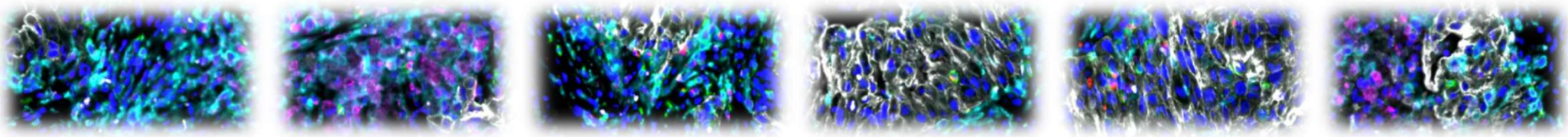

Differentiating Macrophages are Regulated by PARP Inhibitors and can be Harnessed to Overcome PARP-Inhibitor Resistance in BRCA-Associated Triple-Negative Breast Cancer

Dr. Anita Mehta
Poster #860

Jennifer Guerriero, PhD

Lead Investigator, Brigham and Women's Hospital
Instructor, Harvard Medical School
Director, Breast Tumor Immunology Laboratory, Dana-Farber Cancer Institute

SITC 35th Annual Meeting
Innate Immunity: The Next Generation of Targets for Anti-Cancer Immunotherapy

@JennGuerriero

Dana-Farber Cancer Institute | Breast Tumor Immunology Lab, Dana-Farber Cancer Institute | Ludwig Cancer Research | Laboratory of Systems Pharmacology | The Center for Cancer Systems Pharmacology | HiHiS Harvard Program in Therapeutic Science | Harvard Medical School | Brigham Health, Brigham and Women's Hospital

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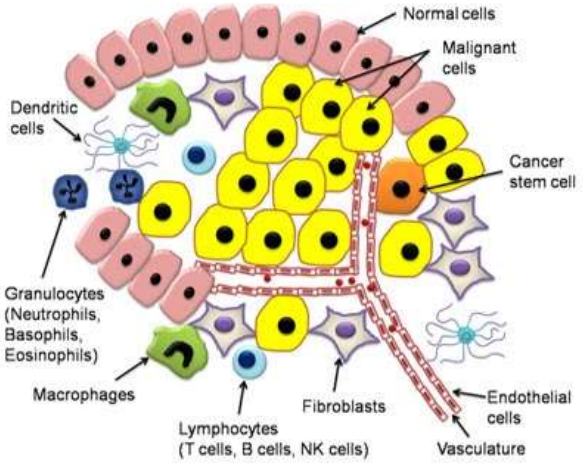
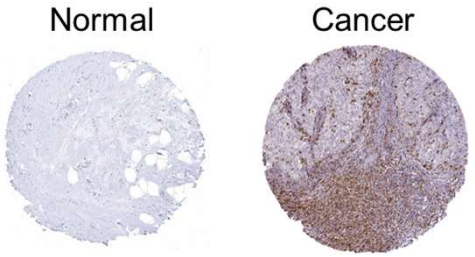
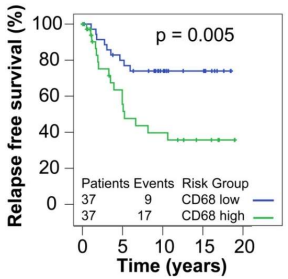
The tumor microenvironment contains a variety of non-malignant cells

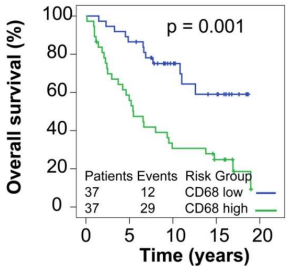
- Play a pivotal role in tumor progression and metastasis
- T-cell immunotherapy has had modest responses in breast cancer
- Macrophages can represent up to 50% of the tumor mass
- Macrophage density is associated with poor prognosis





IHC: CD68 (human macrophage marker)





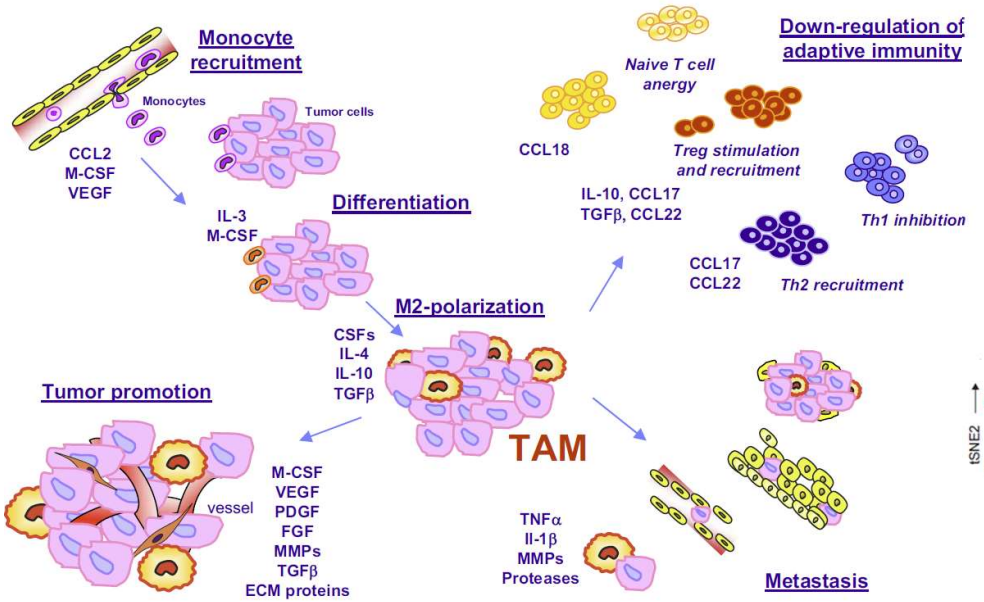
Proteinatlas.org

Tymoszuk et. al. *BMC* 2014.

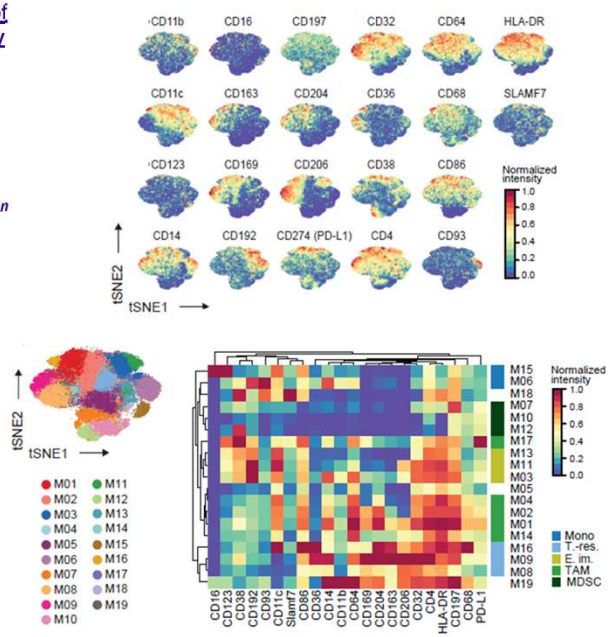
Upreti, Jyoti and Sethi. *Translational Cancer Research* 2013.

Tumor macrophages promote tumorigenesis

- **Pro-tumor**
  - Repair mechanism
  - Pro-tumor
- **Anti-tumor**
  - Defense mechanism
  - Anti-tumor



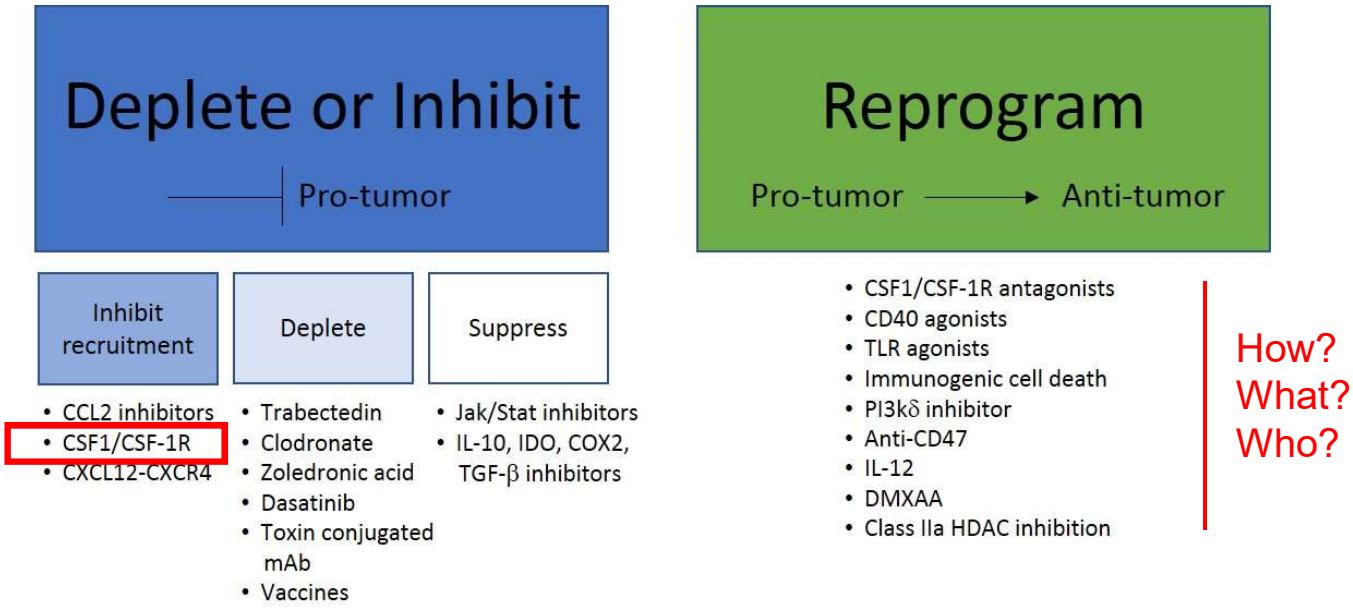
Human breast tumors



Wagner, J. *Cell* 2019.

Solinas, G. *Journal of Leukocyte Biology* 2009.

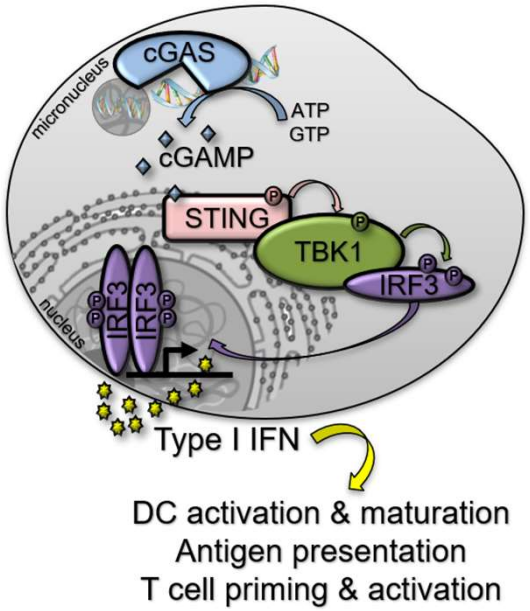
Can we find rational ways to target tumor macrophages for anti-cancer therapy?



Guerriero *et al. Nature*. 2017.
Guerriero, JL. *Trends MM*. May 2018.

The STING pathway is active in *BRCA*-associated TNBC

- TNBC - aggressive, poor survival
- *BRCA*-associated TNBC is homologous recombination (HR) repair deficient
- *BRCA*-associated cancer cells have high levels of cytosolic DNA
  - Activation of the STING pathway
  - Secretion of CXCL10, CXCL9, CCL5
  - Recruitment of immune cells
- BRCA mutations regulation of the TME

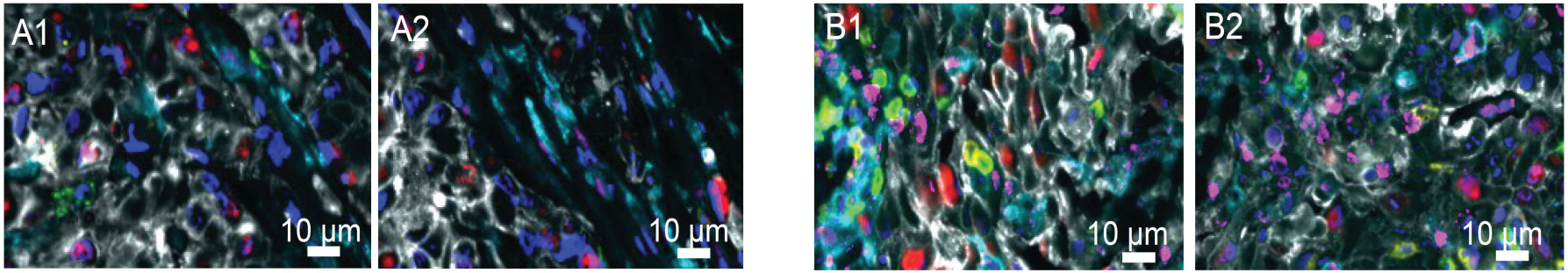


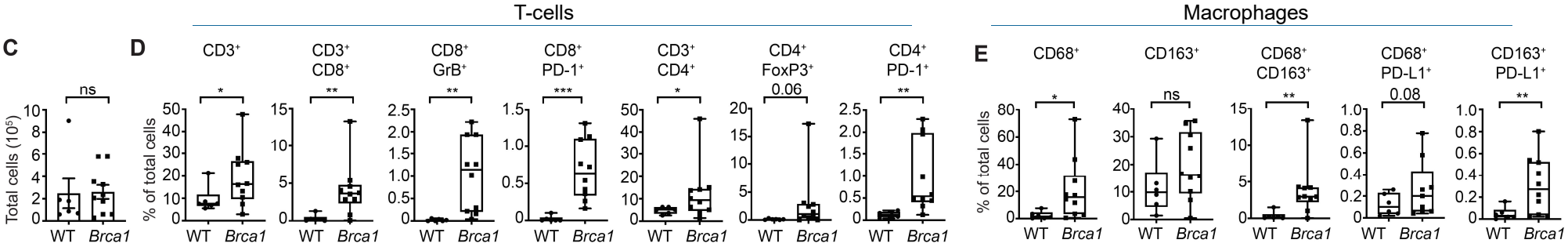
Parkes E.E. *JNCI* 2017.
Panteildou…Guerriero*, Shapiro* et al. *Cancer Discovery* 2019.

BRCA1-associated TNBC are highly infiltrated with macrophages and T-cells

TNBC *BRCA*-wild type

TNBC *BRCA1*-associated





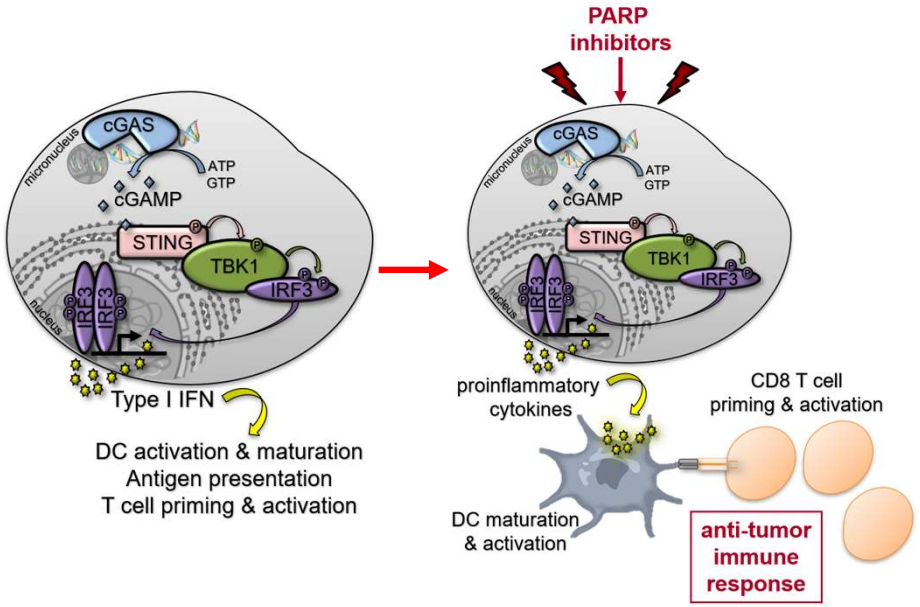
In collaboration with Drs. Judy Garber and Nadine Tung and the laboratories of Drs. Sorger and Santagata

Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

PARP inhibitor efficacy depends on CD8+ T-cell recruitment via intra-tumoral STING pathway activation in *BRCA*-deficient TNBC

<u>TNBC breast cancer model:</u>
K14-Cre BRCA1f/fp53f/f

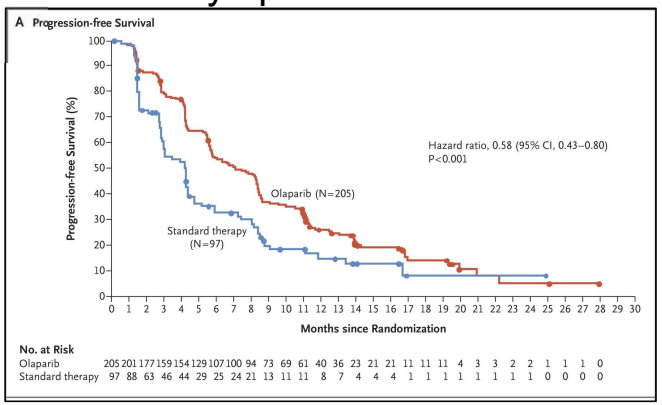
- PARPi therapy further activates the STING pathway
- Efficacy of PARP inhibition is dependent cGAS/STING pathway activation and recruitment of CD8 T-cells
- cGAS/STING activation is more pronounced in *BRCA1*-deficient TNBC compared to *BRCA1*-proficient



Pantelidou….Guerriero*, Shapiro* et al. *Cancer Discovery* 2019.

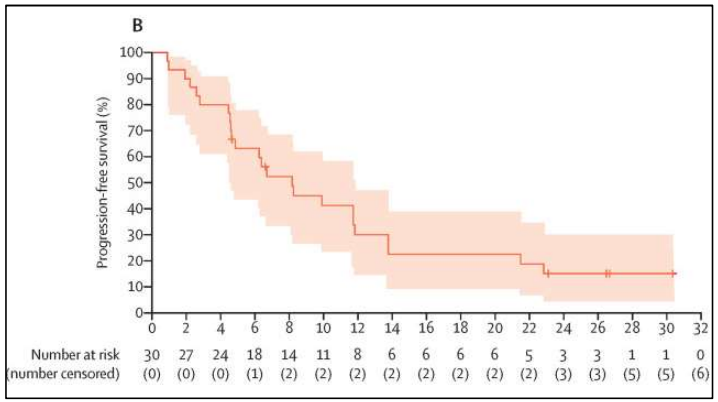
Clinical response to PARPi + ICB have not yet demonstrated activity superior to PARPi monotherapy

OlympIAD: PARPi



ORR: 59.9%
PFS: 7 months

MEDIOLA: PARPi + ICB



ORR: 63.3%
PFS: 8.2 months
DCR at 12 weeks: 80%

Single agent PD-1/PD-L1

Keynote-012 Pembro in TNBC: ORR: 18.5

Atezo in TNBC: ORR 10%

Avelumab in TNBC: 5.2% (22.2% in PD-L1+)

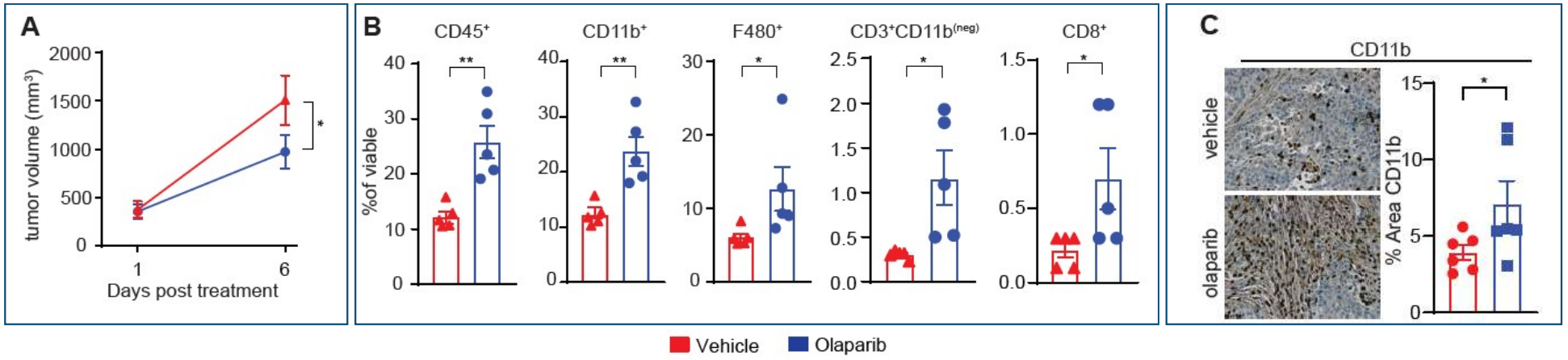
Do macrophages limit the therapeutic response to PARP inhibitors?

Robson M et al. NEJM 2017.
Domchek S, et al. Lancet Oncol 2020.
Nanda, R JCO 2016.
Emens LA, JAMA Oncol 2019.
Dirix LY, BCRT 2018.

PARP inhibitor therapy increases tumor macrophages in *BRCA1*-def TNBC

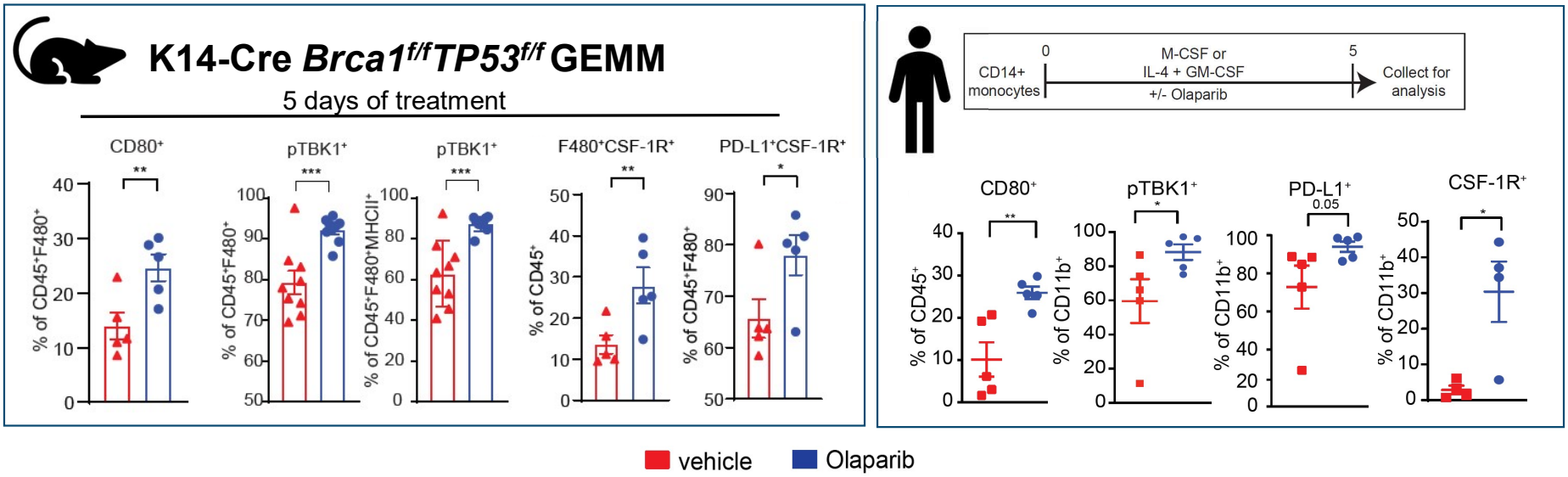
K14-Cre *Brca1$^{f/f}$TP53$^{f/f}$* GEMM

Liu *et al.*, *PNAS*, 2007
Rottenberg *et al. PNAS,* 2008.



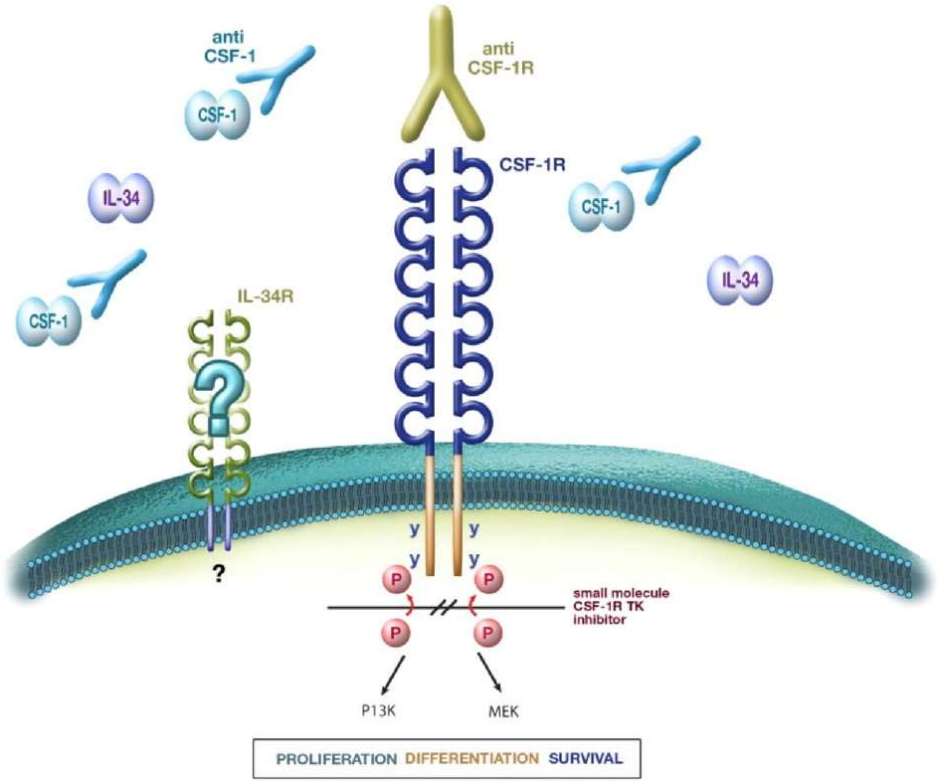
Mehta…Guerriero et al. *In Revision*.

PARP inhibitor therapy modulates differentiating macrophages

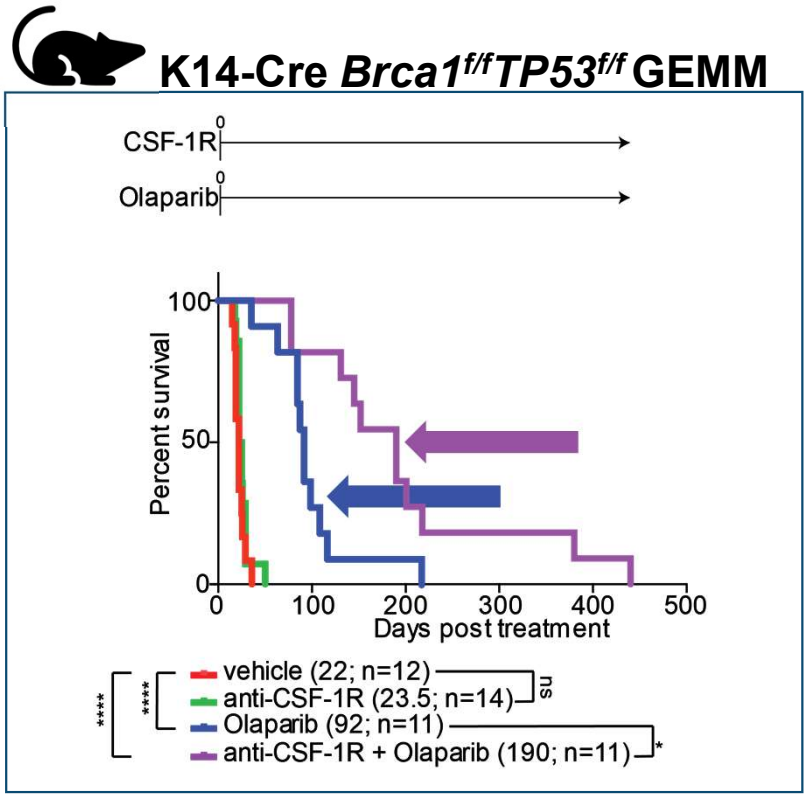


Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

CSF-1R is expressed by mature macrophages



Anti-CSF-1R enhances PARP inhibitor therapy in *BRCA1*-def TNBC

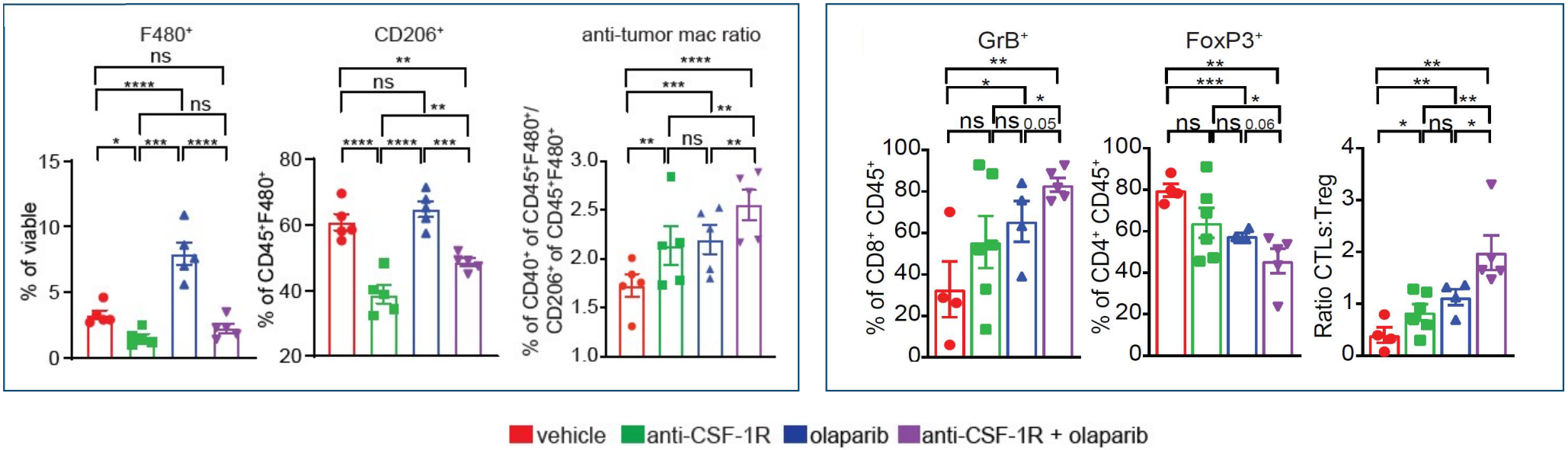


Macrophage-mediated immune suppression as a liability of PARP inhibitors.

Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

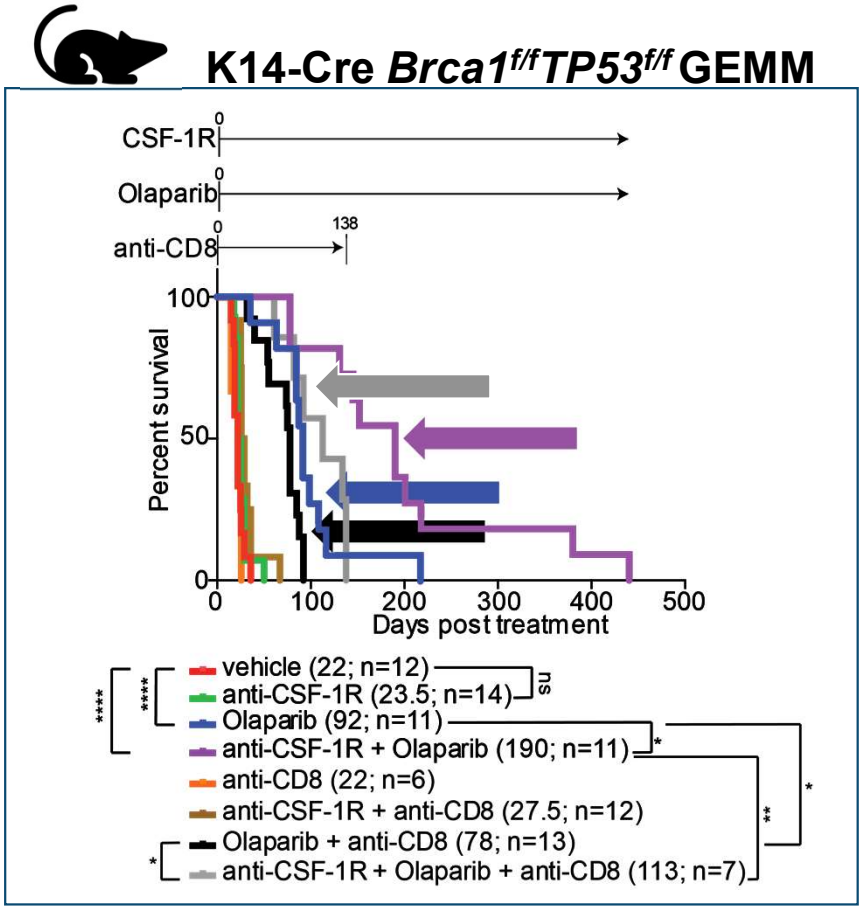
Does anti-CSF-1R and Olaparib therapy activate anti-tumor innate and adaptive immunity?

K14-Cre *Brca1$^{f/f}$TP53$^{f/f}$* GEMM



Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

Anti-CSF-1R enhances PARP inhibitor therapy and is CD8 T-cell dependent



Both innate and adaptive anti-tumor activity will be necessary for durable clinical outcomes.

Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

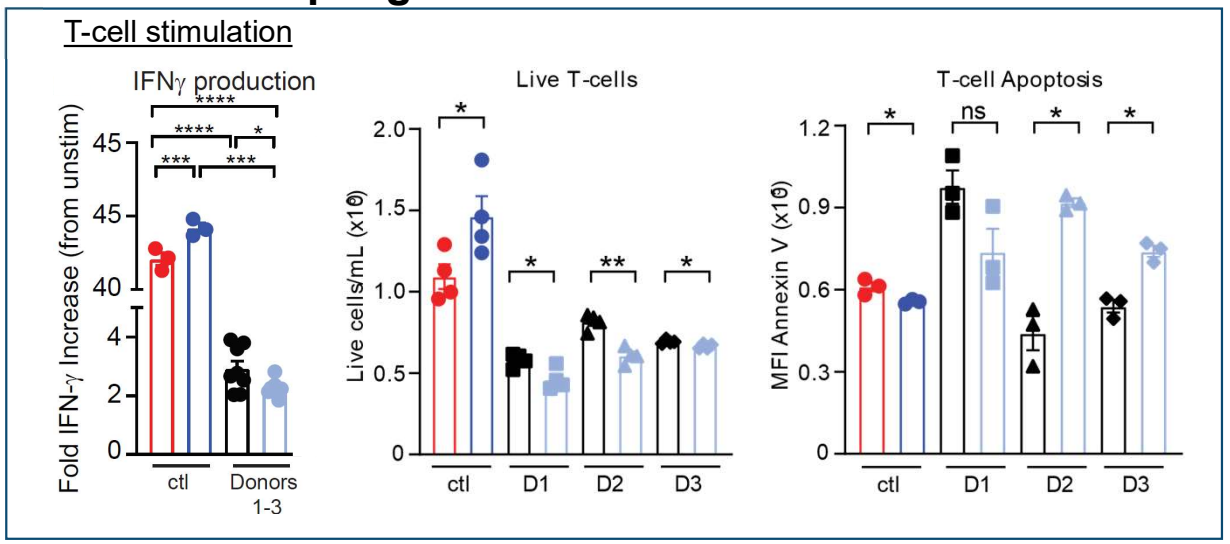
How do Olaparib-treated macrophages suppress T-cell function and survival?

MUSC Medical University of South Carolina

Jessica Thaxton, PhD

Katie Hurst

Human macrophage conditioned media



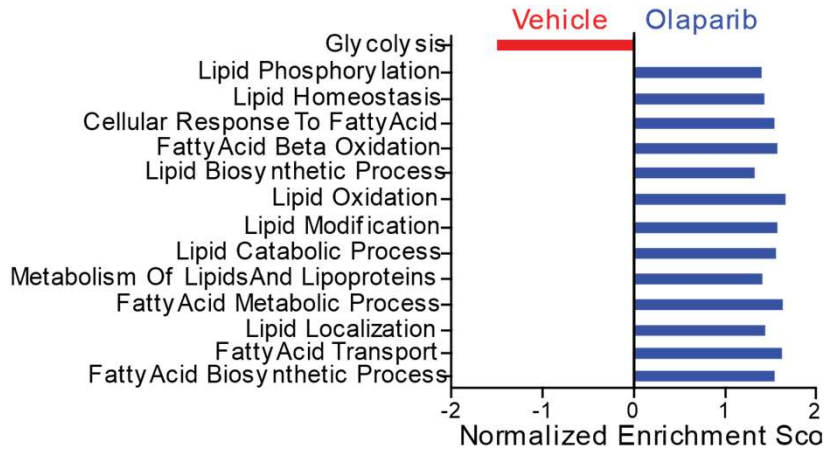
Olaparib-treated macrophages inhibit T-cell function and induce T-cell apoptosis.

Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

Unbiased approaches reveal PARP inhibitor-induced macrophage lipid metabolic processes

Human macrophages

RNA sequencing



Nathan Johnson, PhD, Sarah Boswell, PhD

Proteomics

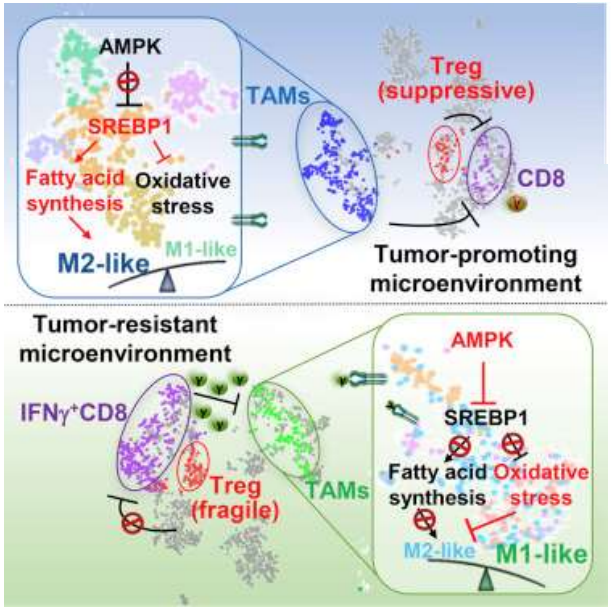
100 most significantly upregulated proteins with FDR <0.05

GO-ID	Description	p-val
6629	lipid metabolic process	1.65E-07
8152	metabolic process	7.69E-06
44255	cellular lipid metabolic process	6.00E-05
5506	iron ion binding	1.63E-04
40009	regulation of growth rate	1.86E-04
5789	endoplasmic reticulum membrane	6.31E-04
6633	fatty acid biosynthetic process	1.40E-03
10876	lipid localization	1.63E-03
32787	monocarboxylic acid metabolic process	1.64E-03
6633	fatty acid biosynthetic process	1.40E-03
42769	DNA damage response	6.46E-04
20037	heme binding	6.27E-04
51938	L-glutamate import	4.63E-04

Marian Kalocsay, PhD and Matthew Berberich

Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

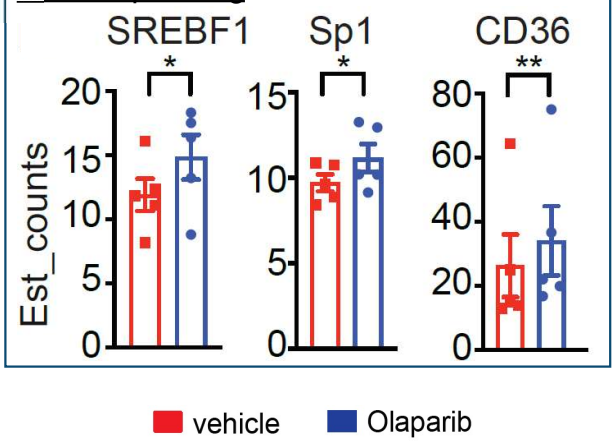
The SREBP1-mediated fatty acid synthesis pathway is associated with pro-tumor macrophages



Liu et al. *Immunity*. 2019

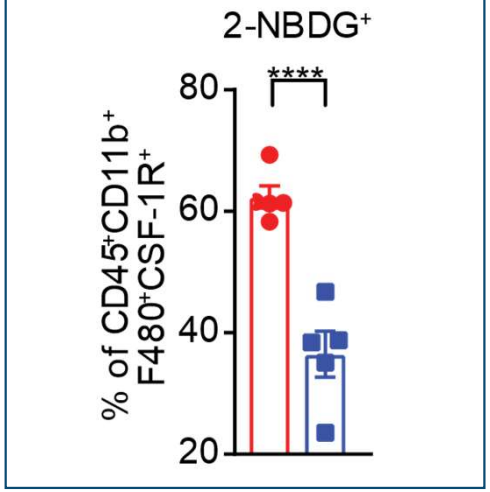
Human macrophages

RNA sequencing



Murine macrophages

Ex vivo uptake of labelled glucose

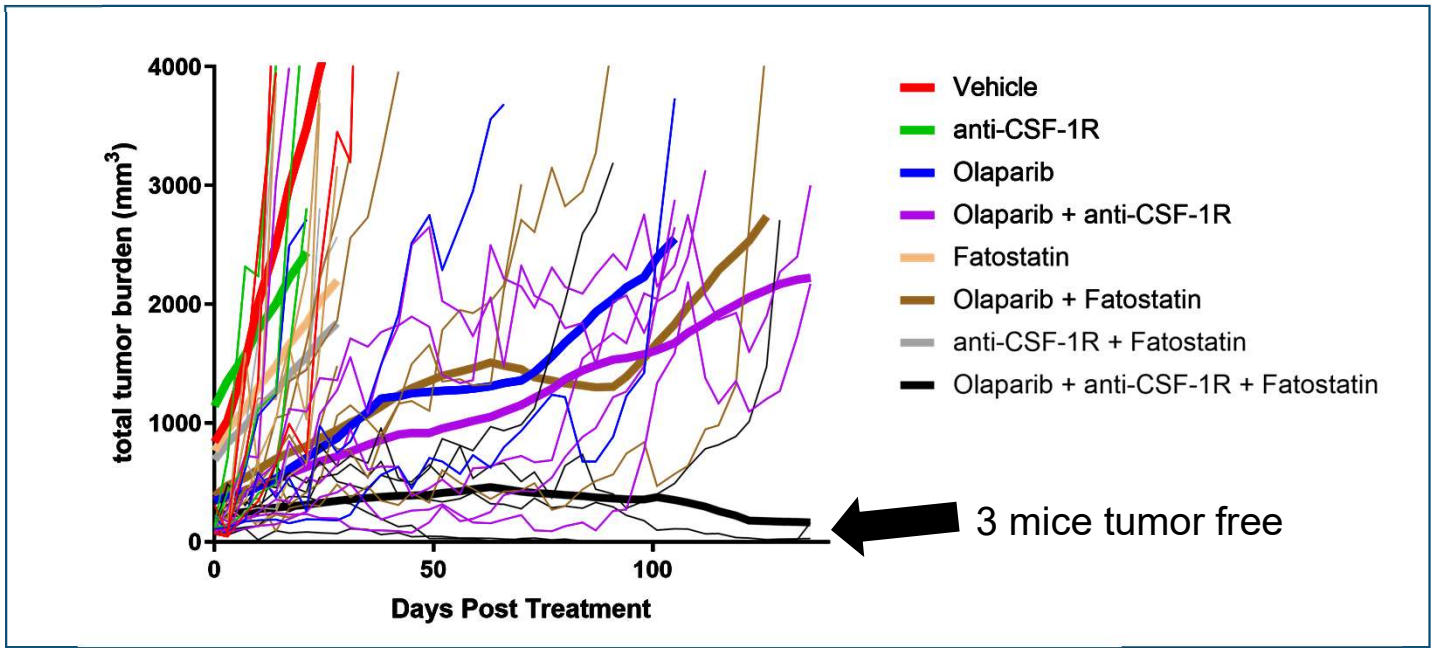


Sterol regulatory element-binding protein 1 (SREBP1)

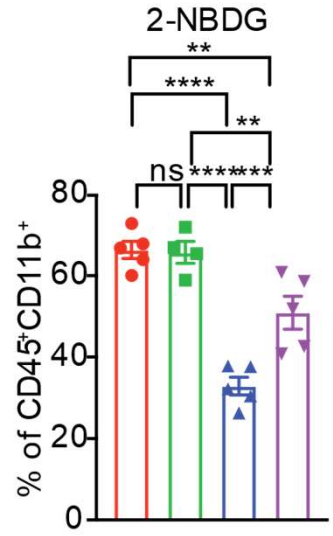
Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

Can SREBP1 inhibition enhance PARP inhibitor therapy?

K14-Cre *Brca1$^{f/f}$TP53$^{f/f}$* GEMM

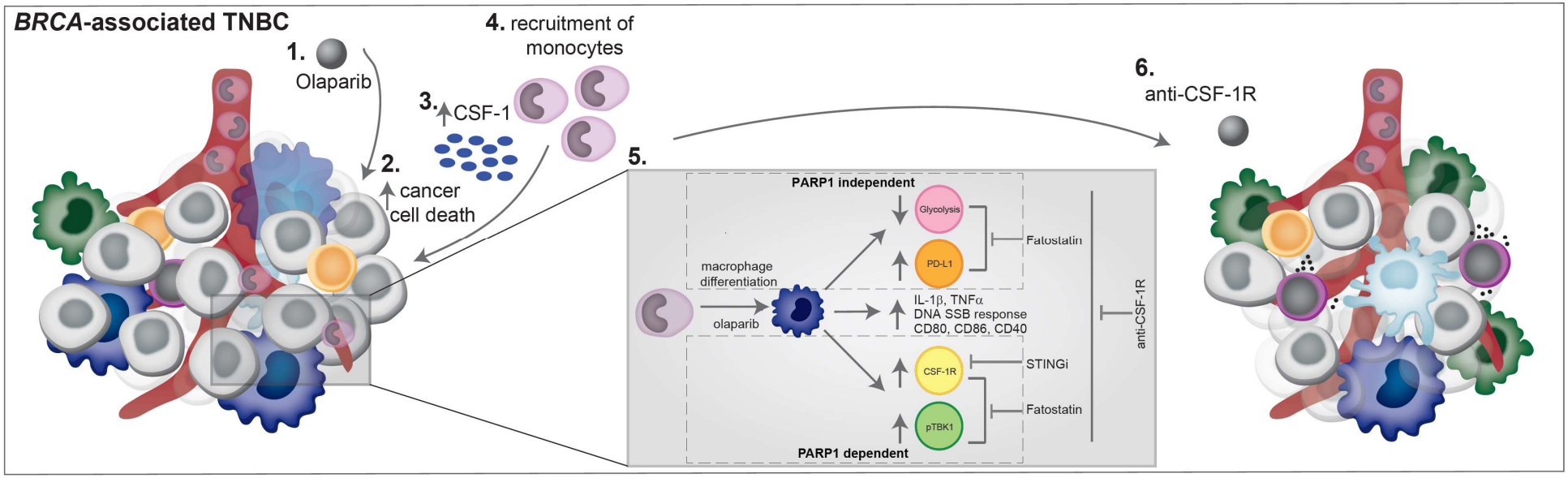


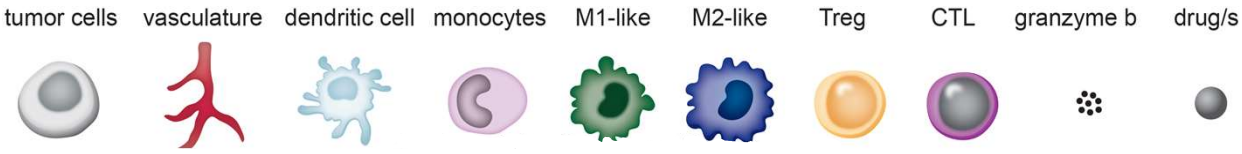
In vivo glucose uptake



Mehta…Guerriero et al. *Prov. Acceptance. Nat. Cancer.*

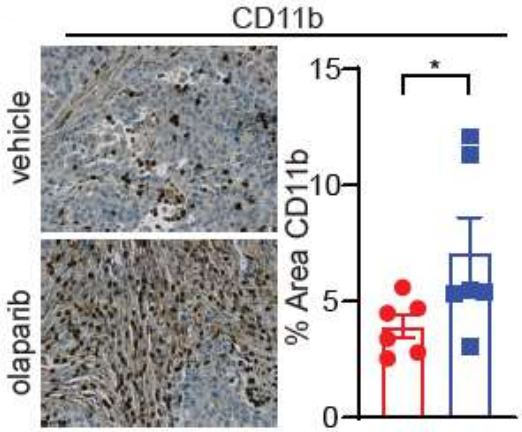
Anti-CSF-1R therapy overcomes PARP inhibitor-induced immune-suppressive macrophages and activates an anti-tumor immune response in *BRCA*-associated TNBC





TAM modulation for anti-cancer therapy needs to be tailored to each patient

- *BRCA*-deficient have high levels of cytosolic DNA/STING activation
- Olaparib further activates the STING pathway
- Recruitment of suppressive macrophages
- PARPi treated cancers may benefit from anti-CSF-1R treatment



Anthony Letai
Elizabeth Mittendorf
Geoffrey Shapiro
Peter Sorger

Brest Tumor Immunology Lab (BTIL)
Elizabeth Mittendorf
Kene Adigwe
Jessica Castrillon
Emily Cheney
Janae Davis
Jonathan Goldberg
Christina Hartl
Nathan Johnson
Anita Mehta
Madisson Oliwa
Ricardo Pastorello
Tuulia Vallius

Geoffrey Shapiro
Shawn Johnson
Constantia Pantelidou

DF/HCC
Women's Breast Program
Judith Agudo
Alan D'Andrea
Deborah Dillon
Anniina Farkkila
Judy Garber
Stuart Schnitt
Nadine Tung
Gerburg Wulf

Medical University of South Carolina
Jessica Thaxton
Katie Hurst

Laboratory of Systems Pharmacology (LSP)
Peter Sorger
Sandro Santagata
Matthew Berberich
Sarah Boswell
Alyce Chen
Yu-An Chen
Marian Kalocsay
Jerry Lin
Shaolin Mei
Zoltan Maliga
Laura Maliszewski
Jeremy Muhlich
Rumana Rashid
Denis Schapiro
Artem Sokolov
Madison Tyler

Harvard Medical School
Marcia Haigis
Bruce Spiegelman

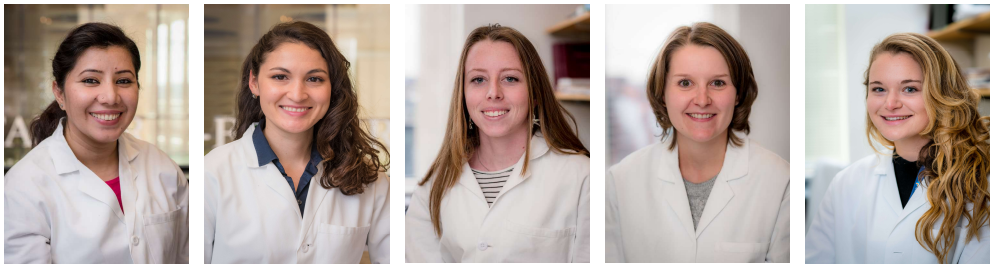
Hospital del Mar Medical Research Institute
José Yélamos

Brigham and Women's Hospital
William Oldham
Scott Rodig

Patient Advocates
Ruth Fax
Elizabeth Frank

Core Facilities at DFCI/HMS
Flow Cytometry Core
Animal facility
Pathology core
Institute of Chemistry and Cell Biology
Center for Functional Cancer Epigenetics

Guerriero Lab/Team Macrophage



Dr. Anita Mehta Jessica Castrillon Emily Cheney Christina Hartl Madisson Oliwa

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