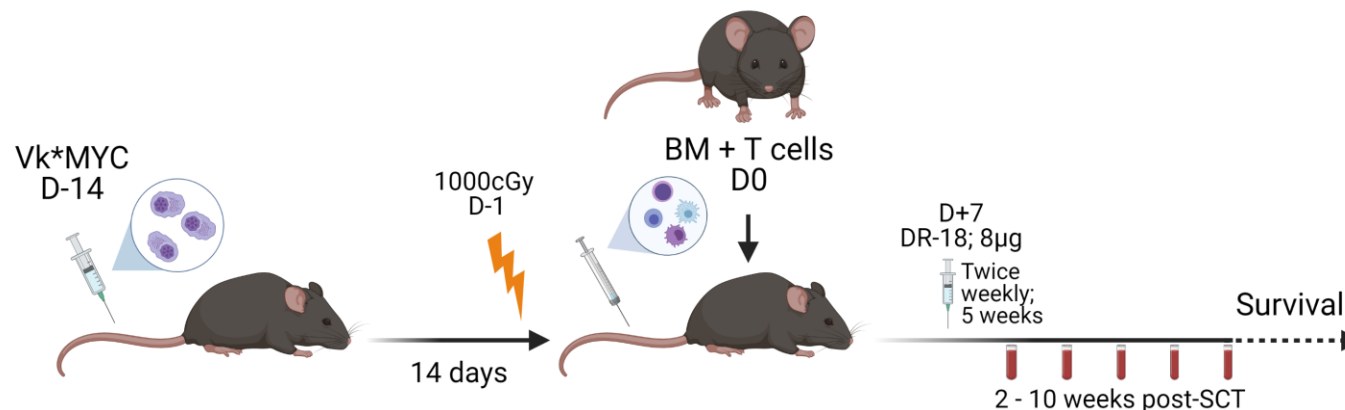


Murine Model of Autologous SCT



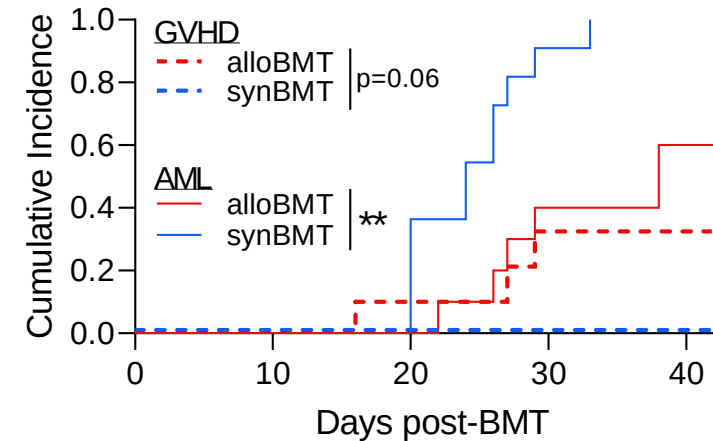
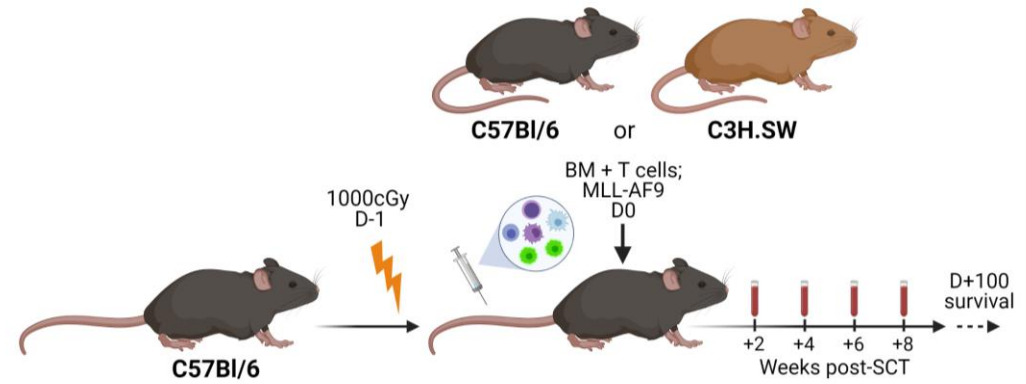
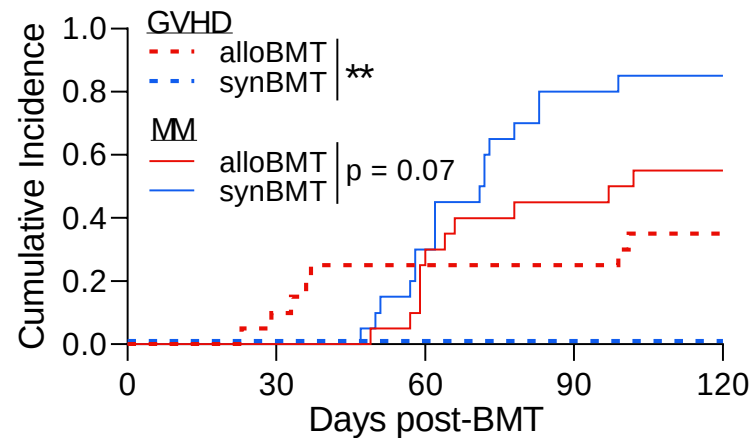
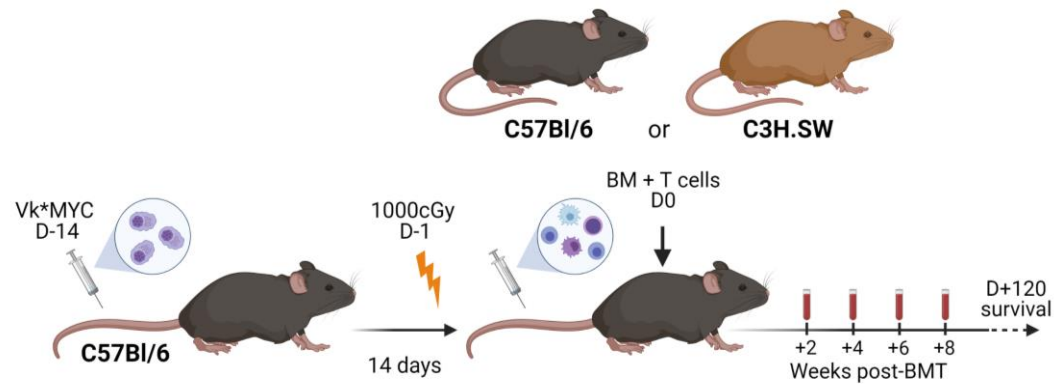
Adoptively transferred T cells limit relapse post-SCT

DR-18 enhances anti-myeloma effects

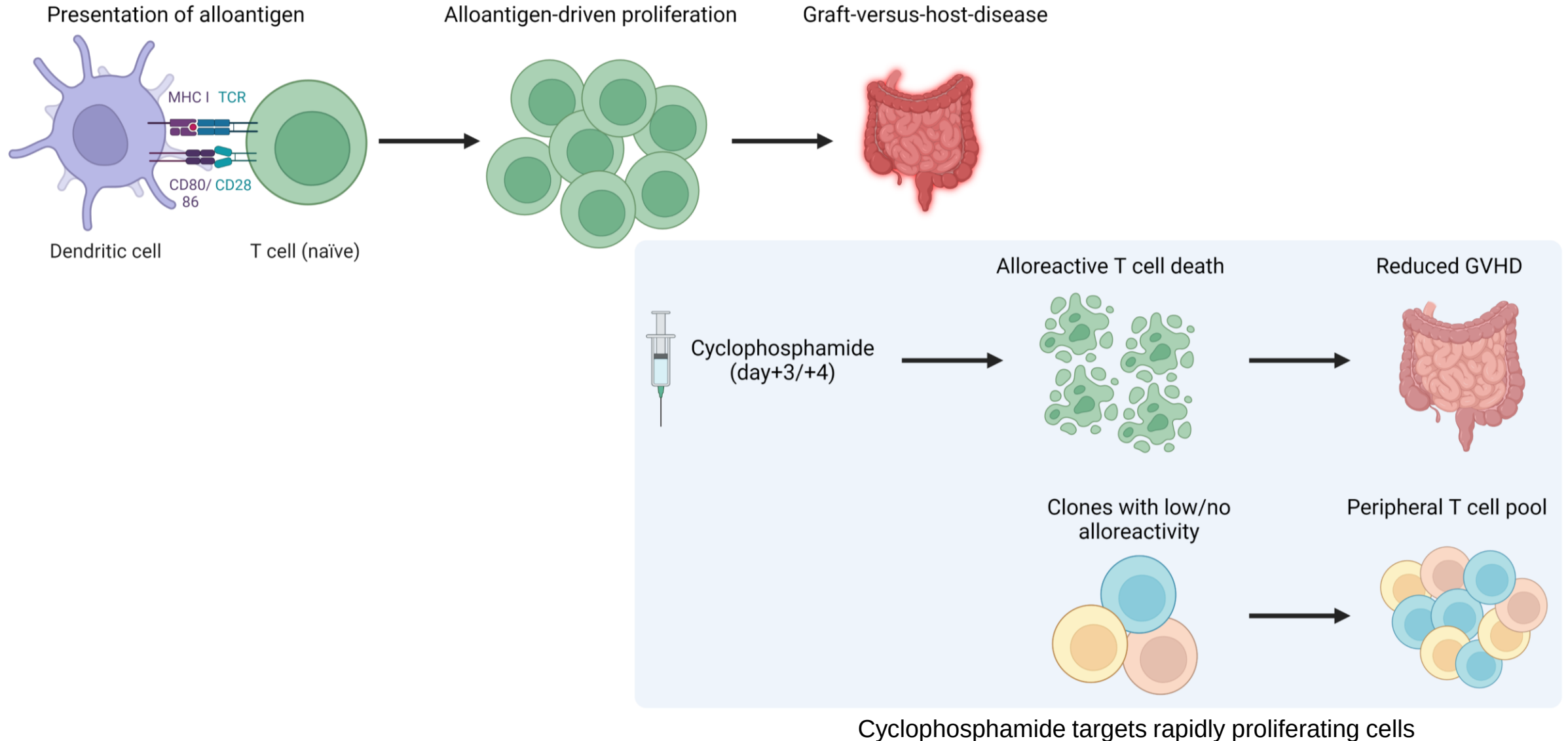


DR-18 promotes tumor-specific control of myeloma post-SCT

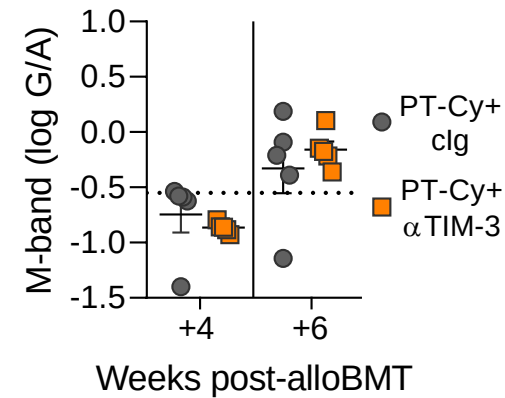
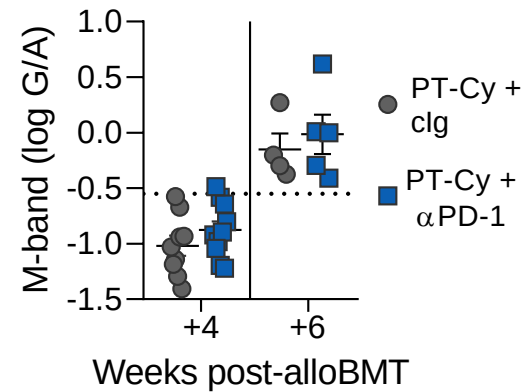
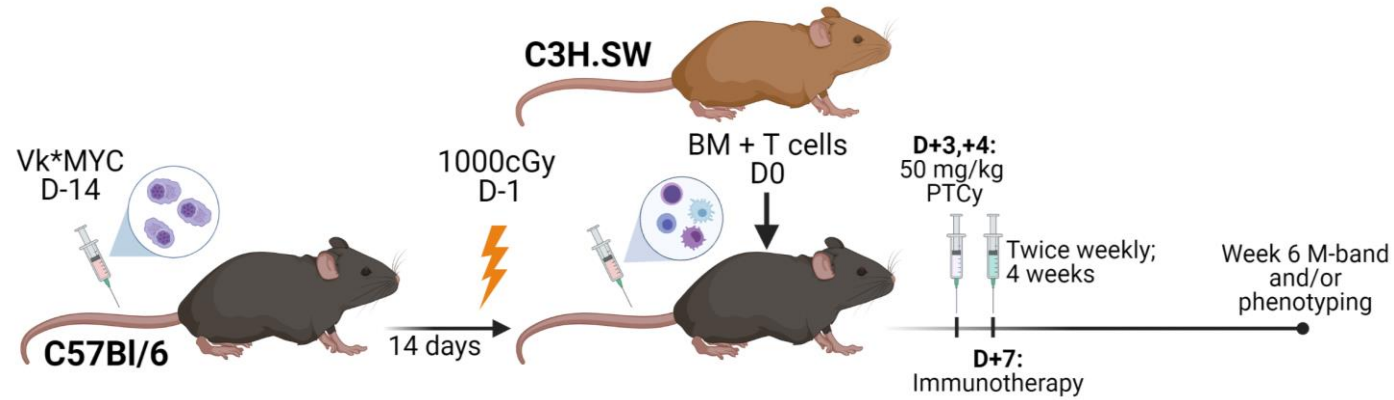
Murine Models of Allo-SCT



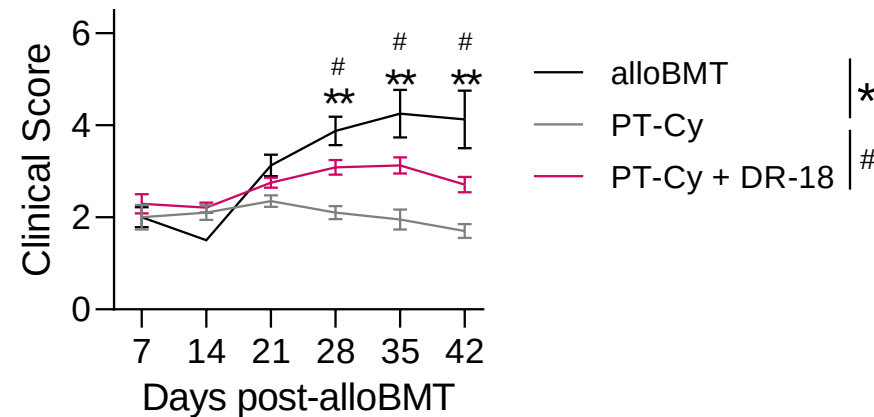
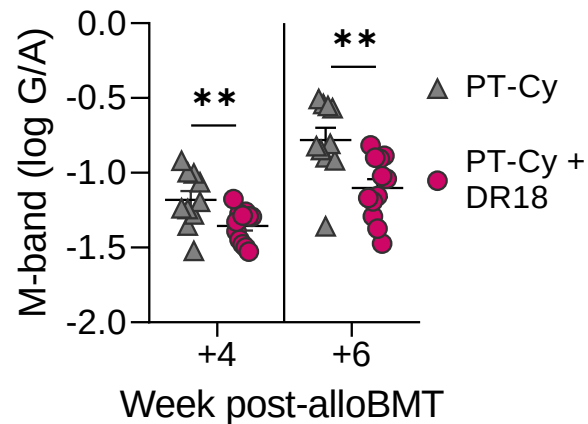
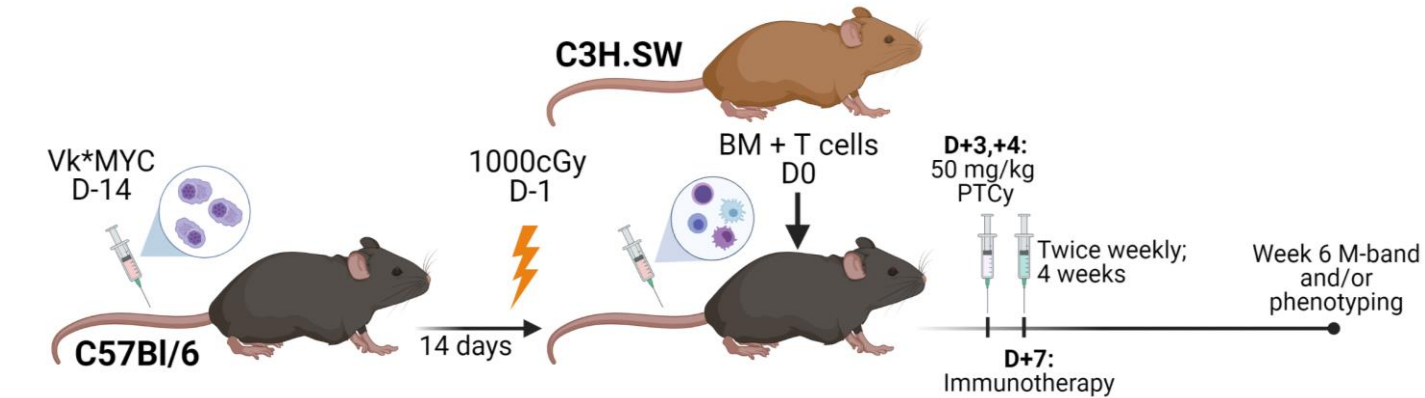
Limiting GVHD after Allo-SCT with PT-Cy



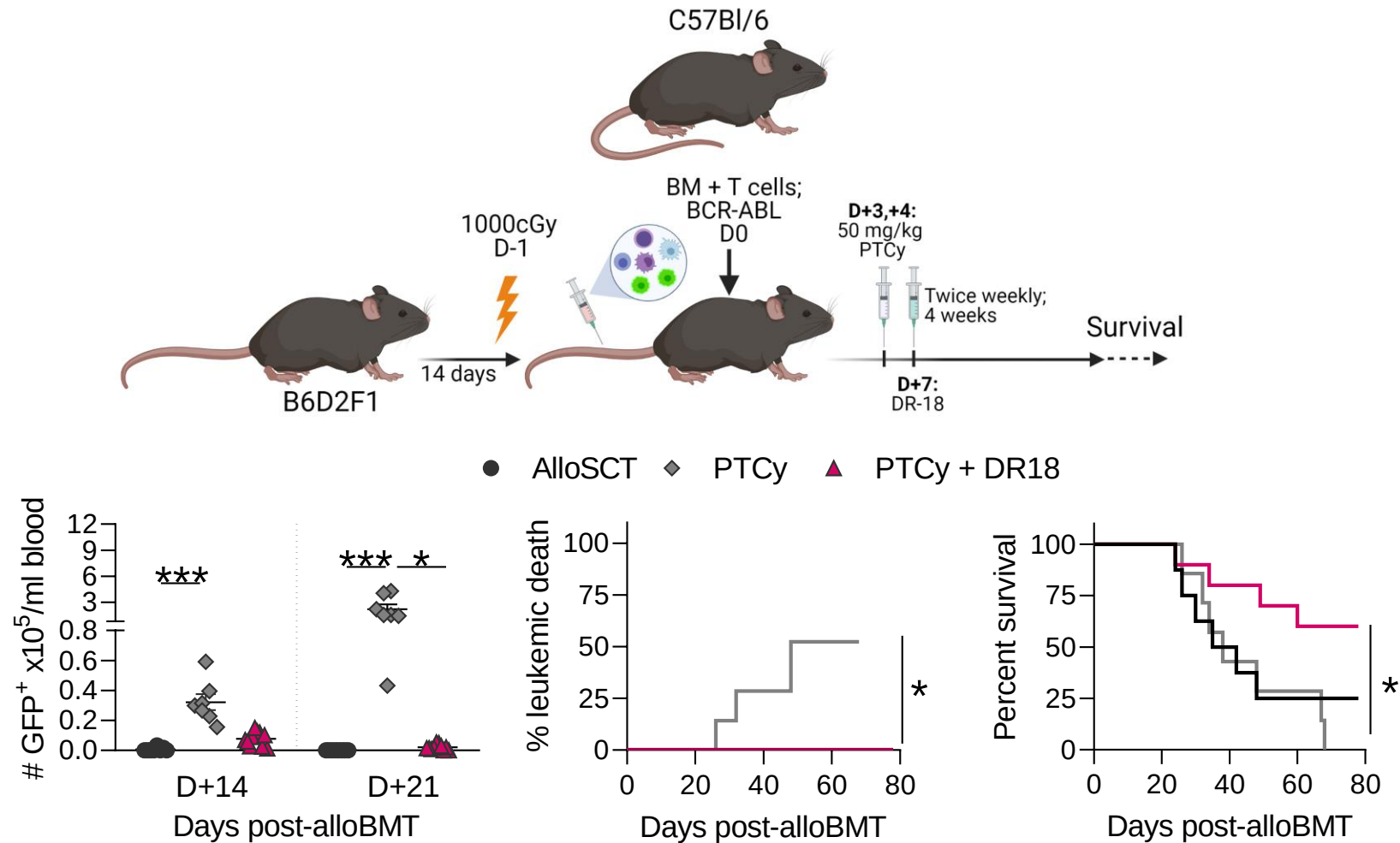
Checkpoint blockade is ineffective after PT-Cy



DR-18 is effective after PT-Cy: Myeloma



DR-18 is effective after PT-Cy: Leukemia



Conclusions/Future Directions

- IL-18 could be a highly effective partner for ALL adoptive T cell therapies
 - ‘armored’ CAR T cells
 - Decoy-resistant IL-18
- Key to success will be balancing anti-tumor efficacy with toxicities
- Future directions:
 - Initiate clinical trials in hematological malignancies
 - IL-18 doesn’t act alone, combination therapies could further enhance anti-tumor activity

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Comprehensive Cancer Center

- Marta Chesi

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