the MIRACLE of SCIENCE with SOUL

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"Advancing Immunotherapy Platforms for the Treatment of Prostate Cancers"

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City of Hope

Disclosures

- I am on the **SAB** of **Mustang Therapeutics** and **Imugene Ltd**
- I am a **consultant** for **Mustang Therapeutics**, **Apterna**, **Imugene Ltd**, **Bayer**
- I have **equity** in **Imugene Ltd**
- I receive **grant support** from **Mustang Therapeutics** and **Imugene Ltd**

Adapted from Roberts et al, *Leuk & Lymphoma* 2017

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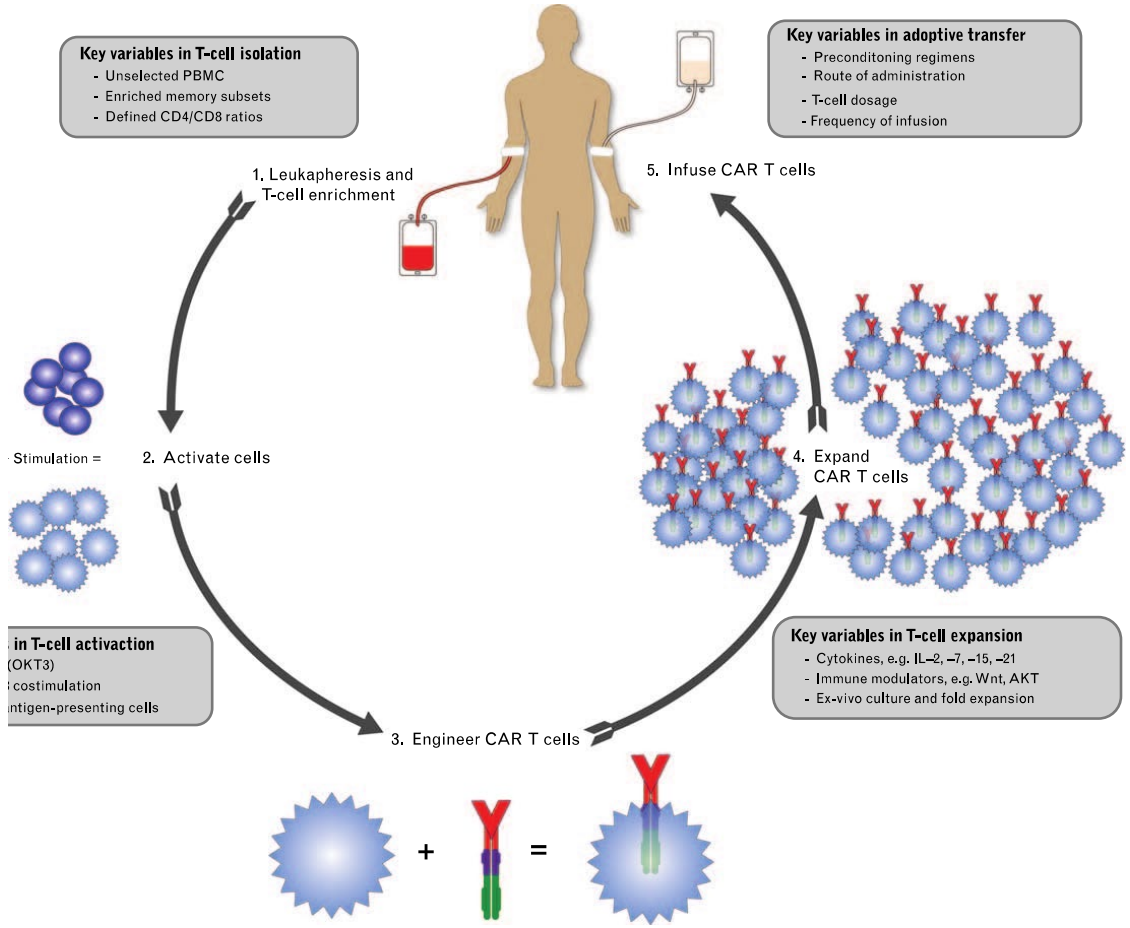
Adoptive Therapy using CAR-Engineered T Cells



Priceman, et al. *Curr Opin Oncol* 2015

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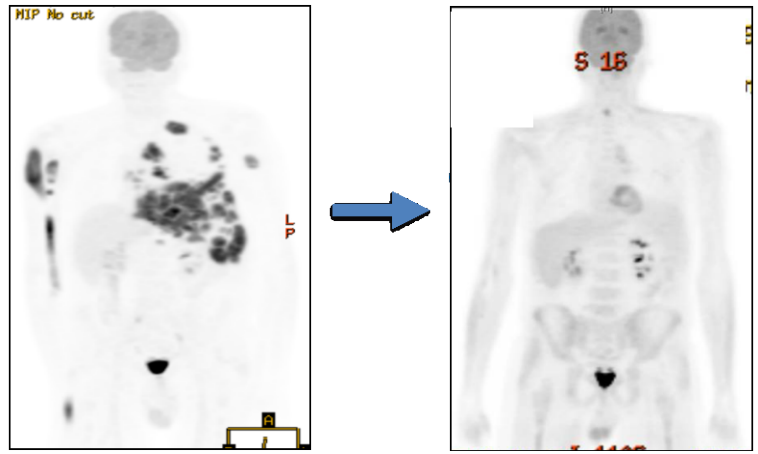
CD19-CAR T Cells for Relapsed B-Cell Lymphoma and Leukemia

Case Report:
61 yr; male
Relapsed high-grade B cell lymphoma
Lymphodepletion: Flu/Cy
CD19-28z CAR T cells (200M; Tn/mem)
Grade 2 CRS (1x toci); no neurotoxicity



Pre-treatment **Post CAR T cells: 28 days**

Clinical Trial	Disease	Cell Population	Cell Dose (CAR+)	Treated Patients	Response Rate
NCT 02051257	NHL w/ auto-transplant *(MRD; low/neg antigen)*	Tn/mem	200M	6	Pending
NCT 02153580	CD19+ B cell Neoplasms *(Active disease)*	Tn/mem	200M 600M	5 2	1 of 1 CR (4 Pending) Pending
NCT 02146924	B-ALL *(Active disease)*	Tcm	200 M	3	30% CR (1 of 3)
		Tn/mem	**200 M**	**13**	**100% CR (13 of 13)**

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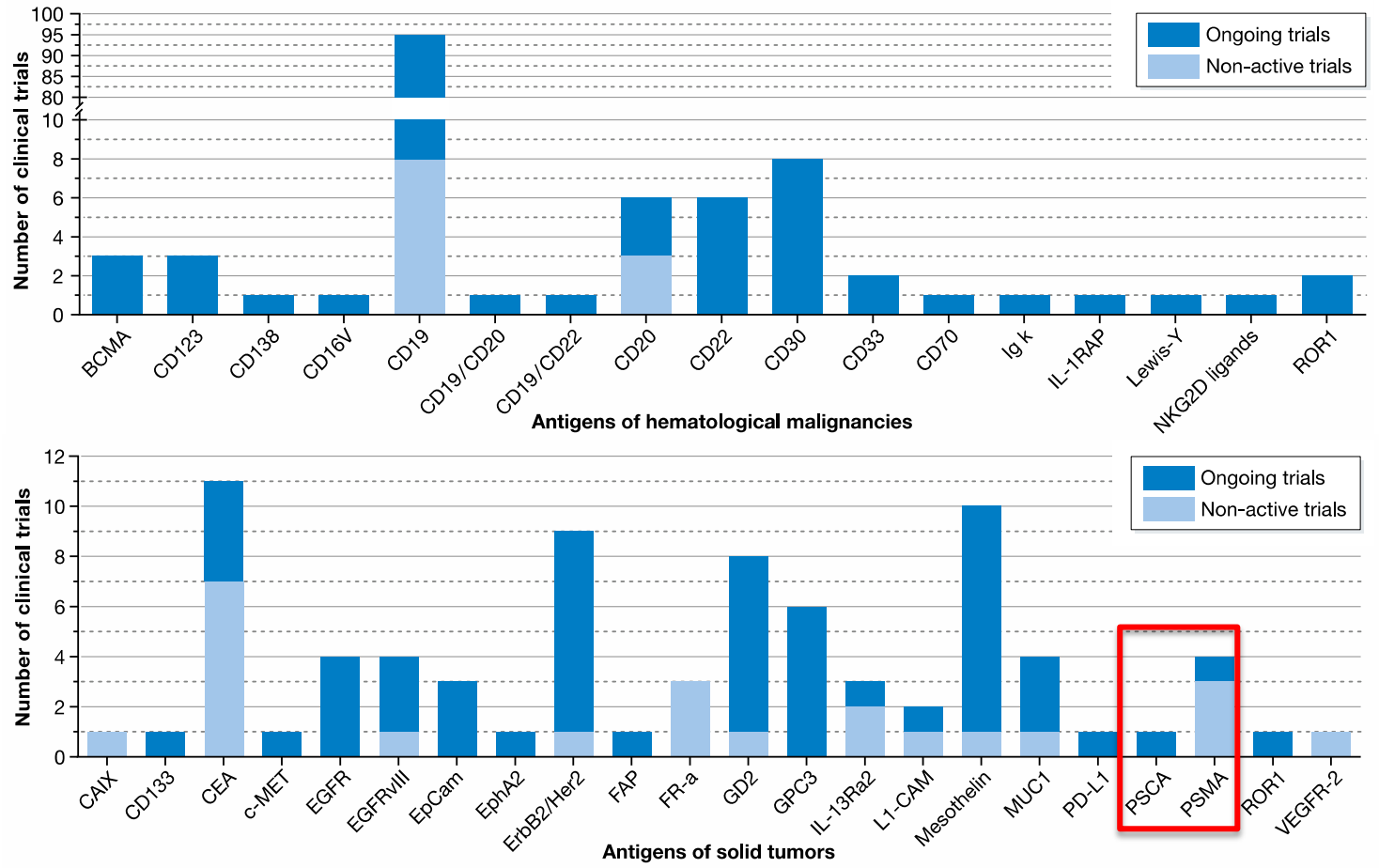
Clinical Development of CAR T Cells



Hartmann, et al. *EMBO Mol Med* 2017

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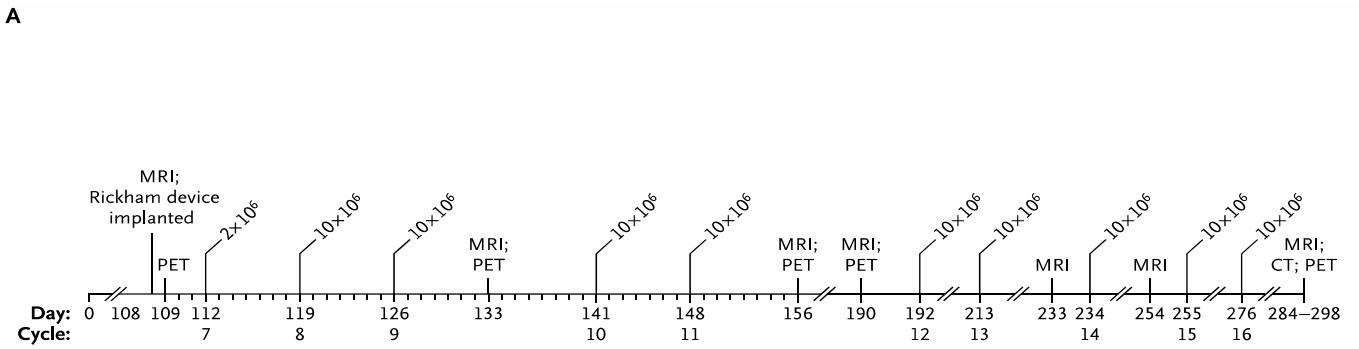
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Regression of Glioblastoma after Chimeric Antigen Receptor T-Cell Therapy

Christine E. Brown, Ph.D., Darya Alizadeh, Ph.D., Renate Starr, M.S., Lihong Weng, M.D., Jamie R. Wagner, B.A., Araceli Naranjo, B.A., Julie R. Ostberg, Ph.D., M. Suzette Blanchard, Ph.D., Julie Kilpatrick, M.S.N., Jennifer Simpson, B.A., Anita Kurien, M.B.S., Saul J. Priceman, Ph.D., Xiuli Wang, M.D., Ph.D., Todd L. Harshbarger, M.D., Massimo D'Apuzzo, M.D., Julie A. Ressler, M.D., Michael C. Jensen, M.D., Michael E. Barish, Ph.D., Mike Chen, M.D., Ph.D., Jana Portnow, M.D., Stephen J. Forman, M.D., and Behnam Badie, M.D.

A



Brown et al., *NJEM* 2016

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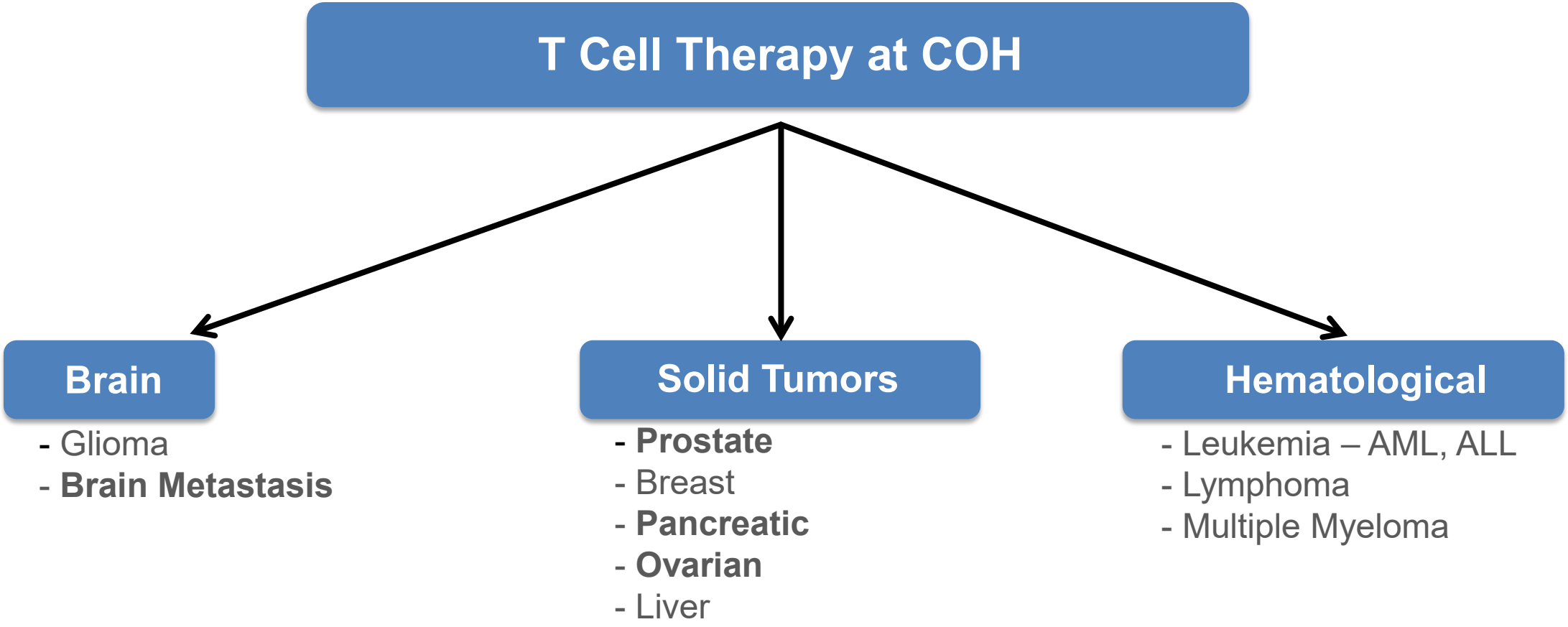
CAR T Cell Therapies for Solid Tumors: *Resistance Mechanisms*

- ***Tumor antigen heterogeneity***
  - *Multitargeted CAR T cell strategies: tandem CARs, universal, syn-notch*
  - *Sparking endogenous anti-tumor immunity?*

- ***Immunosuppressive tumor microenvironment (TME)***
  - *Combination strategies: radiation therapy, chemotherapy, oncolytic viruses*
  - *Intrinsic strategies: gene editing checkpoints, secreting ICB, targeting TGFb*
  - *Preconditioning, routes of T cell administration, repeat infusions*


T Cell Therapy at COH
Brain
- Glioma
- **Brain Metastasis**
Solid Tumors
- **Prostate**
- Breast
- **Pancreatic**
- **Ovarian**
- Liver
Hematological
- Leukemia – AML, ALL
- Lymphoma
- Multiple Myeloma

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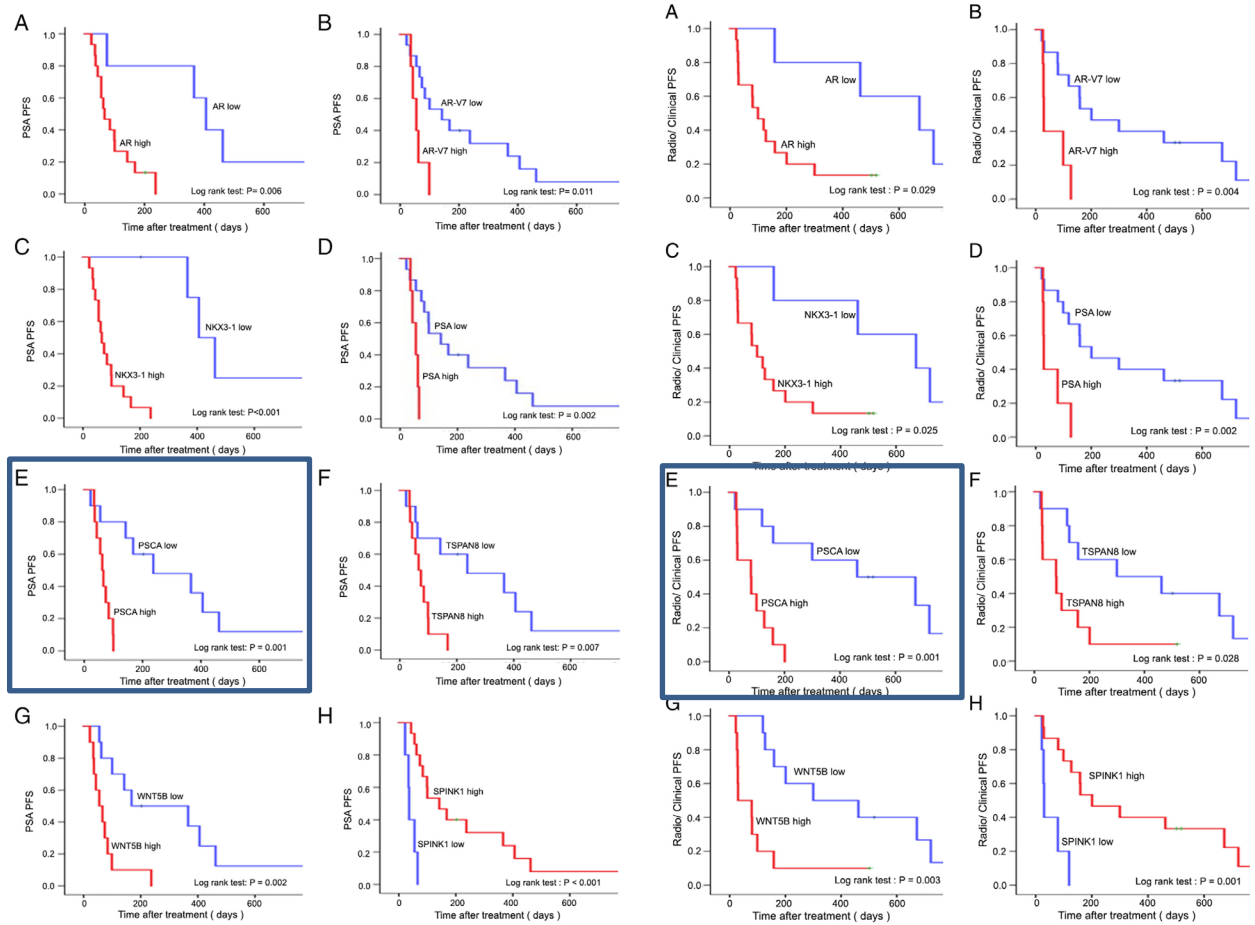
PSCA Expression in Prostate Cancer

- Prostate Stem Cell Antigen (PSCA) was identified by Reiter et al. at UCLA in 1998
- Over-expressed in <60% of primary prostate tumors and 80-100% of metastatic tumors
- Limited expression pattern in normal tissue, making it an ideal target for CAR T cell therapy



Chung et al, Neoplasia 2019

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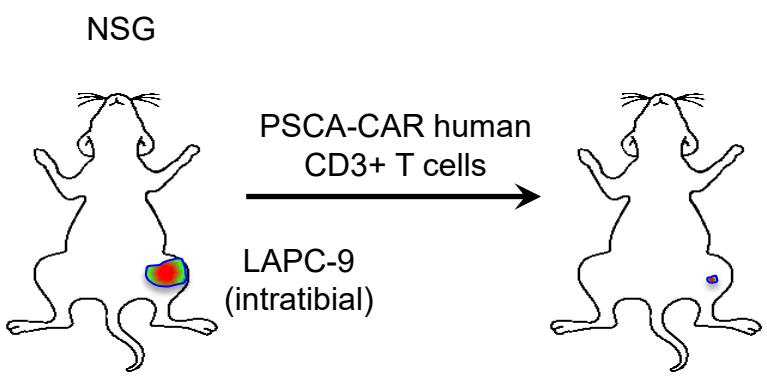
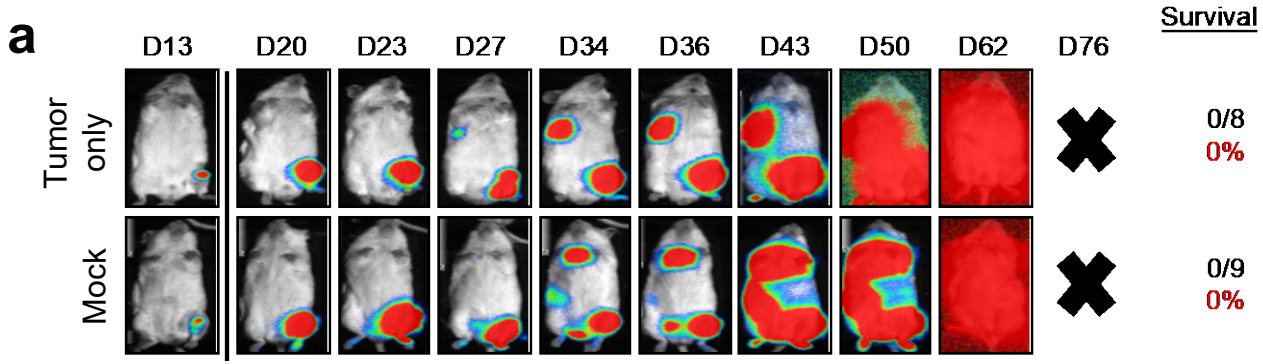
PSCA-41BBζ CAR T Cells Show Increased Control of Disseminated Disease





-4-1BB co-stimulation demonstrates durable anti-tumor activity in patient-derived PSCA+ PCa bone metastasis xenograft model, compared with CD28 co-stimulation

Priceman, et al. *OncoImmunology 2018*

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Phase I Clinical Trials to Evaluate PSCA-BBζ CAR T Cells in Solid Tumors

- **PSCA+ metastatic castration resistant prostate cancer**
  (Clinical PI: Tanya Dorff, MD, Research PI: Saul Priceman, PhD) – Enrolling
- **PSCA+ metastatic pancreatic cancer** – TBD

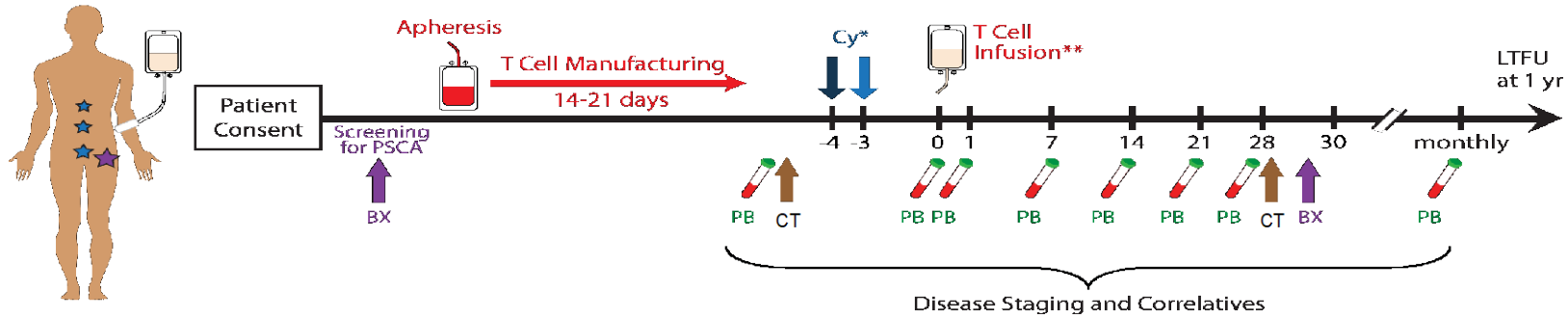

Table 1. CAR+ Cell Dose Schedule				
Dose -1	**Starting Dose 0a**	Dose 0b	Dose 1	Dose 2
50M	**100M**	100M +precond.	300M +precond.	600M + precond.

Prostate Cancer Foundation
Curing Together.

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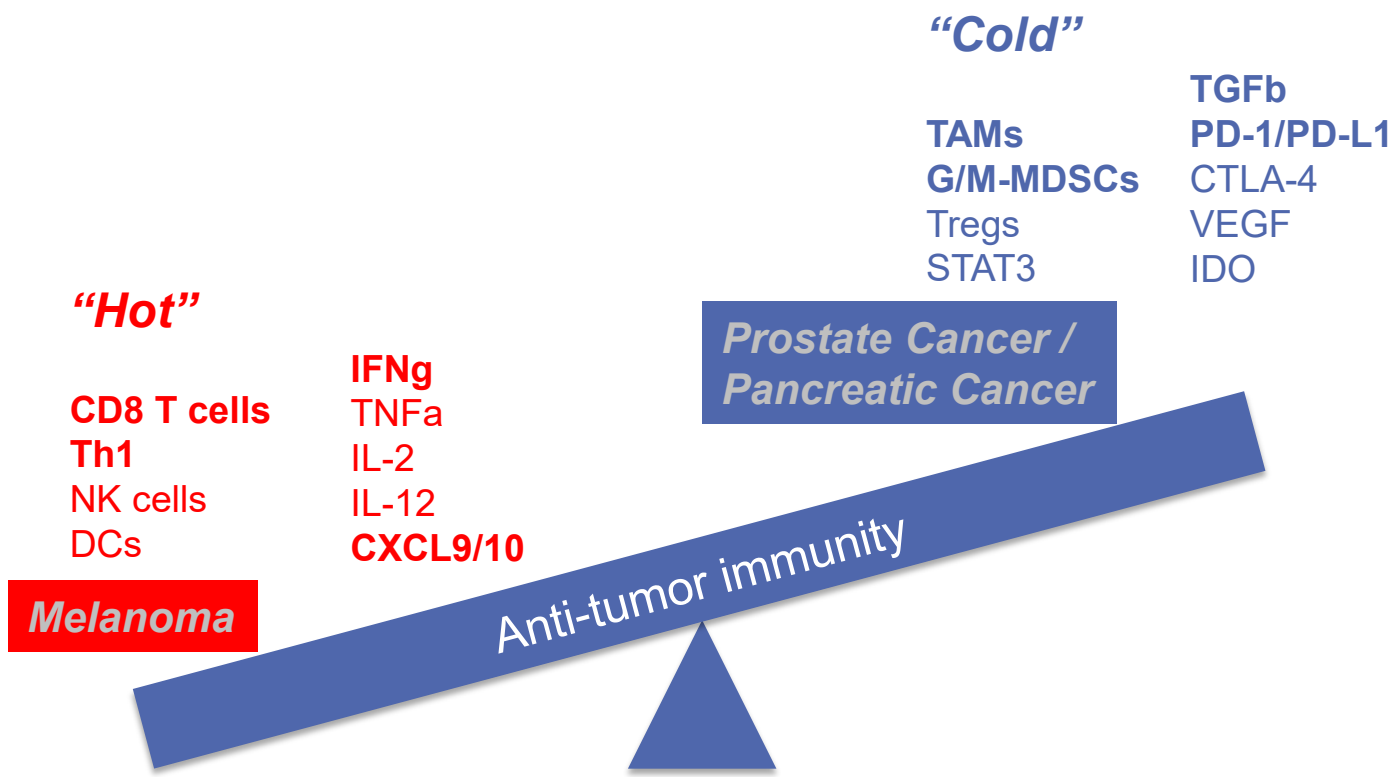
Immunologically "*Hot*" *vs.* "*Cold*" Tumors



Tumor mutational burden	↑	↓
Stromal/Fibrosis contribution	↓	↑
T cell accumulation	↑	↓
High suppressive myeloid/T cells	↓	↑

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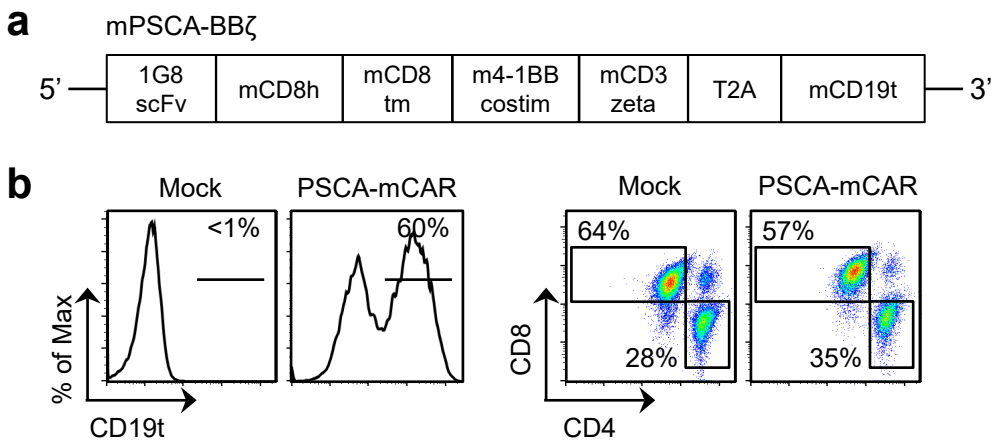
Syngeneic Immunocompetent Cancer Mouse Model "Safety and Efficacy"

- Generation of fully-murine CAR construct in retrovirus

- Effective transduction and *ex vivo* expansion of murine splenic T cells



Murad et al. *Mol Ther* 2021

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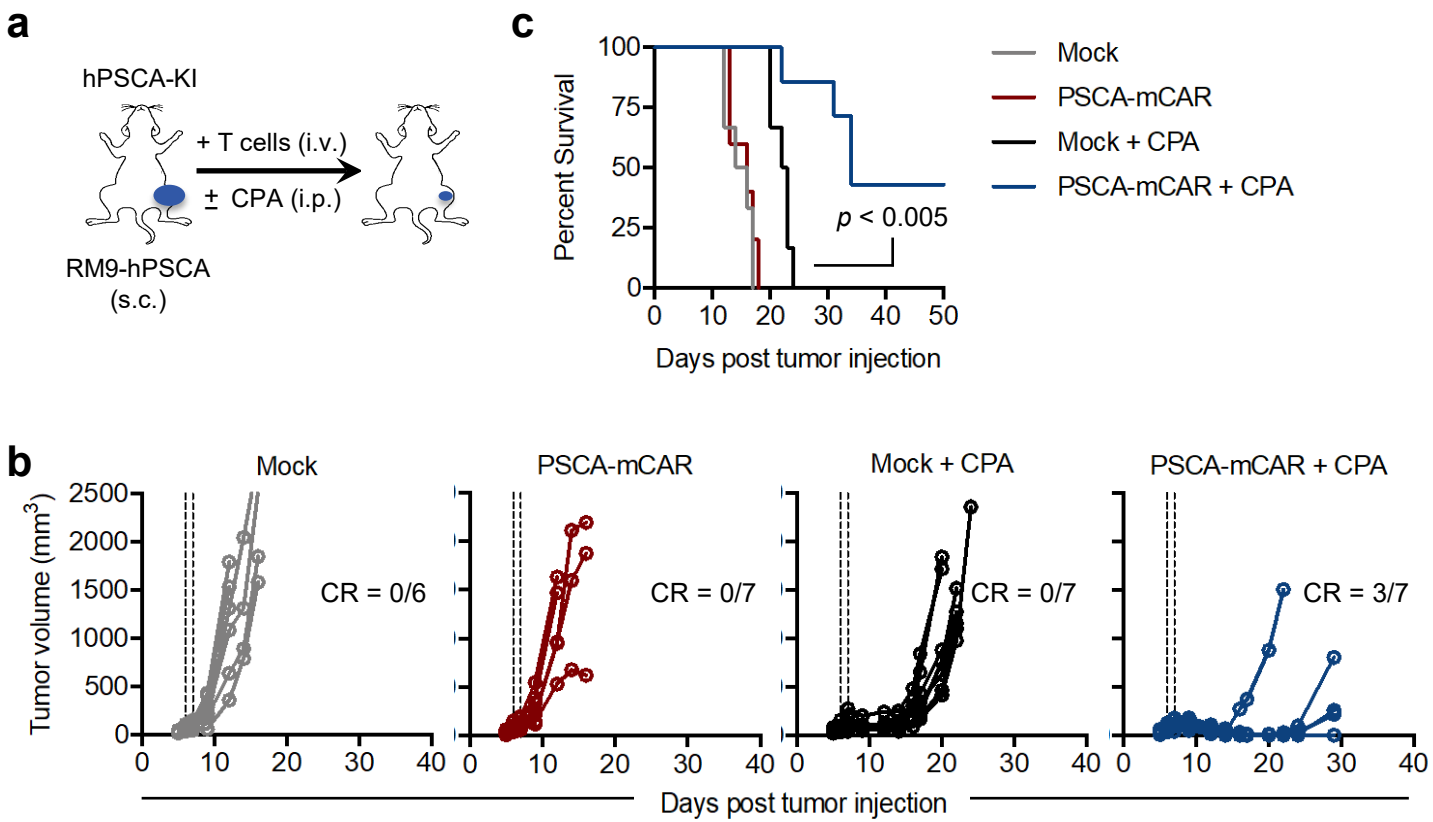
Requirement of Lymphodepleting Preconditioning for Solid Tumor CAR T Cell Efficacy



-Safe and effective CPA-preconditioning and PSCA-CAR T cell-mediated anti-tumor responses

Murad et al. *Mol Ther* 2021

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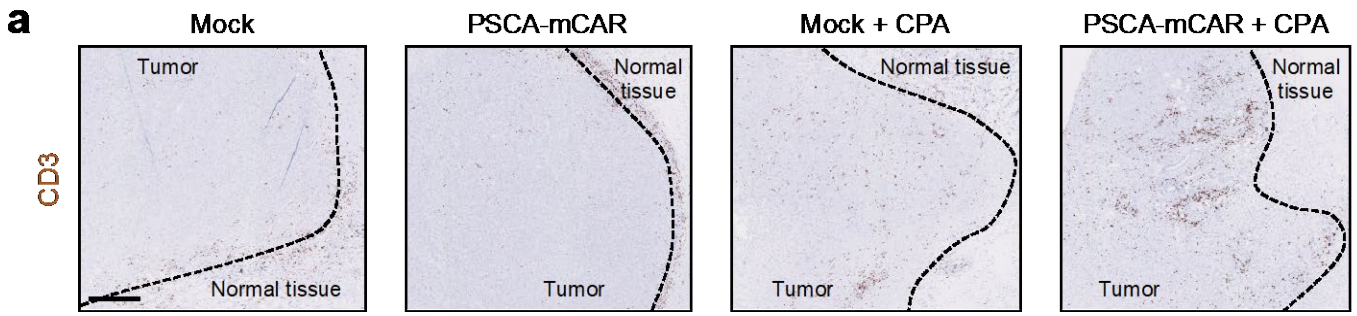
Lymphodepleting Preconditioning Promotes Endogenous and CAR T Cell Infiltration to Solid Tumors



-Tumor infiltration of T cells and PSCA-CAR T cell antitumor activity requires CPA pre-conditioning
-CPA converts to immunologically “warm” tumors with increased CD11c+ DCs and reduced CD206+ M2 macrophages

Murad et al. *Mol Ther* 2021

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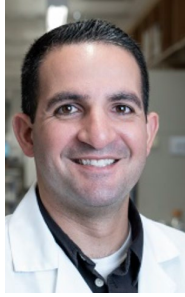
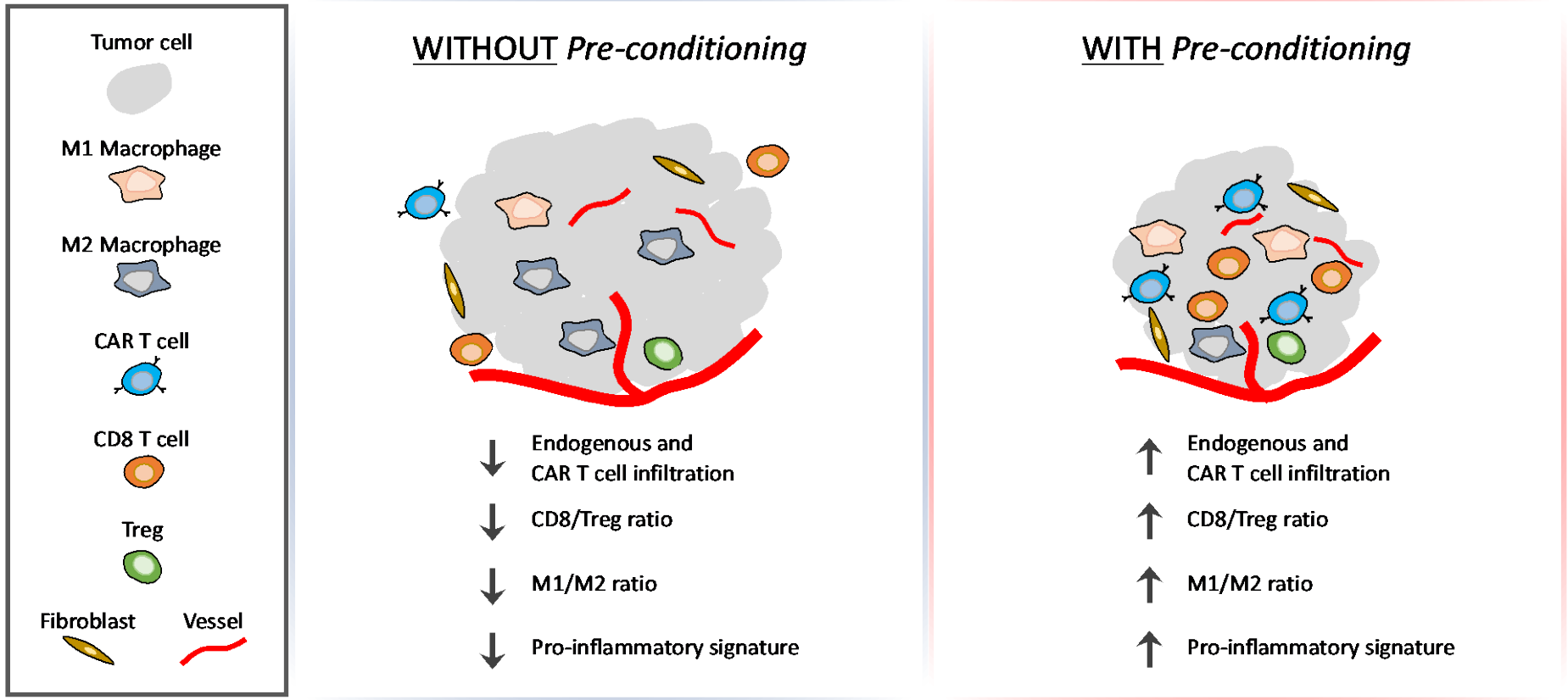
Lymphodepleting Preconditioning Promotes Endogenous and CAR T Cell Infiltration to Solid Tumors





Murad et al. *Mol Ther* 2021

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What are the most rational immunotherapy combinations for CAR T cells?

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XXX Pathway Upregulation Following CAR T Cell Therapy

- Despite the benefits of CPA pre-conditioning, PSCA-mCAR T cells only achieve ~50% CR
- In PSCA-mCAR T cell + CPA treatment groups, IPA analysis of enriched canonical pathway reveals increased XXX signaling:

- Could combination of PSCA-CAR T cell + targeted XXX inhibition improve outcomes?

Murad et al. *Unpublished*

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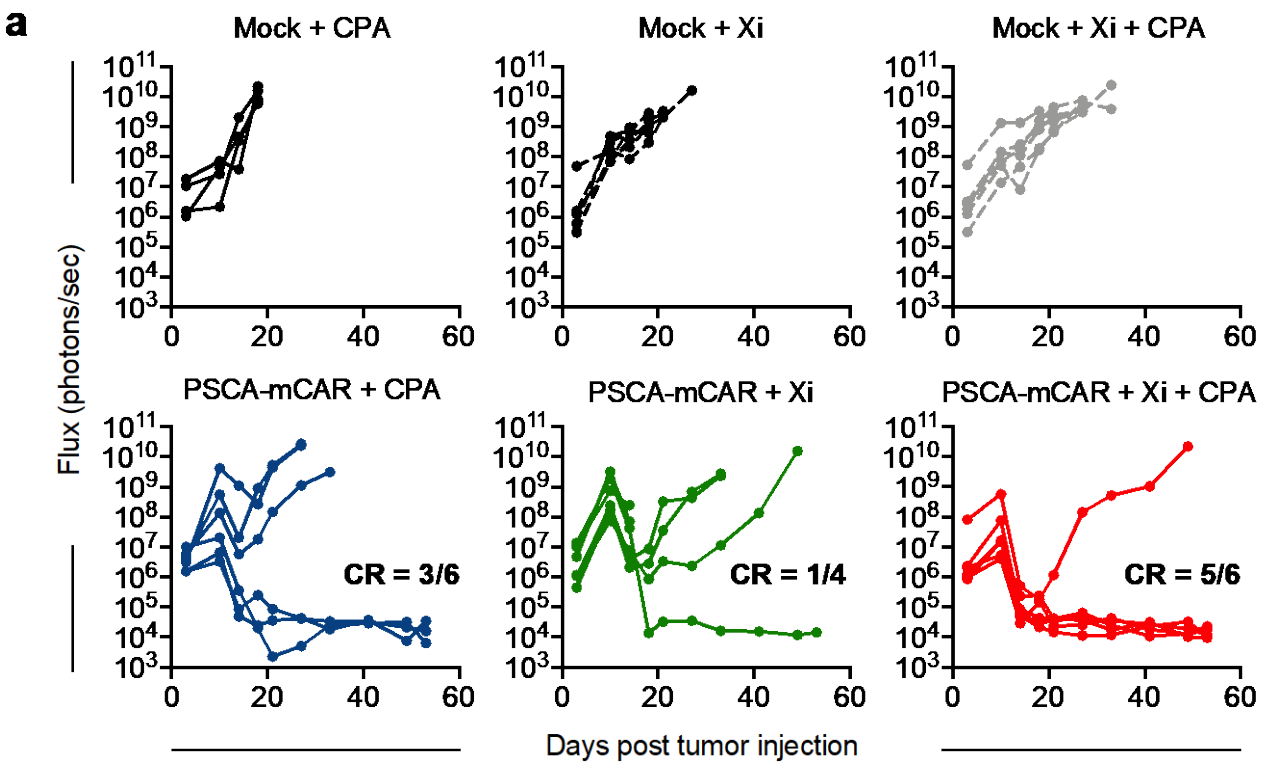
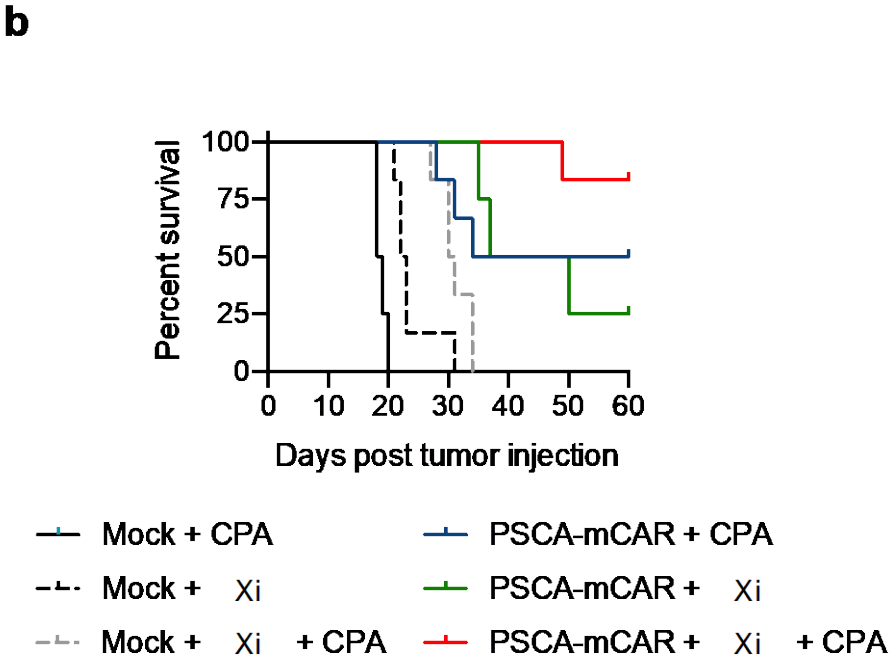
XXX Blockade Promotes CAR T Cell Efficacy





-Xi inhibition promotes anti-tumor efficacy of PSCA-CAR T cells

Murad et al. *Unpublished*

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What are the most rational immunotherapy combinations for CAR T cells?

Oncolytic Viruses?

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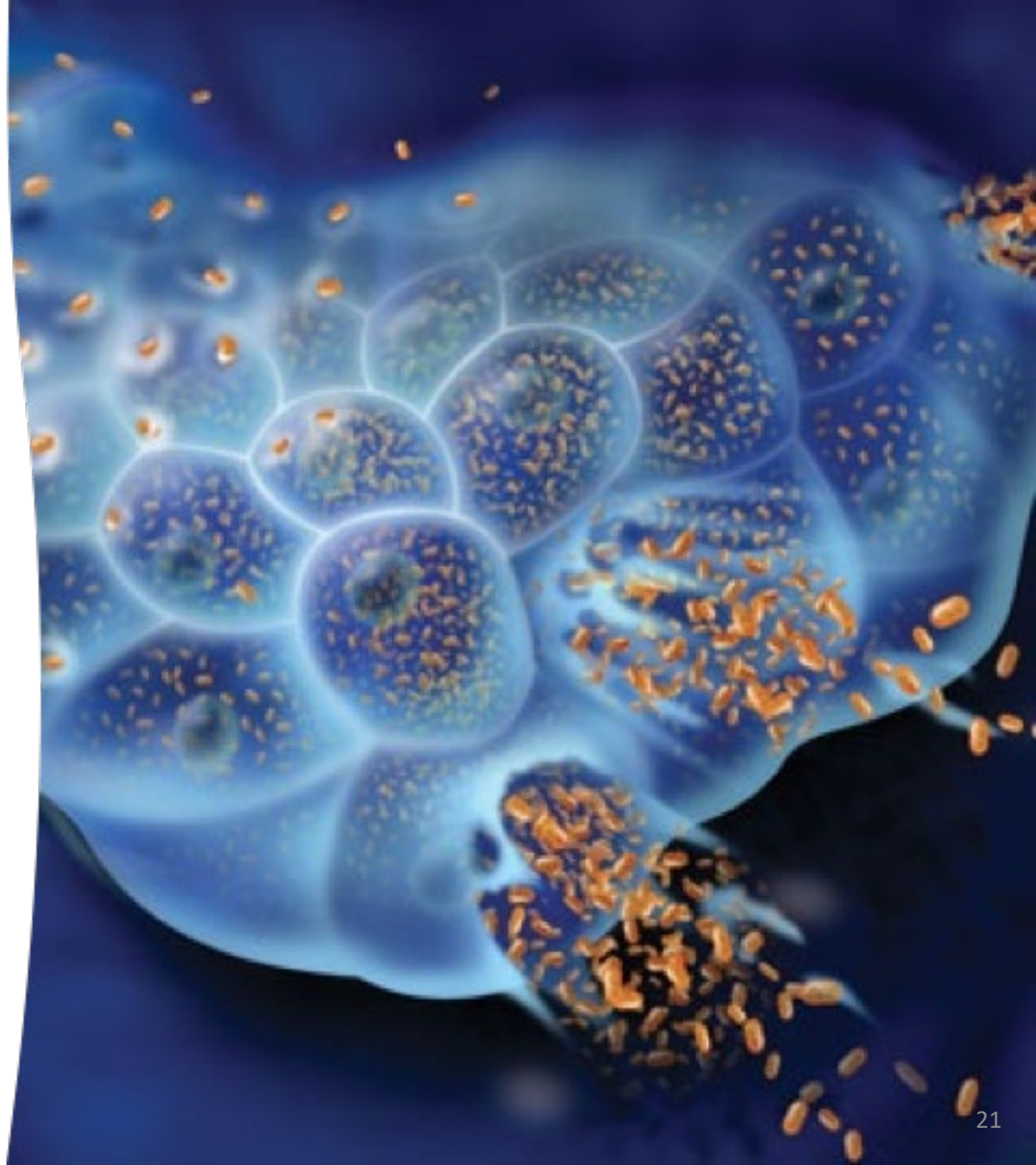
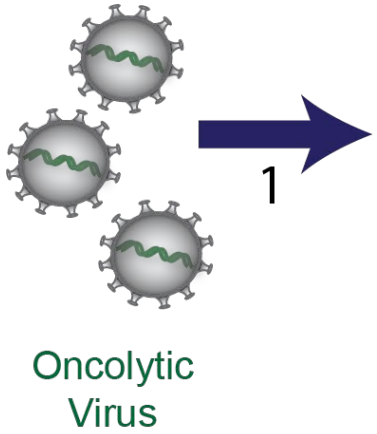
Oncolytic Viruses (OV)

- **Selectively** infect and replicate in tumors, causing direct killing or promoting immunogenic cell death (ICD)
- ICD can induce tumor-associated antigen release, recruitment of APCs, and elicit adaptive antitumor immunity
- Engineer-able to express genes of interest for tumor delivery
- T-VEC – FDA approved HSV-I expressing GM-CSF for metastatic melanoma
- **Challenges with using OV as a single therapeutic reagent**



Oncolytic Viruses Deliver CAR Targets and ‘Warm Up’ Solid Tumors



Park et al. *Science Translational Medicine* 2020

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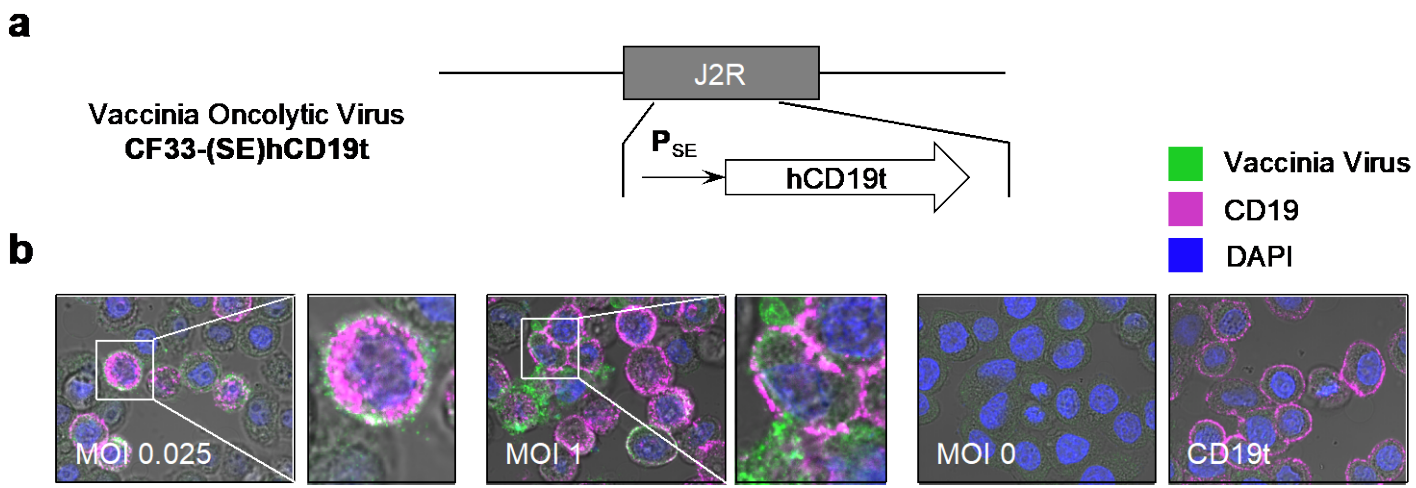
Oncolytic Viruses Deliver CAR Targets to "*Targetless*" Solid Tumors



Park et al. *Science Translational Medicine* 2020

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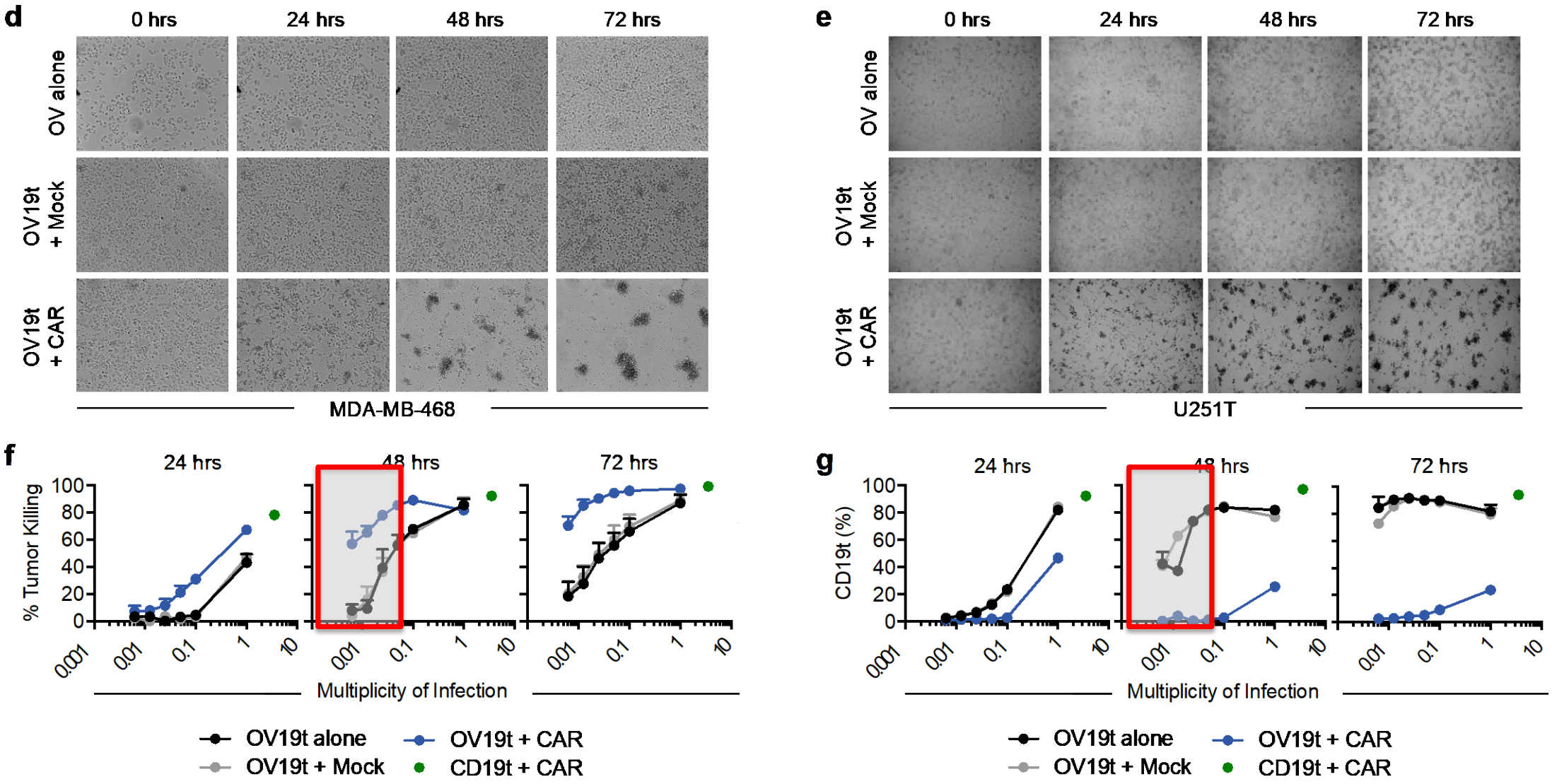
CD19-CAR T Cells Kill OV19t-Infected Tumors



-OV19t + CD19-CAR T cells show potent anti-tumor activity *in vitro*

Park et al. *Science Translational Medicine* 2020

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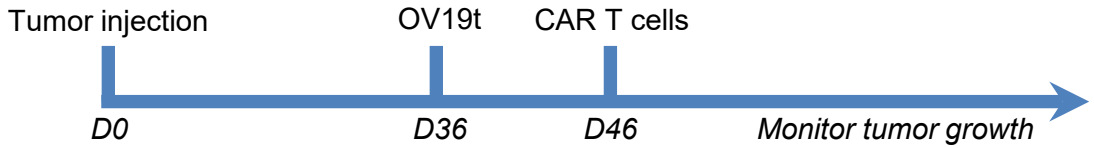
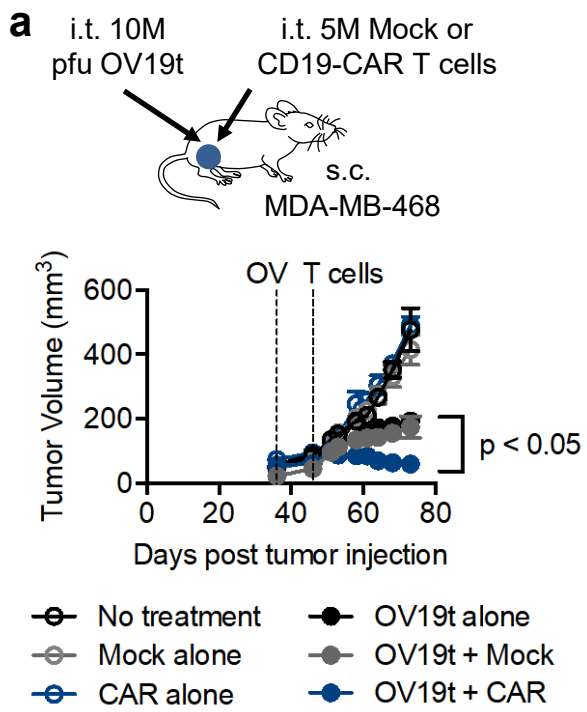
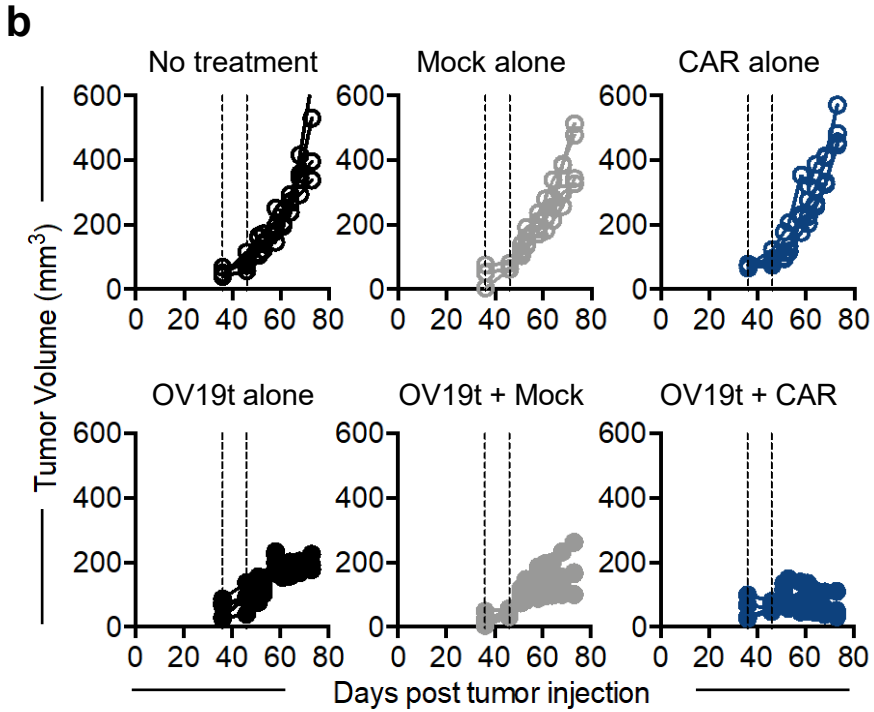
OV19t Drive CD19-CAR T cell Anti-Tumor Responses in Solid Tumors







-Combination of OV carrying CD19t and CD19-CAR T cells promotes tumor regression in xenograft model of TNBC

Park et al. *Science Translational Medicine* 2020

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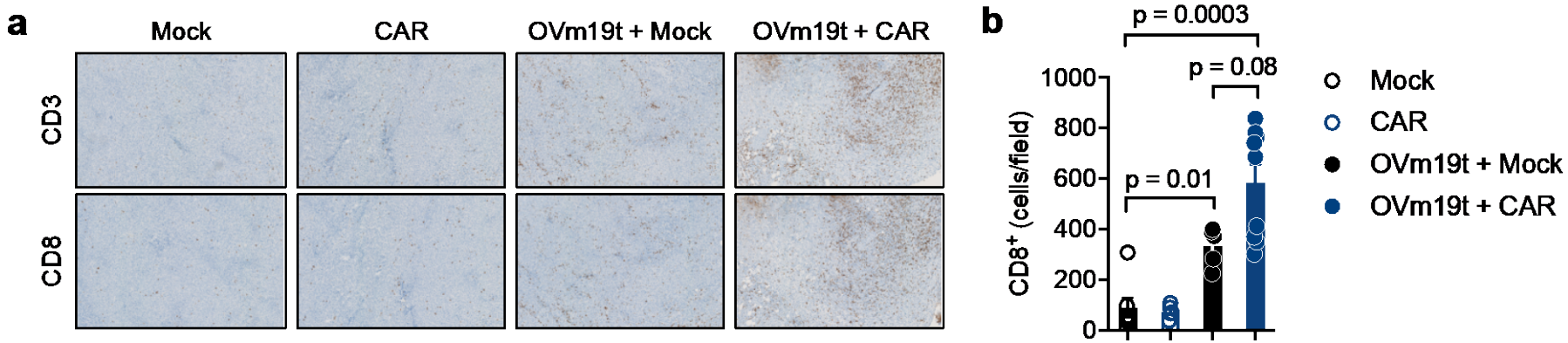
OV19t Promotes Endogenous and CAR T Cell Tumor Infiltration



-Combination of OV carrying CD19t and CD19-CAR T cells promotes endogenous cytotoxic T cells and CAR T cells, and memory T cell responses

Park et al. *Science Translational Medicine* 2020

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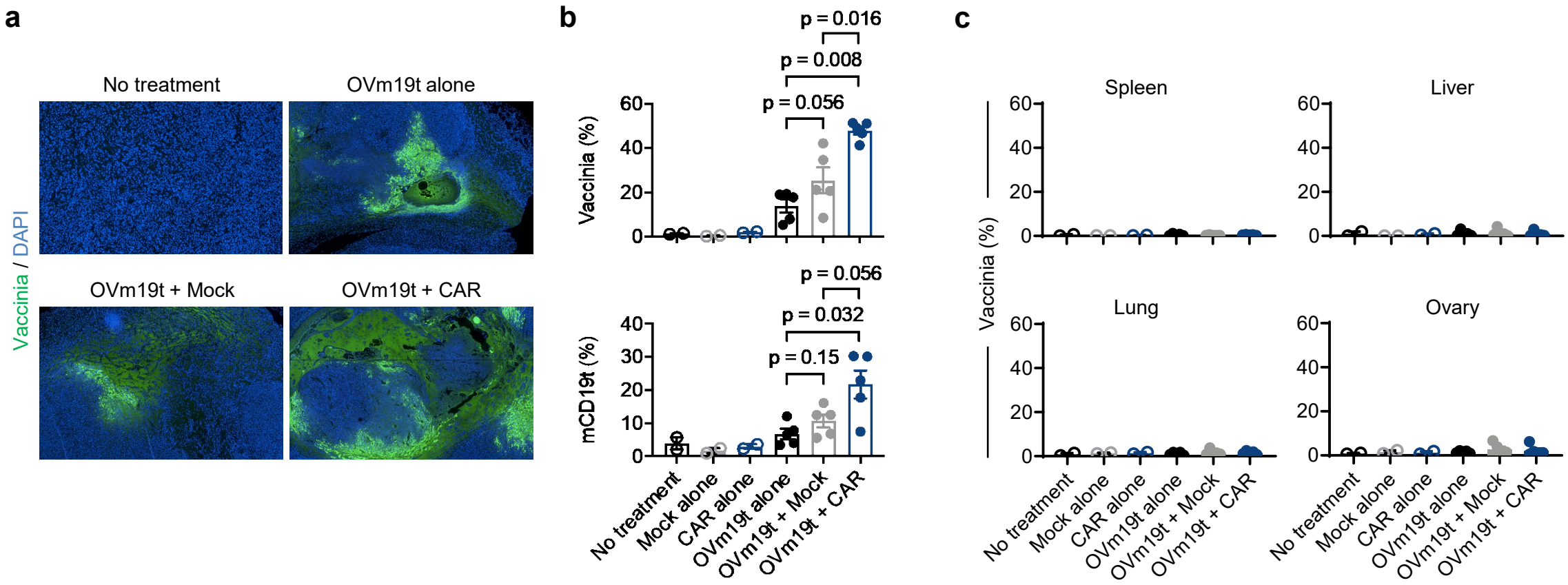
CD19-CAR T Cells Drive Intratumoral OV Spread



-CD19-CAR T cells amplify viral spread in solid tumors

-CD19-CAR T cells do not amplify virus spread in normal tissues

Park et al. *Science Translational Medicine* 2020

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Where do we go from here?

- **Lessons from phase 1 trials: reverse translation**
  - Prostate, brain metastasis, ovarian cancer, pancreatic cancer

- **Overcoming tumor antigen escape / immunosuppression**
  - Do immunologically “warm” tumors following better engage endogenous immunity (ICB, CAR, etc)?
  - What is the right combination approach?
  - What is the optimal timing and duration of combination strategies for durable anti-tumor activity?
  - What constitutes a responsive/non-responsive tumor to immunotherapy?
  - Contribution of microbiome? Contribution of neuro-signaling?

Acknowledgements

Priceman Lab

Current members

John Murad, PhD
Anthony Park, PhD
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Gaurav Dhapola, MS
Jackson Gibson, BS
Eric Lee, BS
Jason Yang, BS
Lupita Lopez, BS (GSR)
Cari Young (GSR)
Kevin Ou, BS
Cody Cullen, BS
Catalina Martinez, BS (Proj Mgr)

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Brook Jeang, MS (UCI PhD grad)
Kelly Kennewick, BS (UCLA PhD grad)
Anna Kozlowska, PhD (Poseida)
Rudra Bhowmick, PhD
Achini Bandara, PhD

Not shown: Jason Yang, Kevin Ou, Cody Cullen, Catalina Martinez

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Brenda Aguilar, MS (Animal Mgr)
Elizabeth Budde, MD
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Vanessa Jonsson, PhD (Comp Bio)
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Julie Ostberg, PhD
Kirsten Rood, PhD
Larry Stern, PhD (now USF)
All of the TCTRL

Collaborators

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Curing Together.

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Department of Defense

STOP CANCER
FUNDING RESEARCH FINDING CURES

PARKER INSTITUTE
for CANCER IMMUNOTHERAPY

Meringoff Foundation
Norris Foundation
Horowitz/Marsh funds

CIRM
CALIFORNIA'S STEM CELL AGENCY