



Dual-Switch CAR-T Cells: Inducible Cell Activation and Elimination to Manage Persistence and Toxicity

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Houston, TX

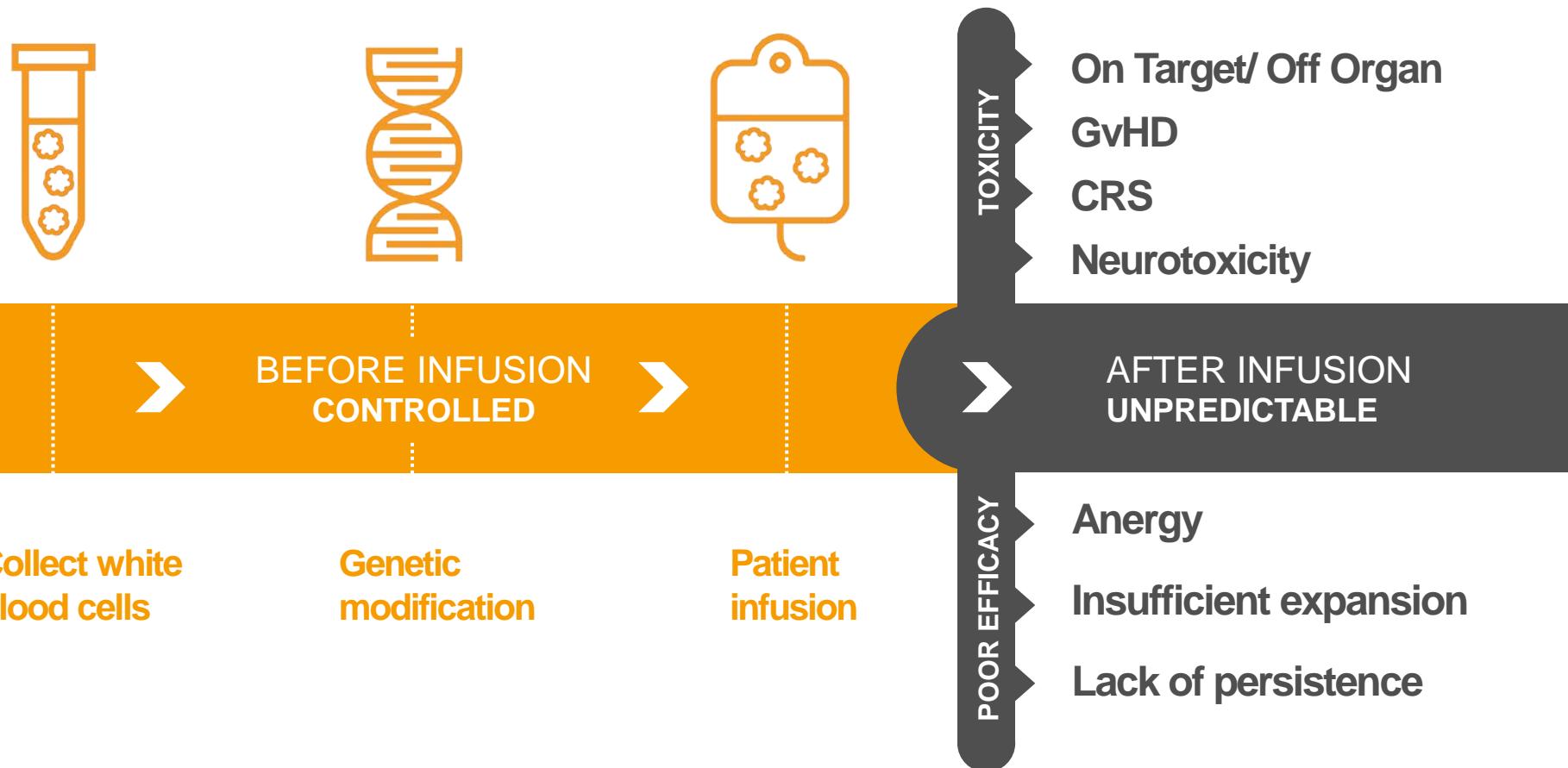
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Disclosure Statement

I am an employee and stockholder of Bellicum Pharmaceuticals, Inc.

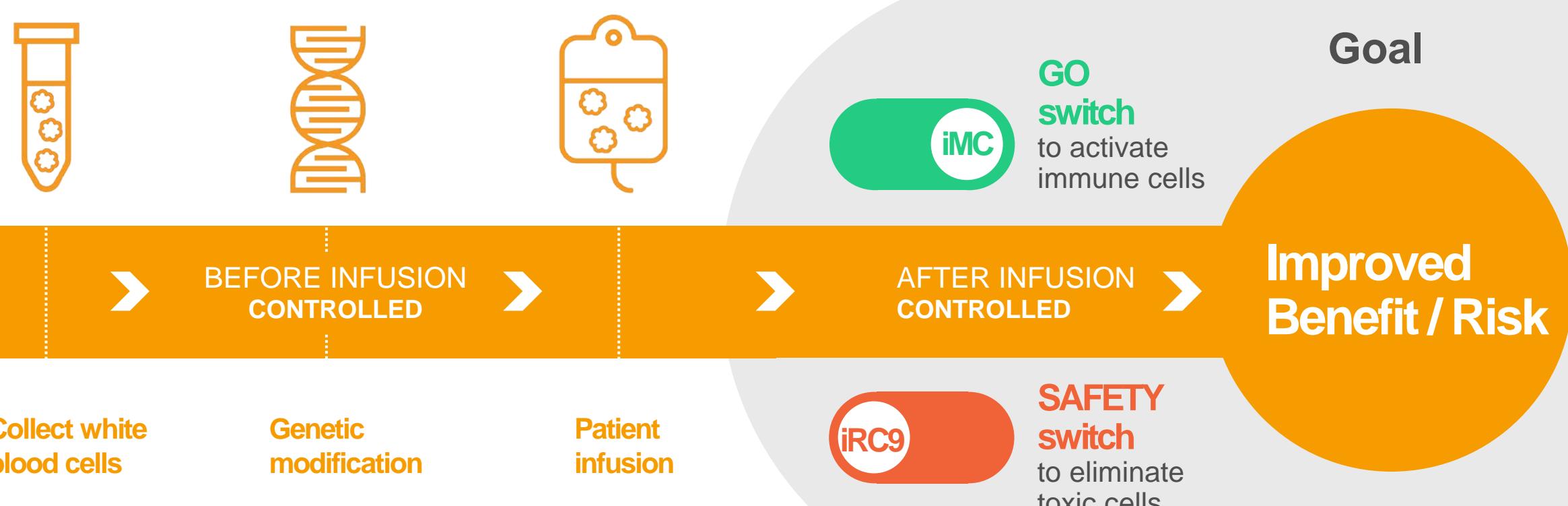
Challenges in Cell Therapy

Most cell therapies can only be controlled **before** infusion, but **not after** infusion



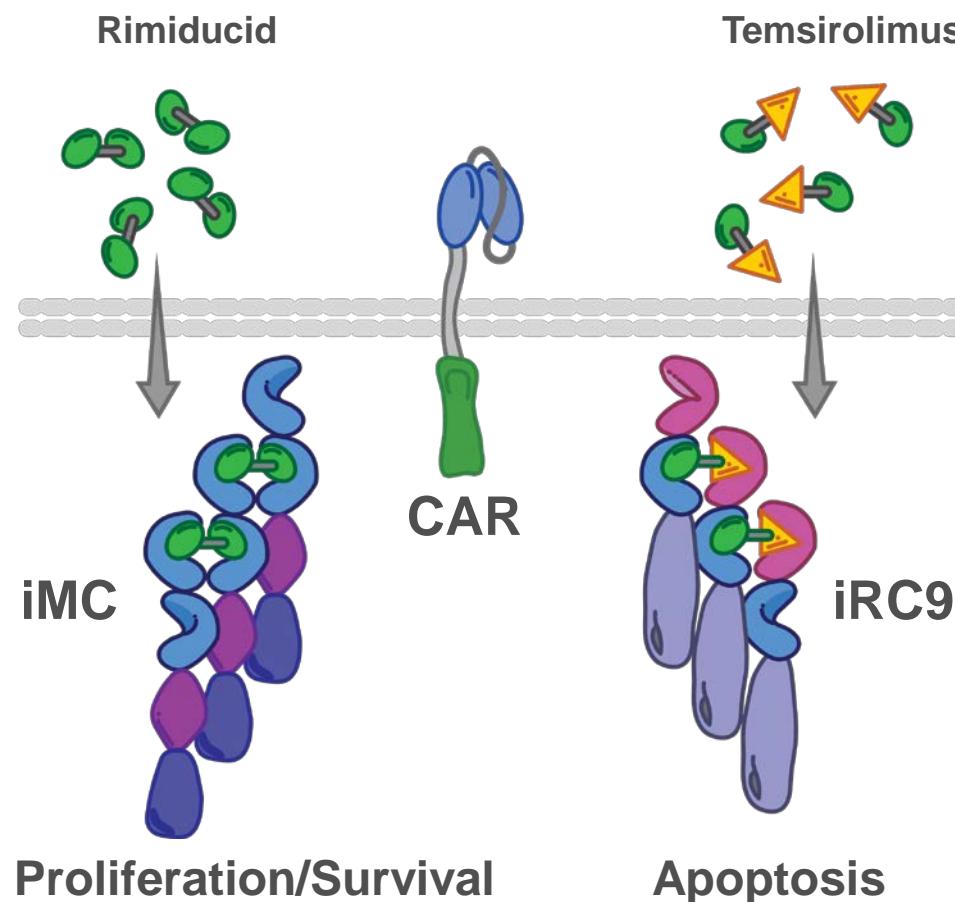
Controllable Cell Therapy

Bellicum's molecular switches allow control **after** infusion



Dual-Switch Technology

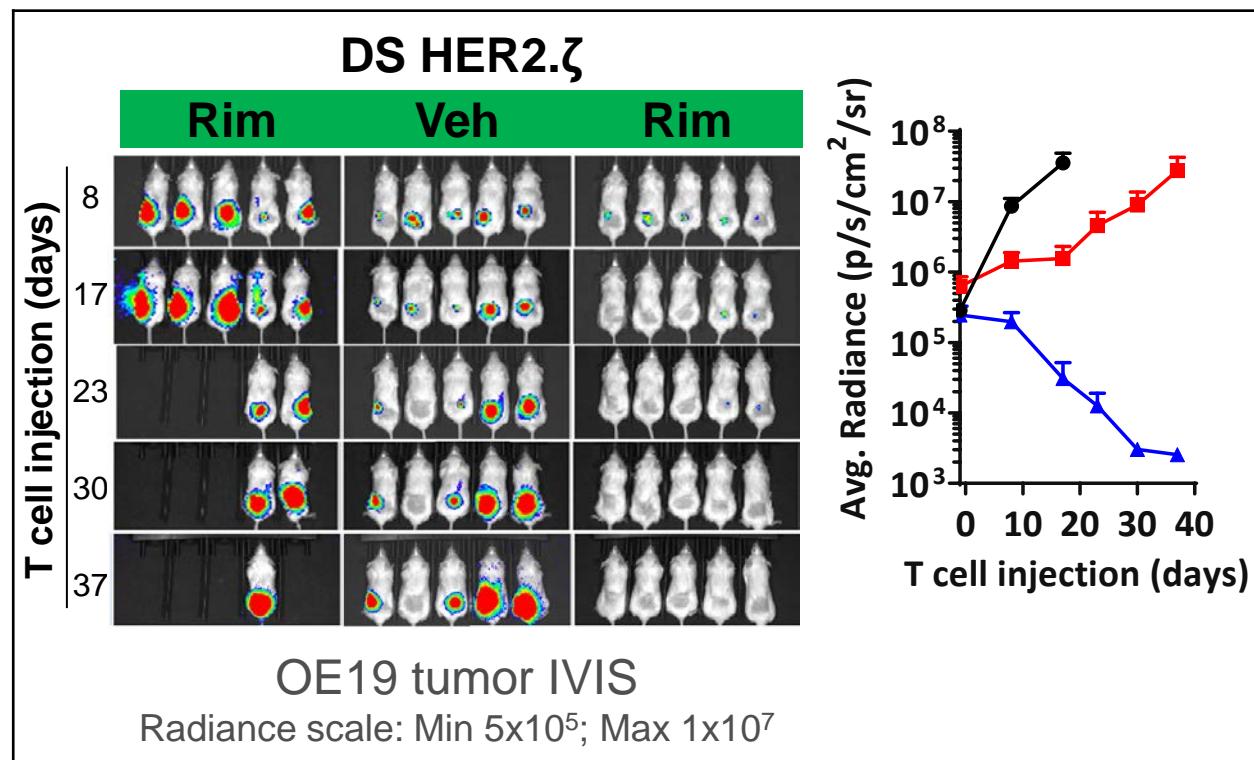
Controlling the activity of CAR-T cells with built-in safety



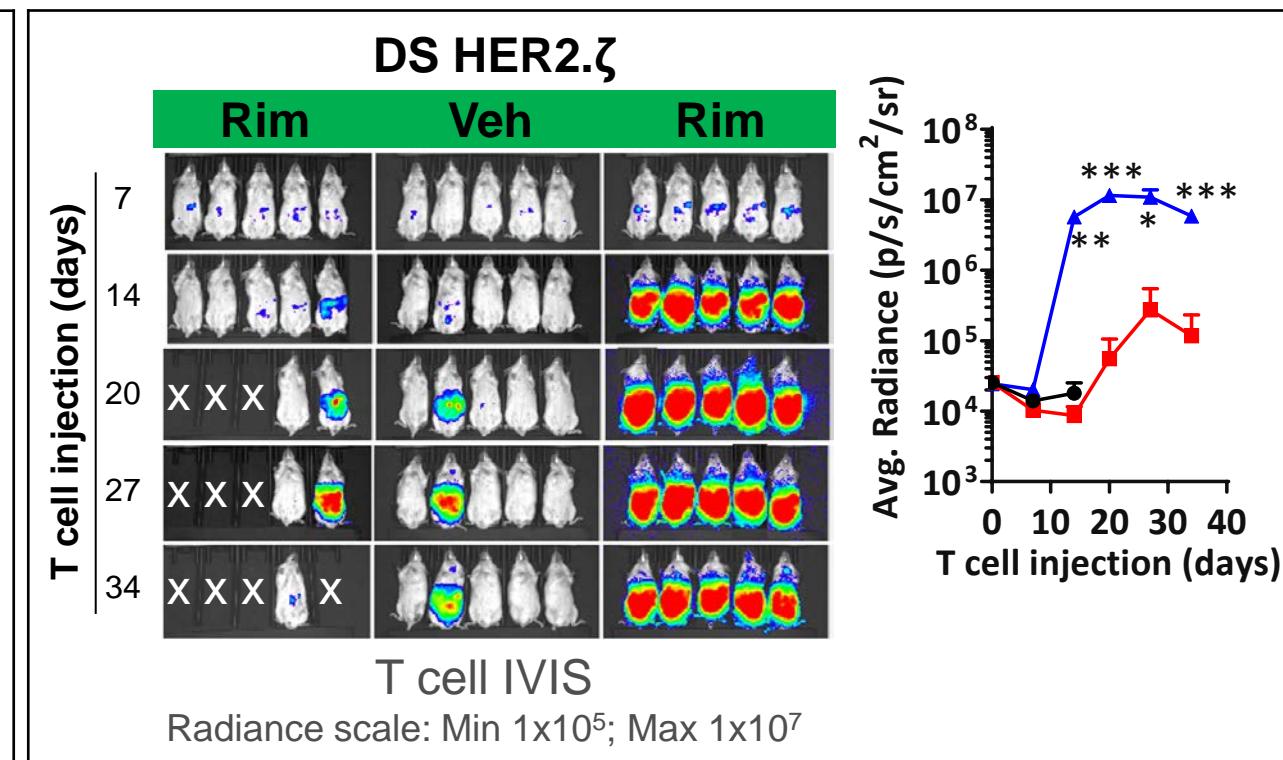
- **iMC inducible costimulation**
 - Increased persistence and survival of CAR-T cells
- **iRC9 inducible cell elimination**
 - Rapid removal of activated CAR-T cells and reduction of inflammatory cytokines
- **Dual control of CAR-T cells allow for**
 - Treatment of aggressive tumors that need additional CAR-T potency
 - Target or indication toxicity concerns

DS HER2 CAR-T cells demonstrate iMC-dependent tumor elimination and T cell expansion.

Rim-dependent elimination of OE19 tumors



Rim-dependent CAR-T cell expansion



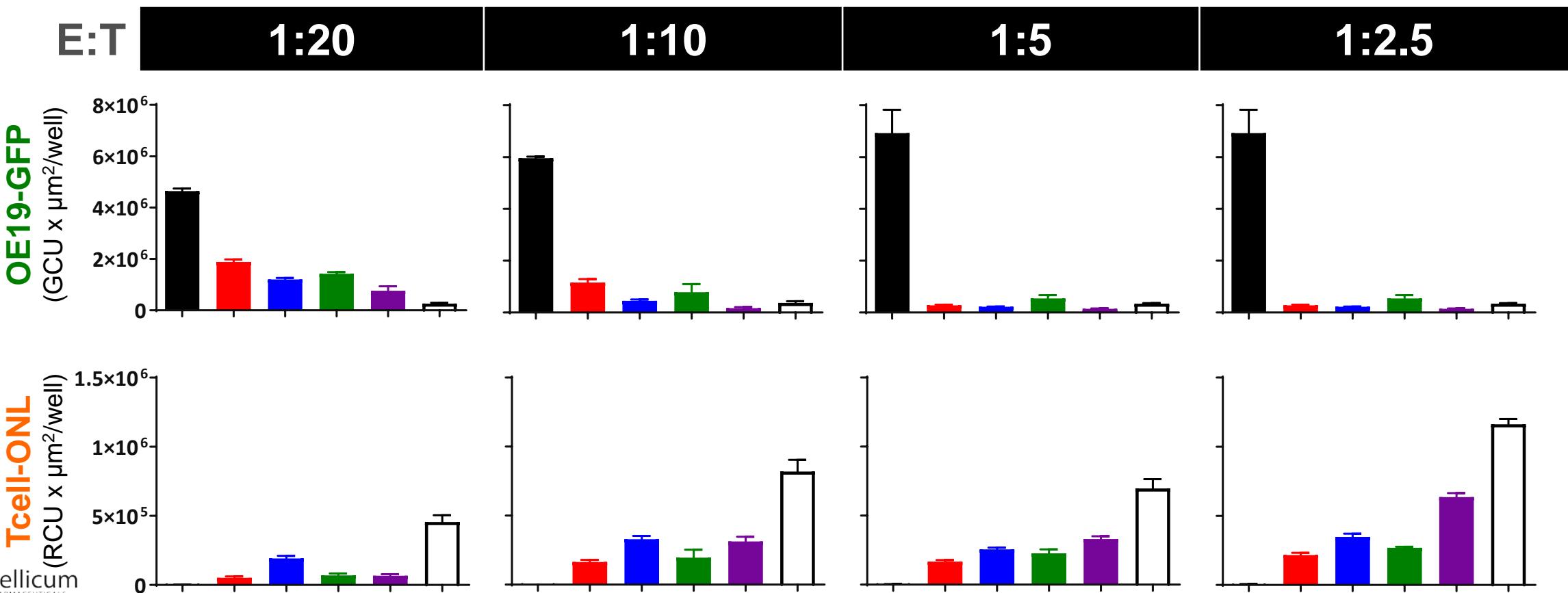
- Mock + Rim
- DS CAR + Veh
- ▲ DS CAR + Rim

x = euthanized due to high tumor burden
Multiple t test; * p < 0.05; ** p < 0.005; *** p < 0.0005

How do DS CAR-T cells compare to conventional 1st and 2nd generation CAR-T cells?

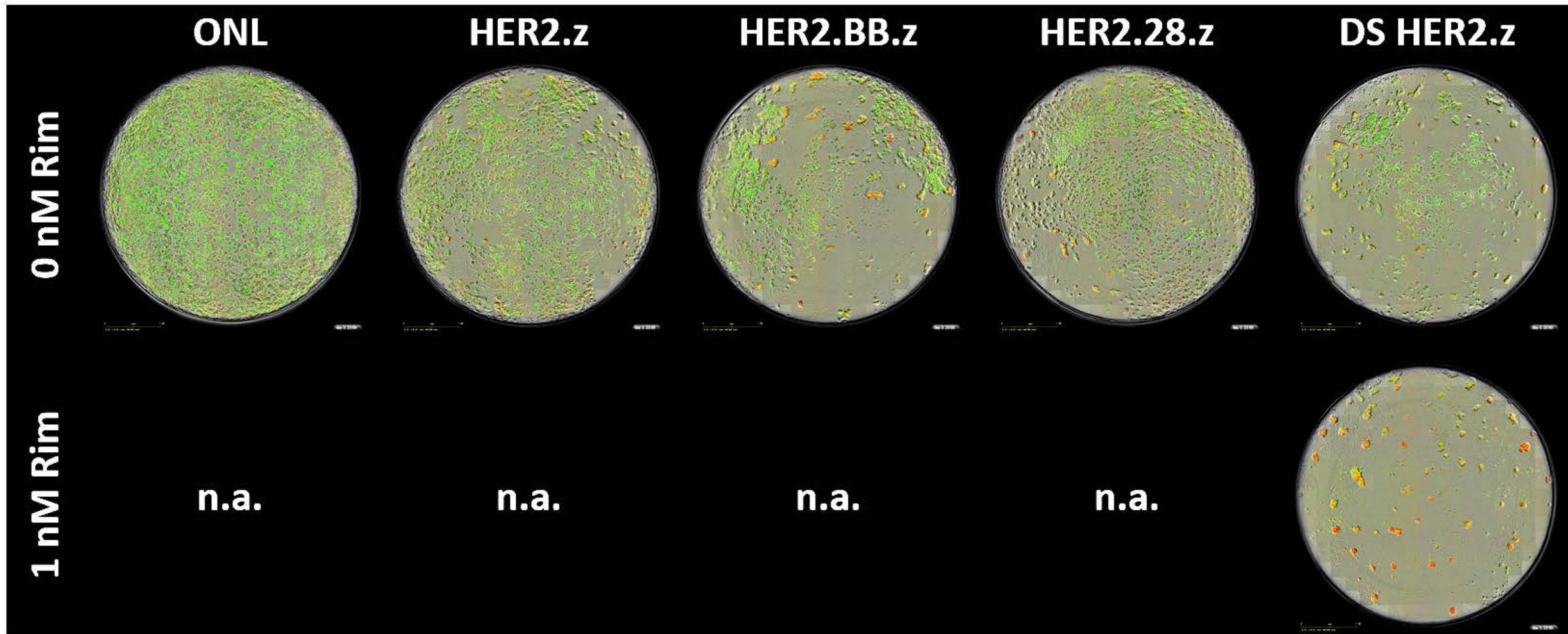
iMC activation enhances antitumor activity and expansion of DS HER2 CAR-T cells.

- Mock
- HER2.z
- HER2.BB.z
- HER2.28.z
- DS HER2.z
- DS HER2.z+Rim

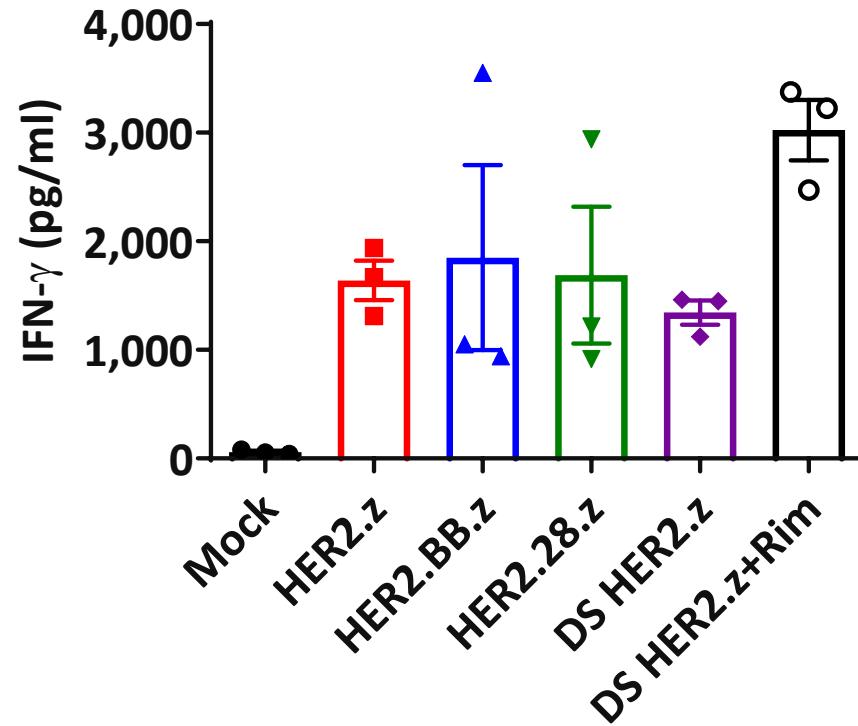
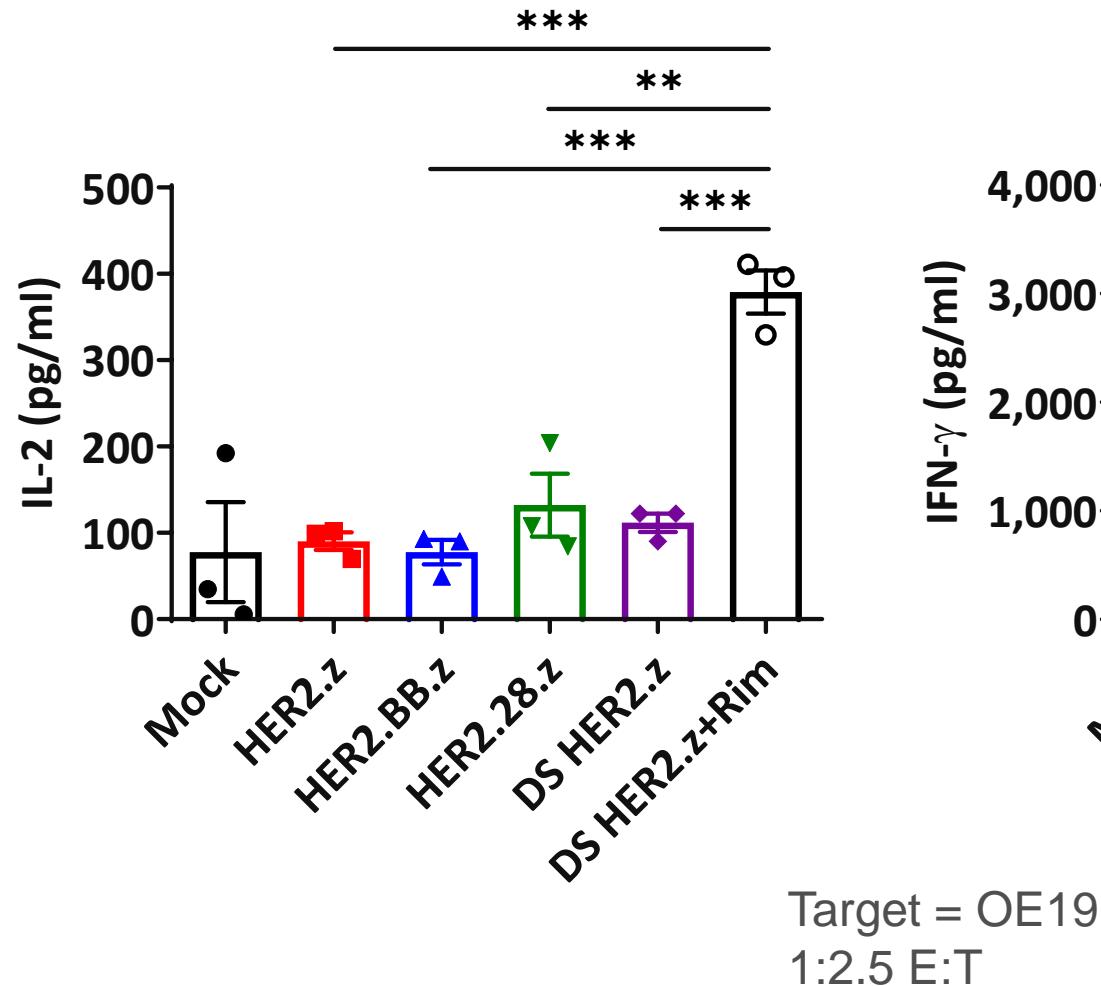


iMC activation enhances antitumor activity and expansion of DS HER2 CAR-T cells.

OE19-eGFP Tcells-ONL 1:20, day 7

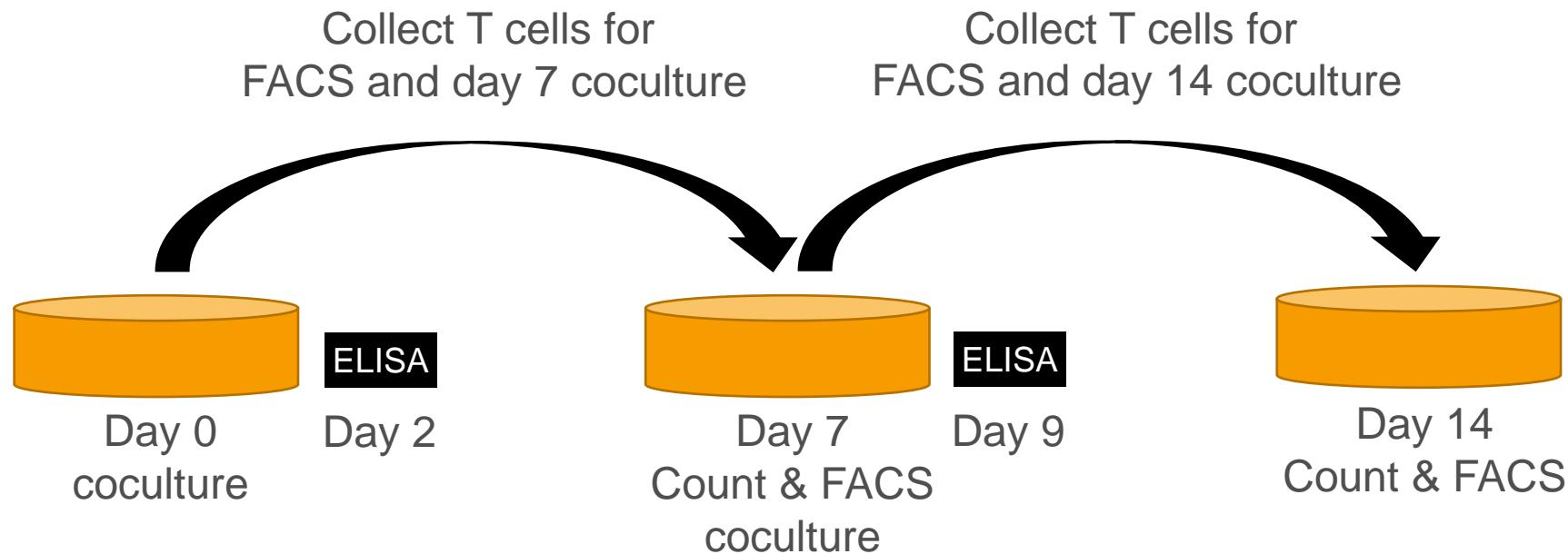


iMC activation enhances proinflammatory cytokine secretion of DS HER2 CAR-T cells.



One-way ANOVA with Tukey's multiple comparison
* p < 0.05; ** p < 0.005; *** p < 0.0005

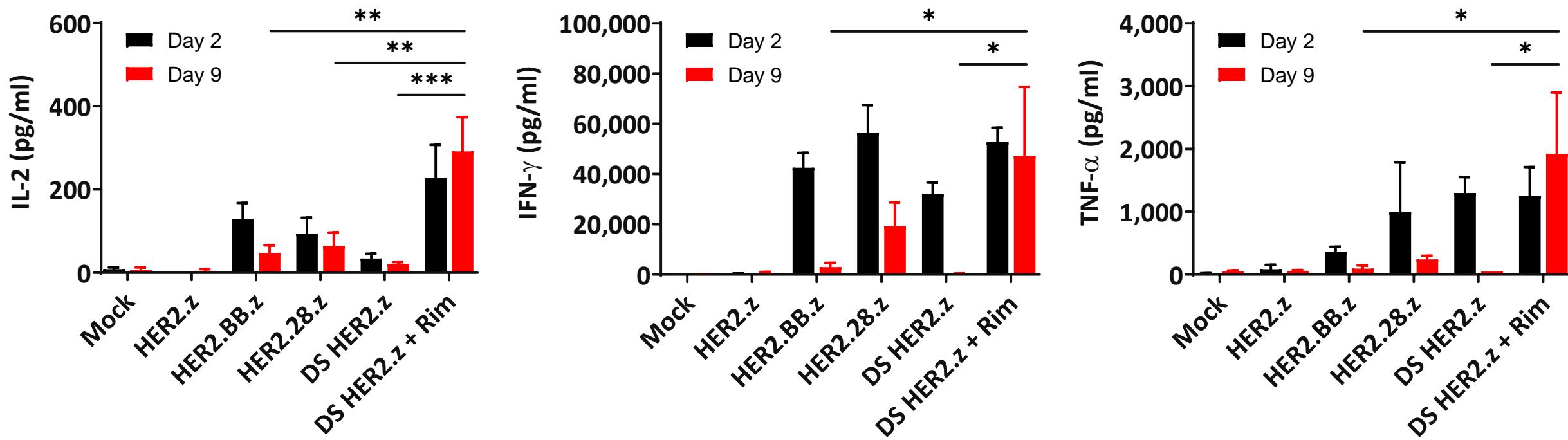
Do HER2 CAR-T cells become exhausted upon repeated antigen exposure?



Effector: HER2 CAR-T cells
Target: OE19 (irradiated)
1:1 E:T

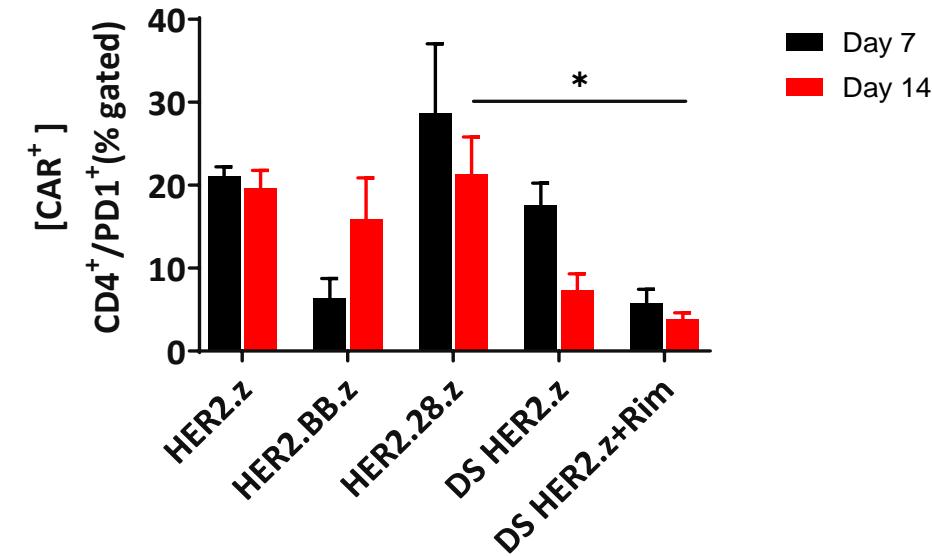
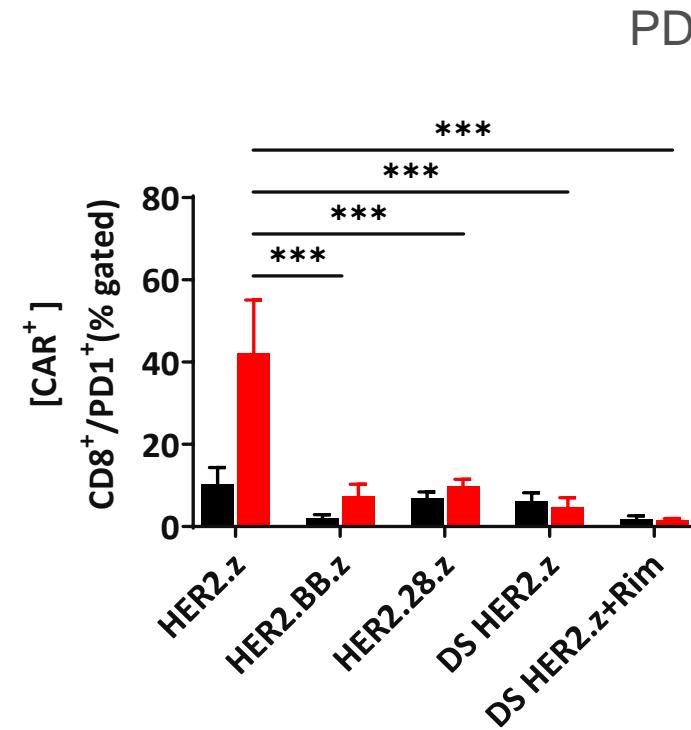
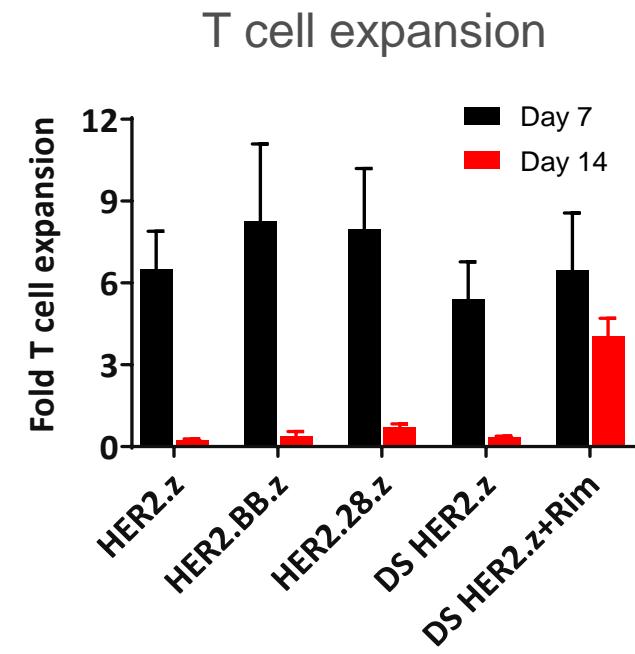
iMC-activated DS HER2 CAR-T cells are not exhausted upon repeated antigen stimulation.

Cytokine release



Two-way ANOVA with Tukey's multiple comparison
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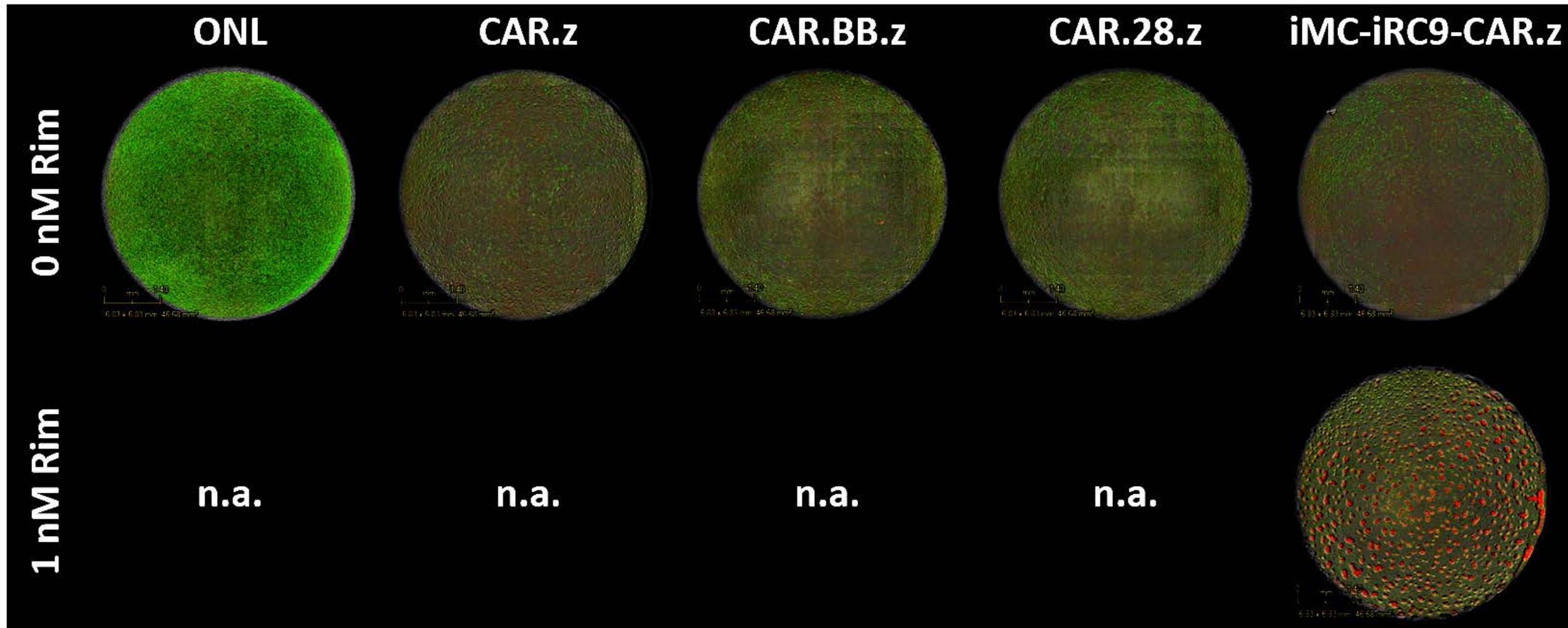
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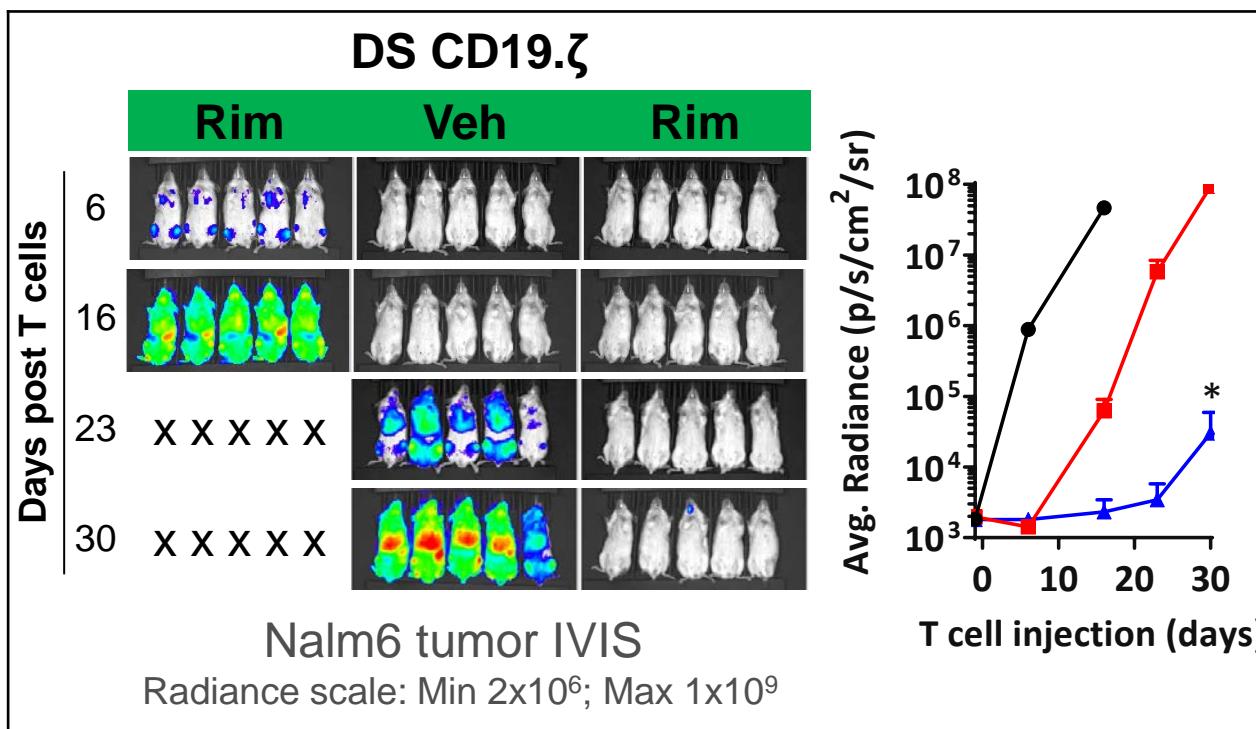
iMC activation enhances antitumor activity and expansion of DS CD19 CAR-T cells.

Nalm6-eGFP Tcells-ONL; D236; 1:5, day 7

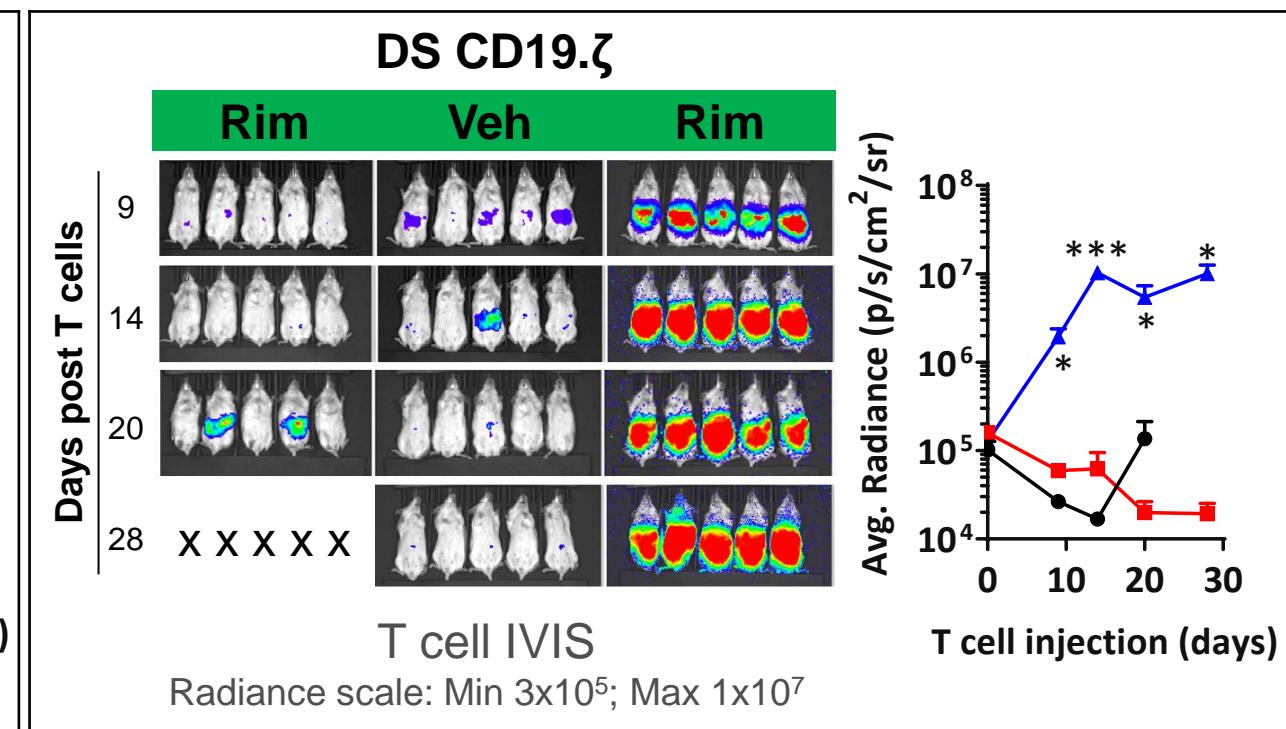


DS CD19 CAR-T cells demonstrate iMC-dependent tumor elimination and T cell expansion.

Rim-dependent elimination of Nalm6 tumors



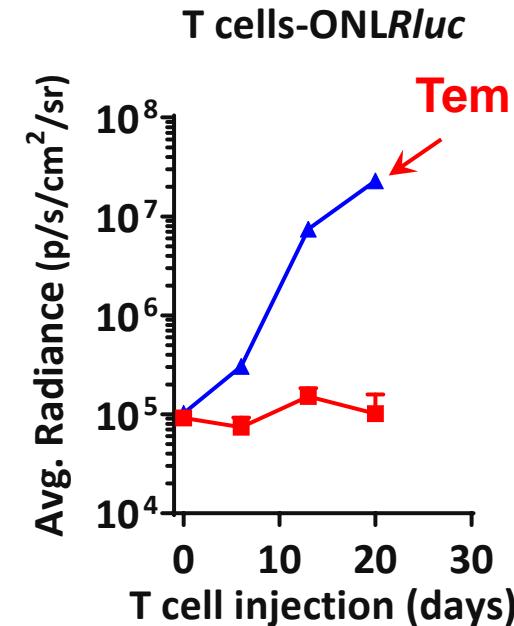
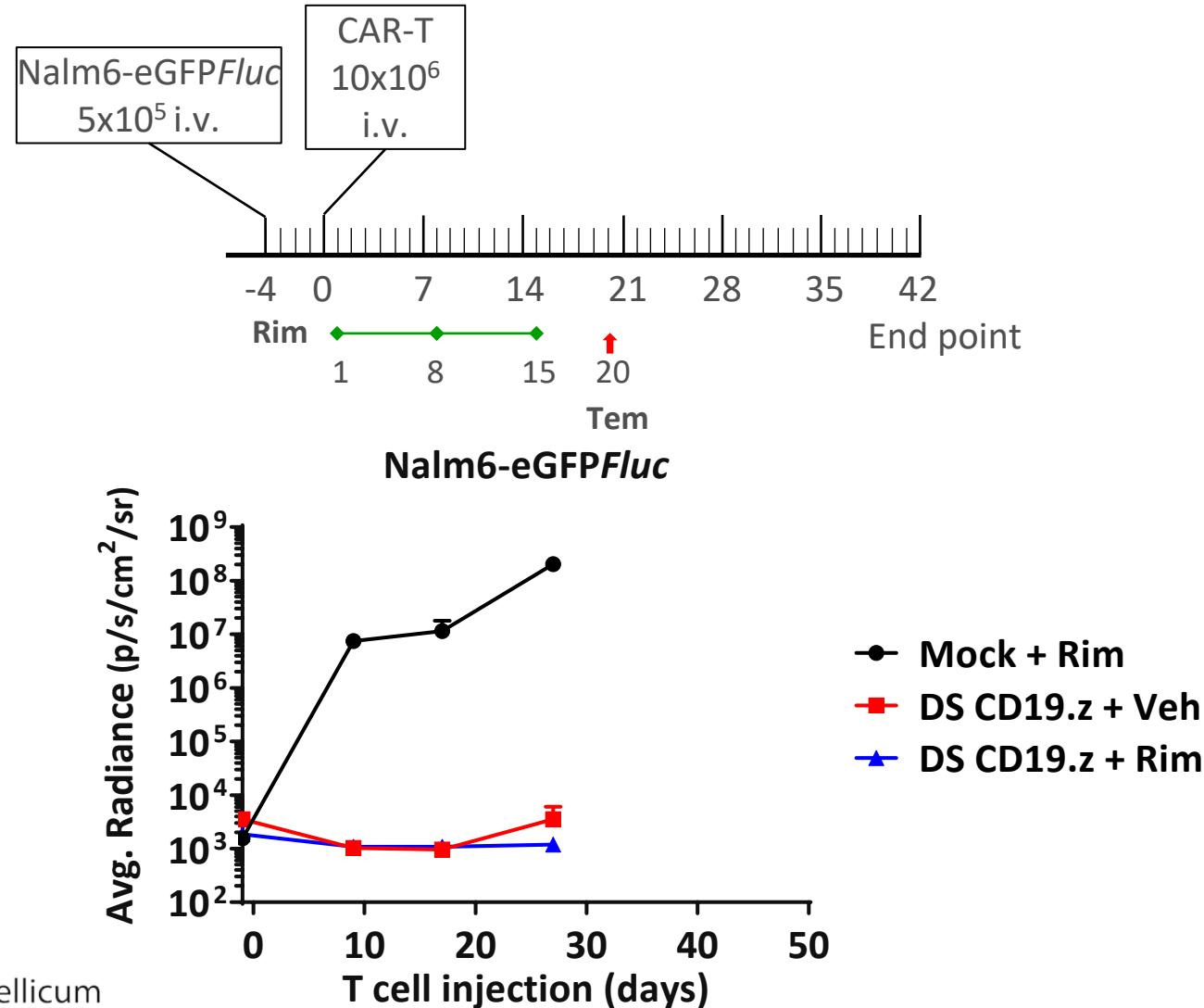
Rim-dependent CAR-T cell expansion



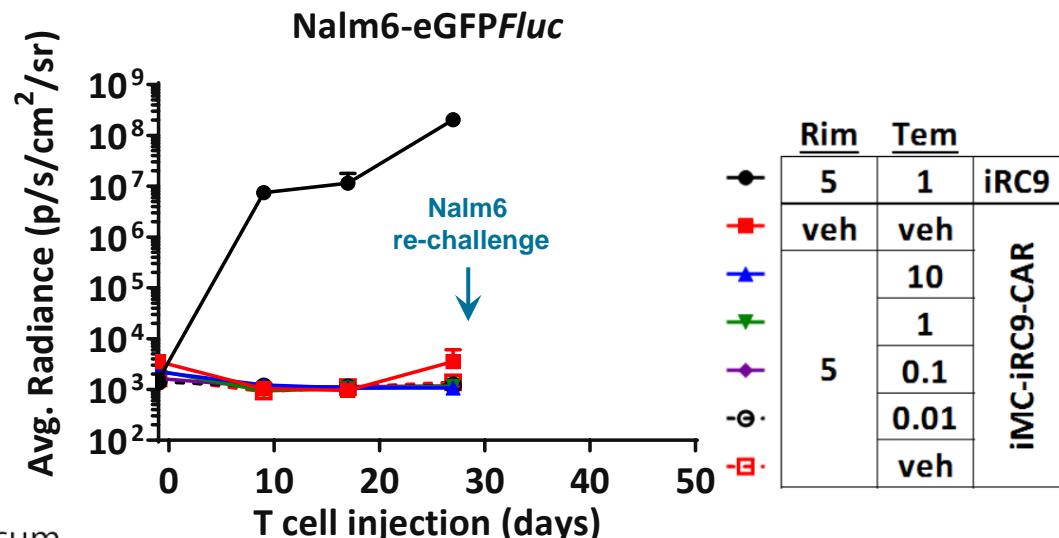
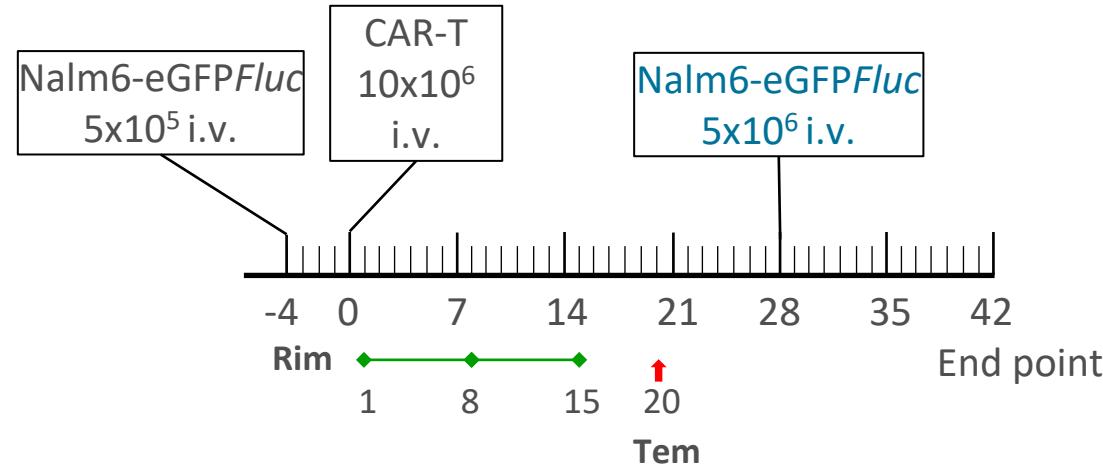
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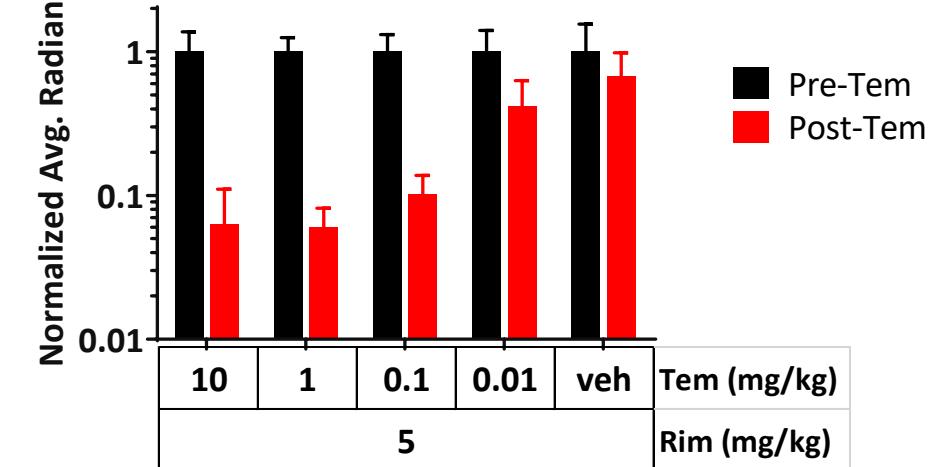
iRC9 activation allowed for titratable T cell elimination and remaining DS CAR-T cells retained the ability to control tumor re-challenge.



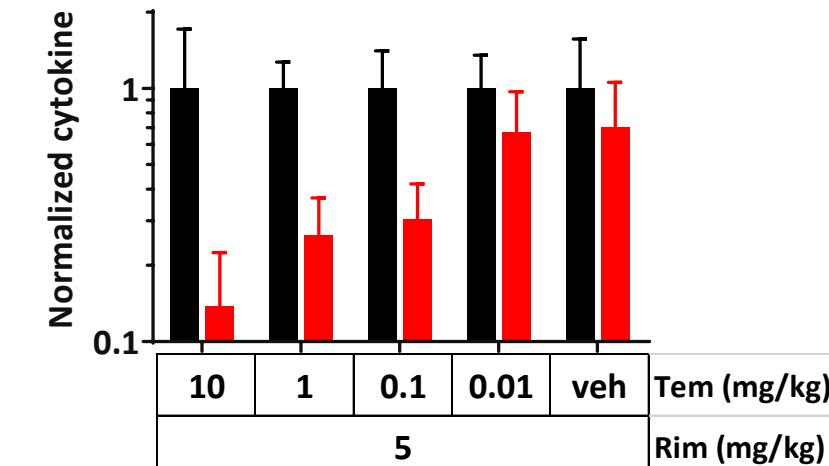
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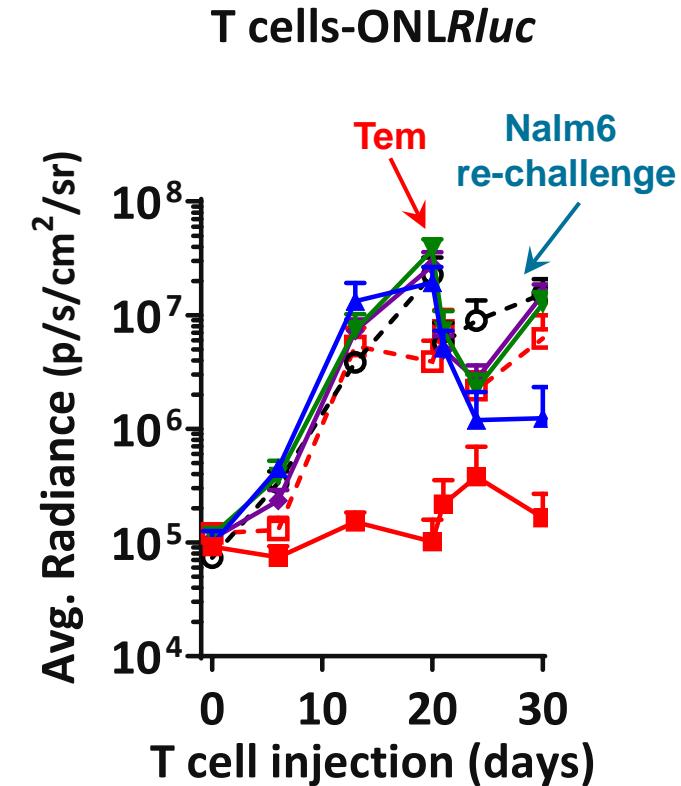
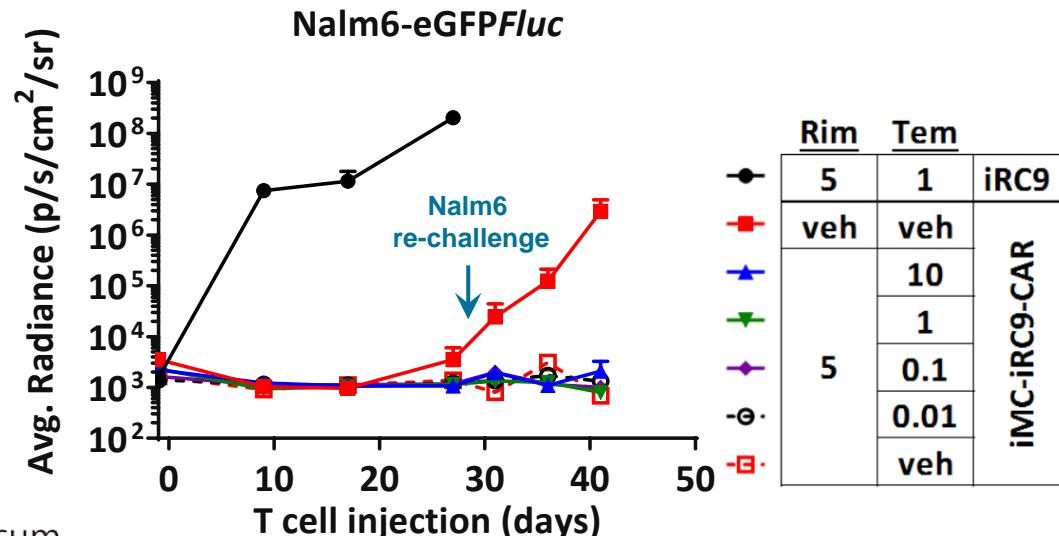
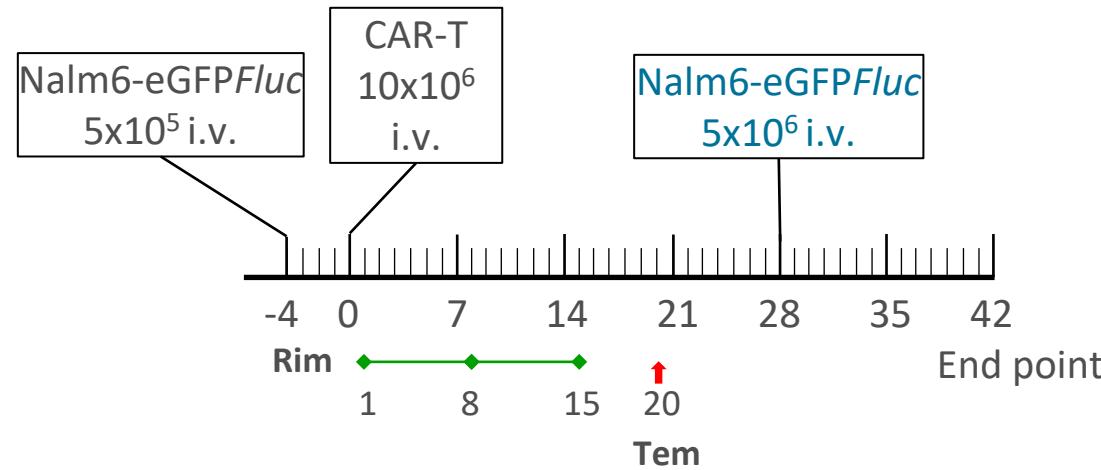
Tem-dependent elimination of DS CAR-T cells



Tem-dependent reduction of IFN- γ



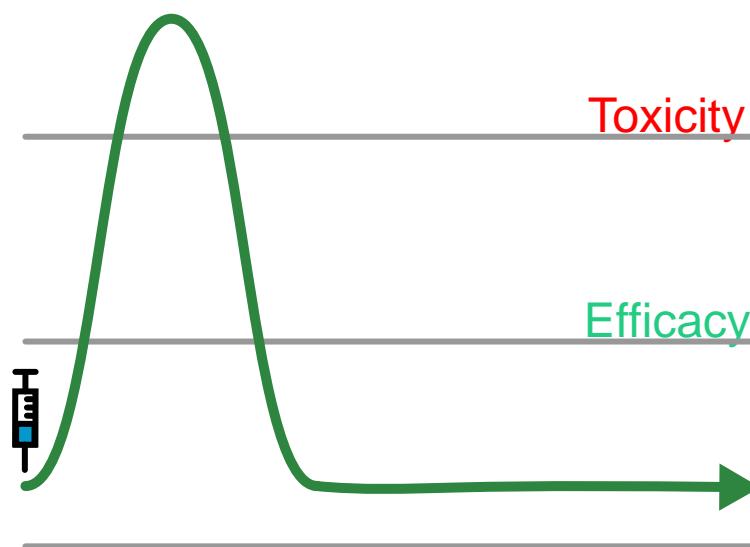
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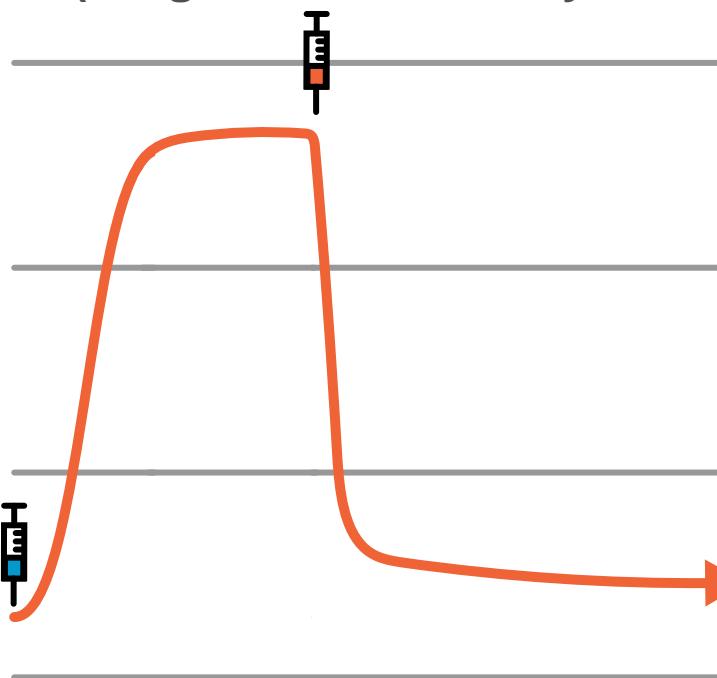
Summary

Molecular switches designed to control CAR-T dynamics *in vivo*

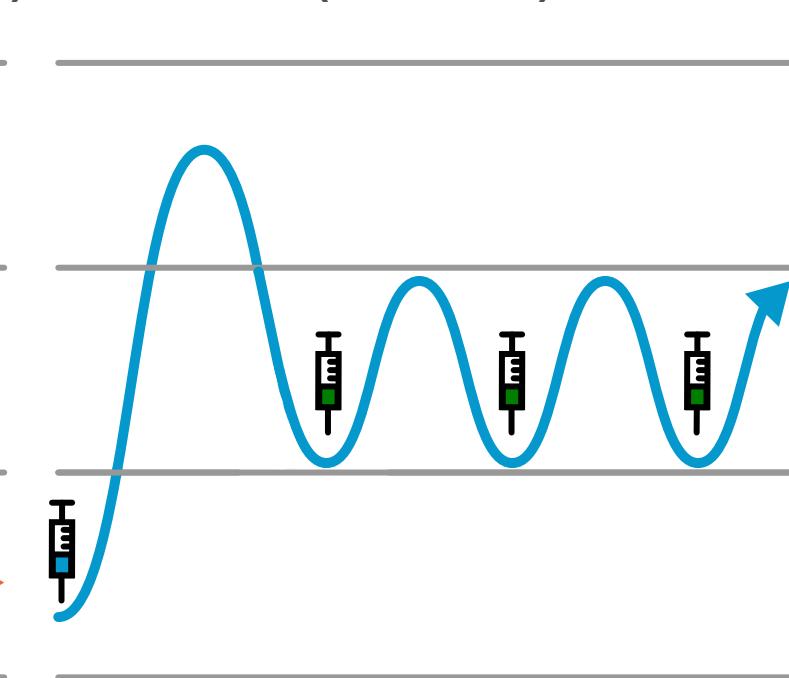
**Transient toxicity and efficacy
(2nd gen CARs)**



**Prompt resolution of toxicity
(2nd gen CARs + safety switch)**

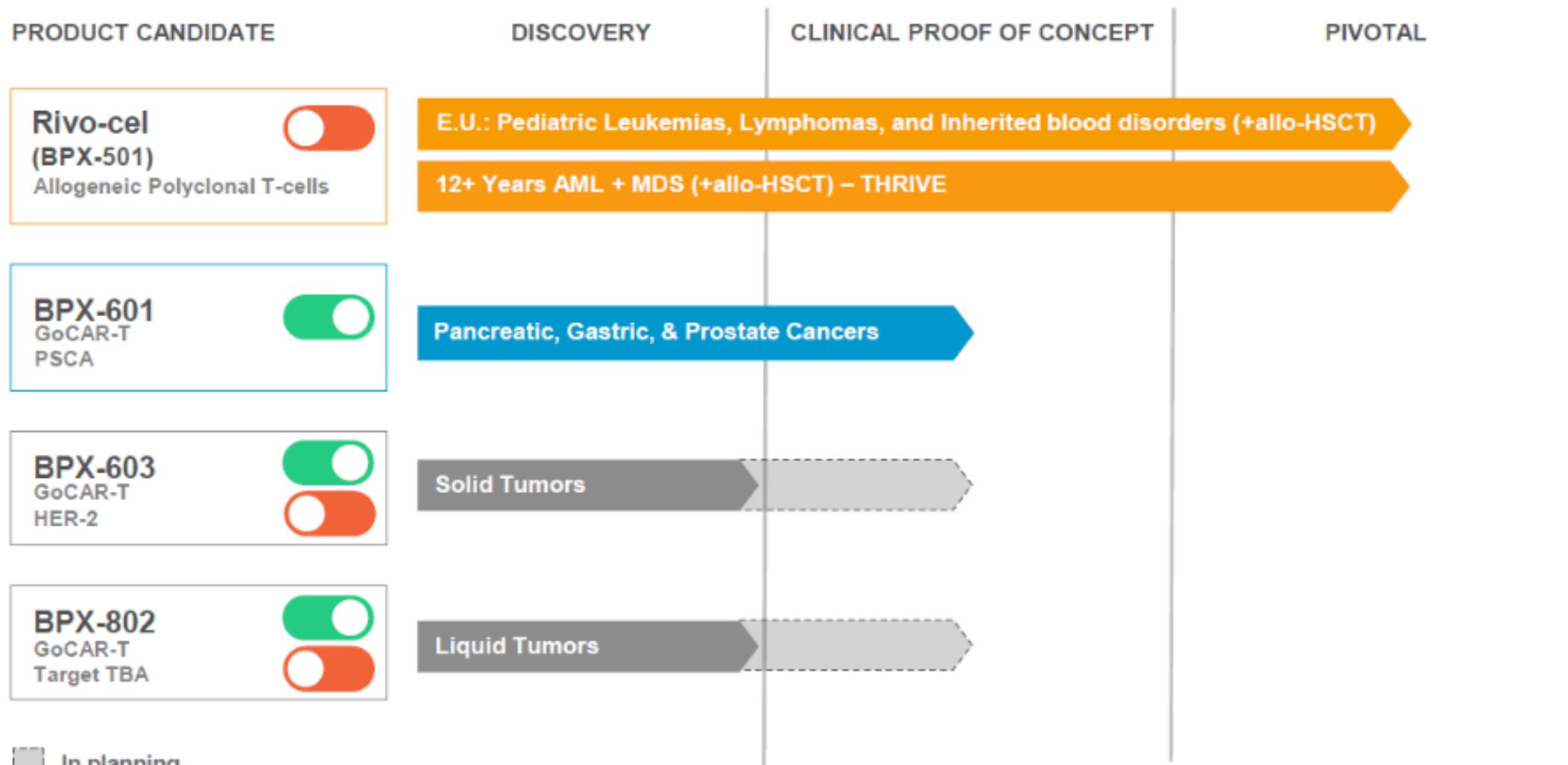


**Prolonged efficacy
(DS CARs)**



Highly Differentiated Portfolio

Control switch(es) selected to address situation-specific challenge



Acknowledgements

Research & Development

- Henri Bayle
- Aaron Foster
- David Spencer
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- Mary Brandt
- Matthew Collinson-Pautz
- Ming Zhang
- Kelly Sharp

