OncoResponse

Interrogating for Cures™

Targeting myeloid cells to overcome suppression in the tumor microenvironment

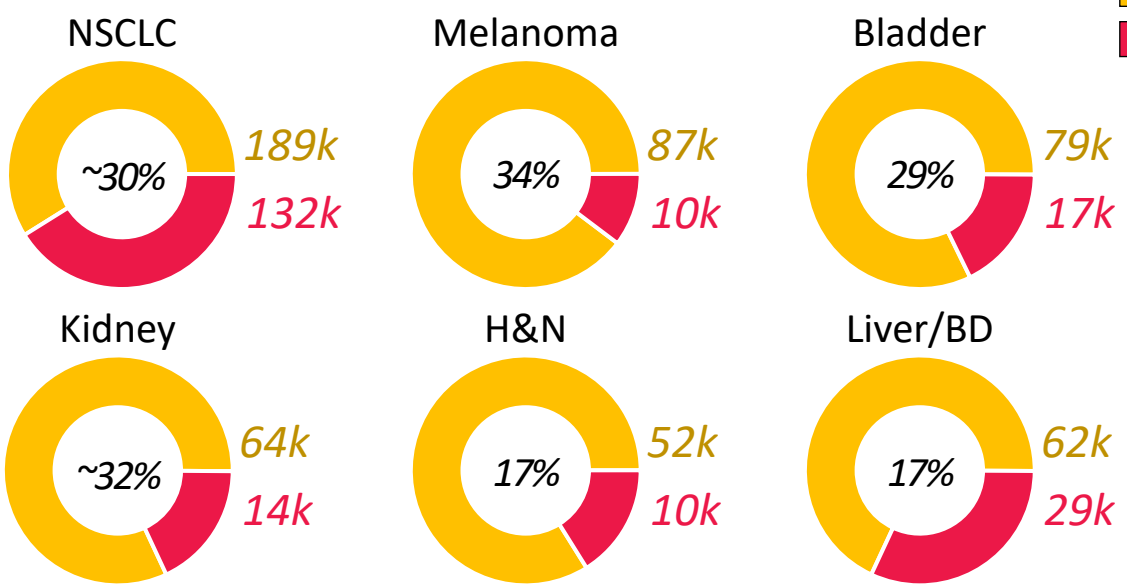
Kamal D. Puri

World Vaccine & Immunotherapy Congress

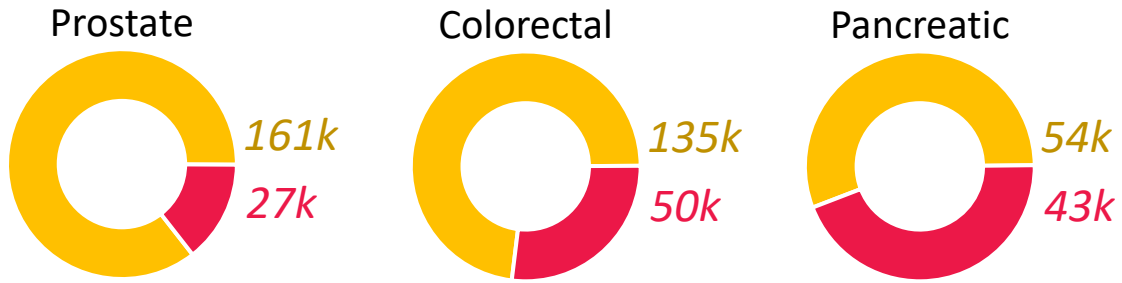
28 Nov – 1 Dec, 2022

The Immuno-Oncology opportunity

CPI-Responsive Cancer Types



CPI-Non-Responsive Cancer Types

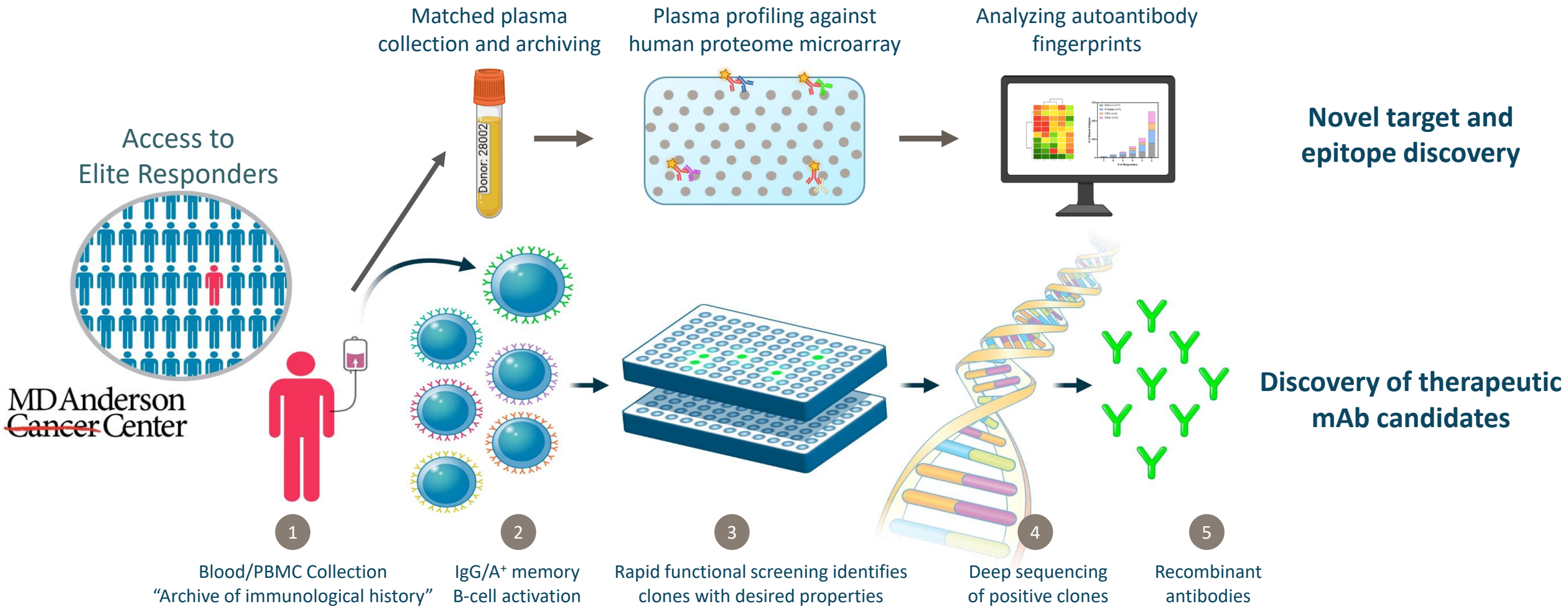


- Response to checkpoint inhibitors (CPI) continue to be low in part due to the suppressive Tumor Microenvironment (TME)
- Large unmet need to overcome immune suppression in the TME to increase response and survival
- B cell enrichment in the tumors correlates with response to CPI in melanoma, sarcoma, lung, head and neck, and kidney cancer[1-6]
- CPI can directly modulate B cell responses and induce antibodies, including to clinically relevant immunomodulatory targets[7-10]

Cancer patients who have successfully responded to CPI, Elite Responders, may harbor antibodies that contribute to the clinical response

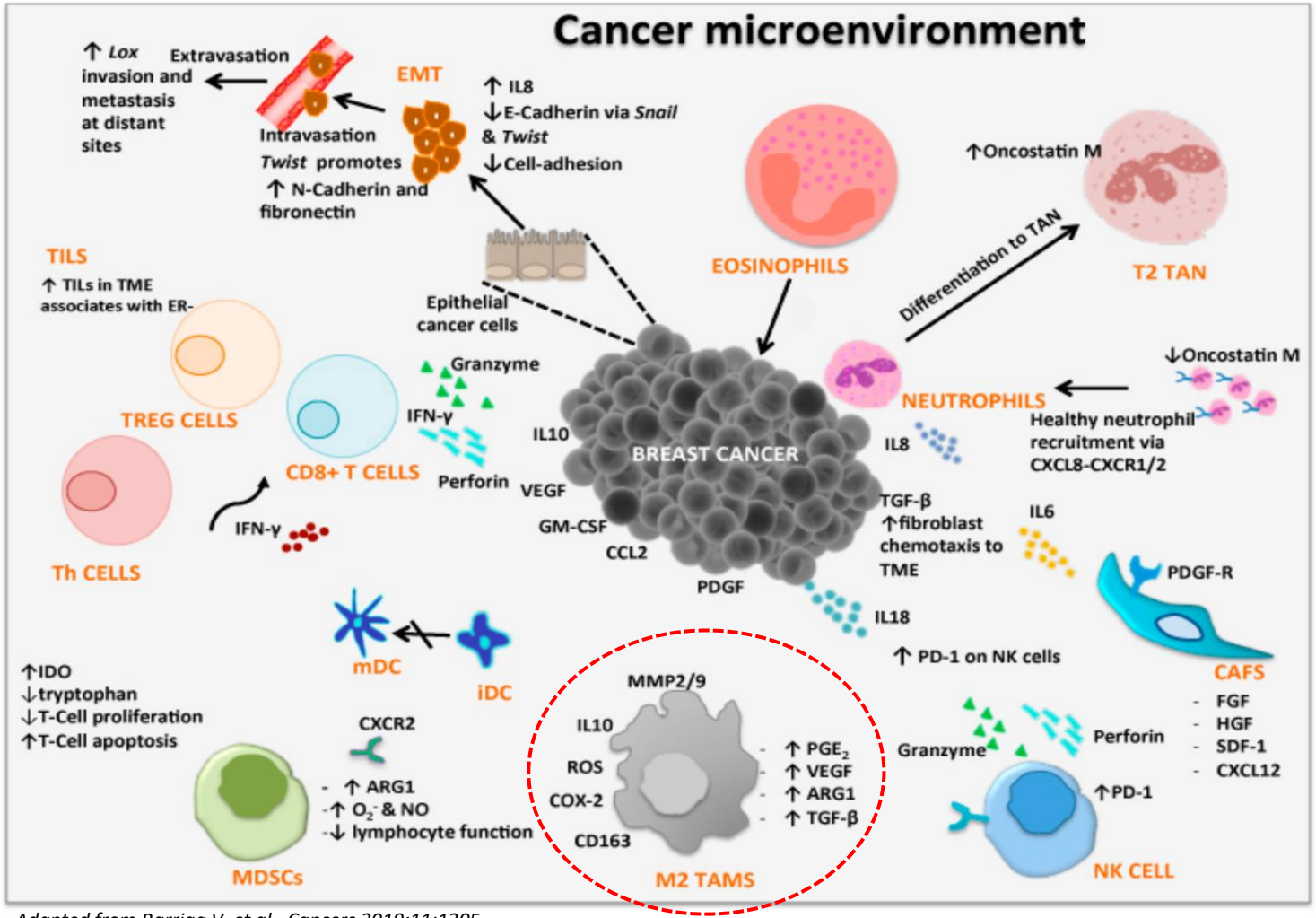
[1]Helmink, et al. Nature. 2020, [2]Petitprez, et al. Nature. 2020, [3]Cabrita, et al. Nature. 2020, [4]Kim, et al. Clin. Cancer Res. 2020, [5]Ruffin, et al. Nat Commun. 2021, [6]Patil, et al. Cancer Cell. 2022, [7]Jinushi, et al. PNAS. 2006, [8]Schoenfeld, et al. Cancer Res. 2010, [9]Kwek, et al. J Immunol. 2012, [10]Kouo, et al. Cancer Immunol Res. 2015

The OncoResponse platform interrogates the antibody and B-cell repertoire of Elite Responders for clues to attack cancer



Antibody discovery with the OncoResponse platform

- Interrogate multiple cell types
- Screen for functional activity
- Identify rare regulatory antibodies
- Modulate immune responses within the tumor microenvironment (TME)



Adapted from Barriga V. et al., Cancers 2019;11:1205

OncoResponse pipeline summary

ANTIBODY	Mechanism	Discovery	IND-Enabling	Phase 1	Phase 2
OR2805 (anti-CD163)	Reprograms TAMs/MDSCs				
OR502 (anti-LILRB2)	Reverses immunosuppression & reprograms TAMs				
TME 2.0	Interrogate B-cell repertoire for mAb candidates				

- Lead drug OR2805 advancing through clinical studies across multiple tumor types
- Several antibodies in development that modulate immune cell activity
- Platform for ongoing discovery of rare human antibodies from Elite Responders

Abbreviations: TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; mAb, monoclonal antibody

OncoResponse

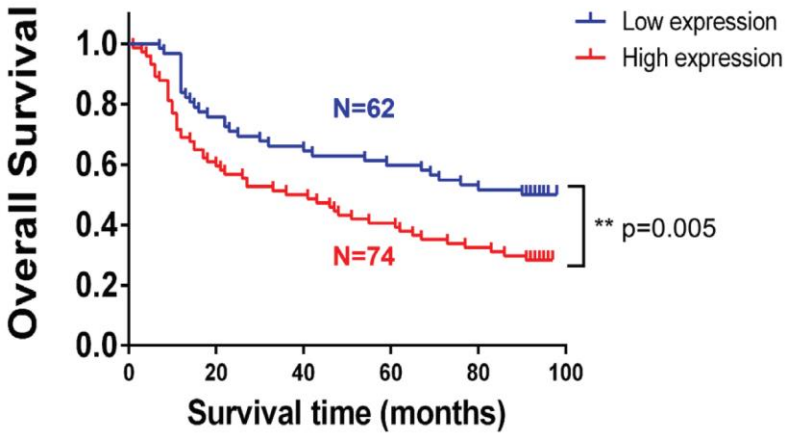
OR2805
Anti-CD163 human-derived mAb

Targeting M2 macrophages to reverse immunosuppression of the tumor microenvironment

CD163 is a negative prognostic marker in cancer

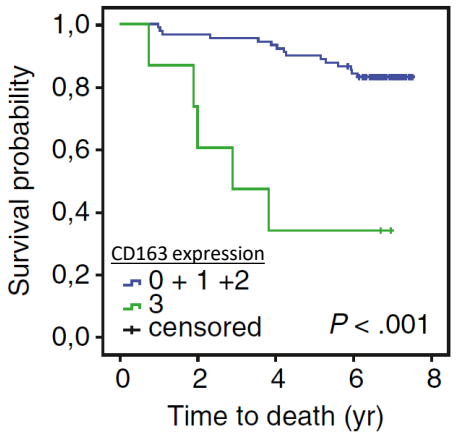
Gastric Cancer[12]

Overall survival



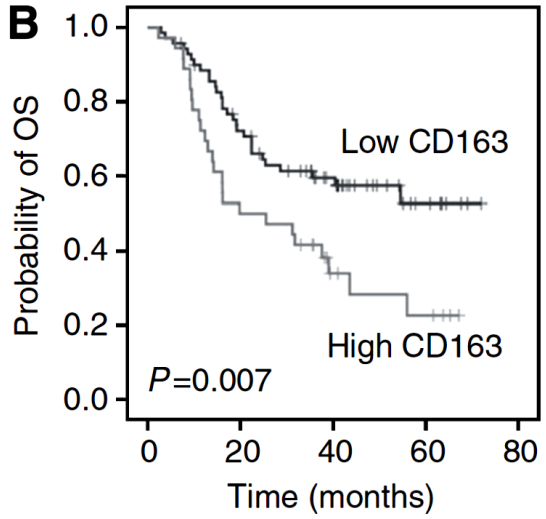
Breast Cancer[13]

Survival probability

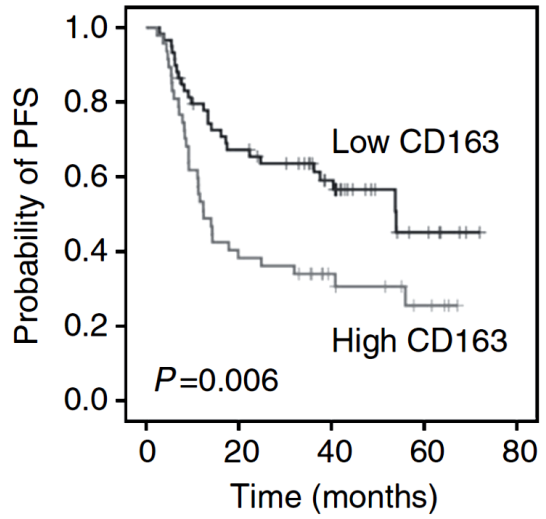


Head and Neck Cancer[14]

Overall survival

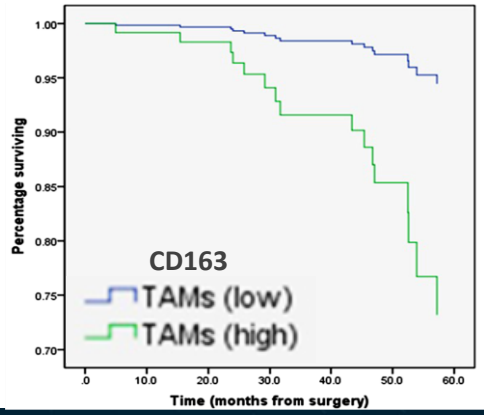


Progression-free survival

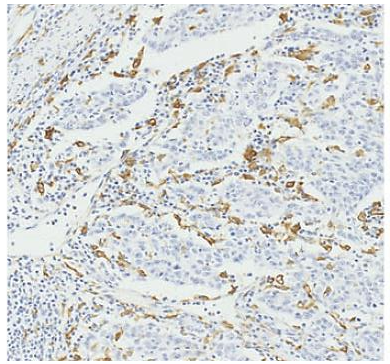


Colorectal Cancer[16]

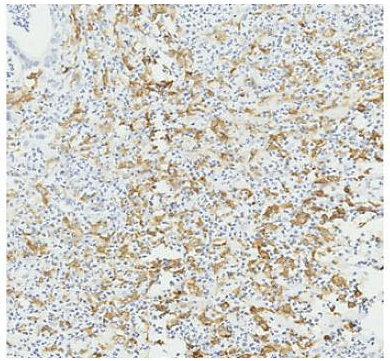
Overall Survival



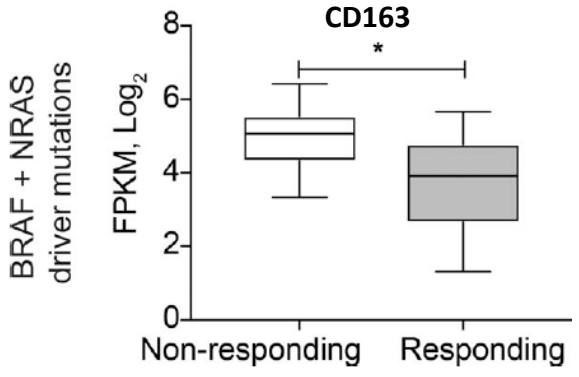
Low TAM Infiltration

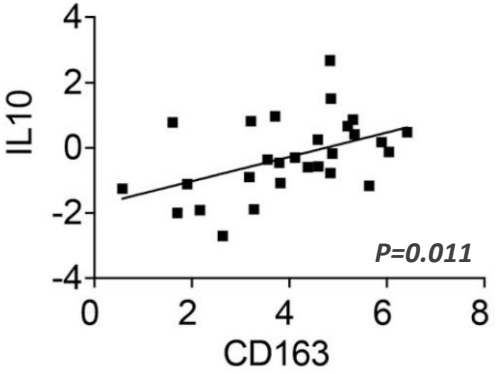


High TAM Infiltration

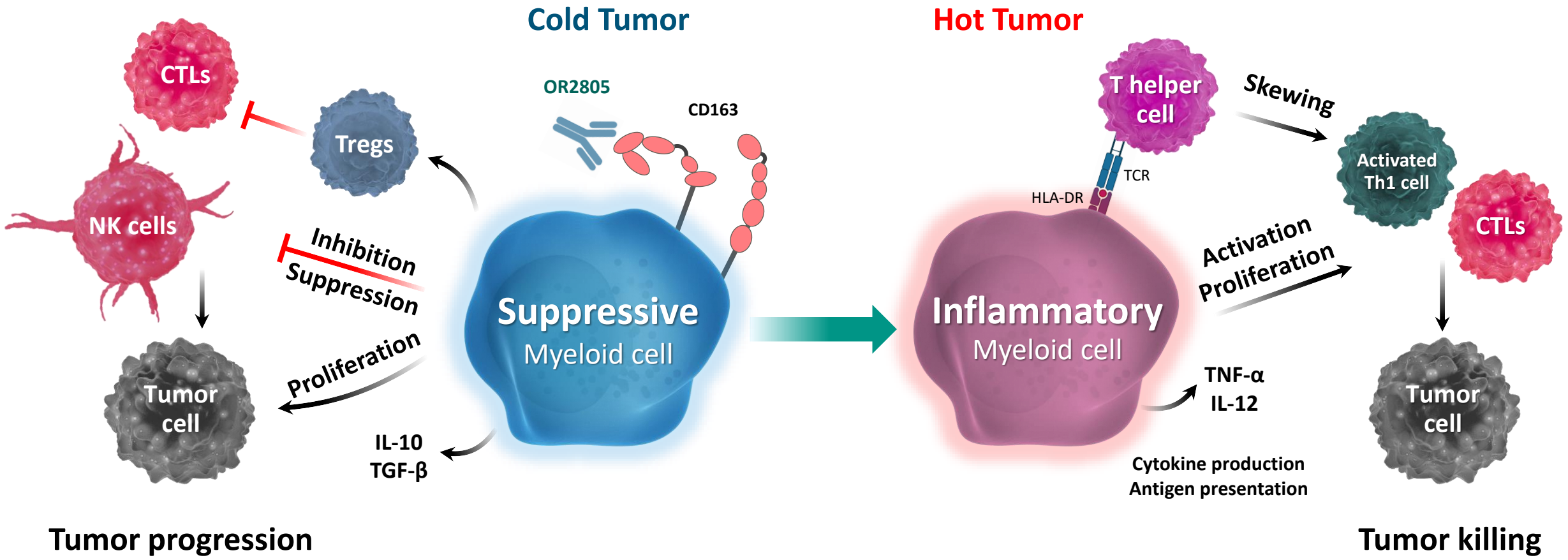


Melanoma patients on anti-PD-1 therapy[15,38]



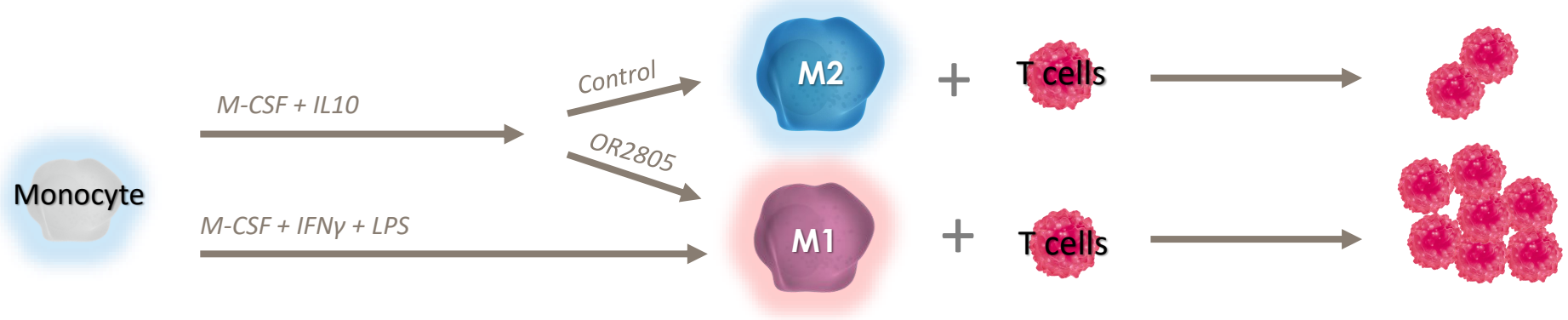


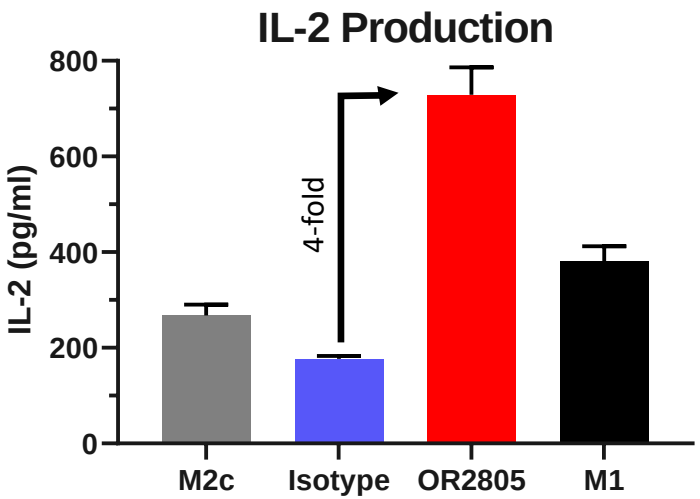
OR2805 relieves myeloid cell mediated immune suppression in the TME

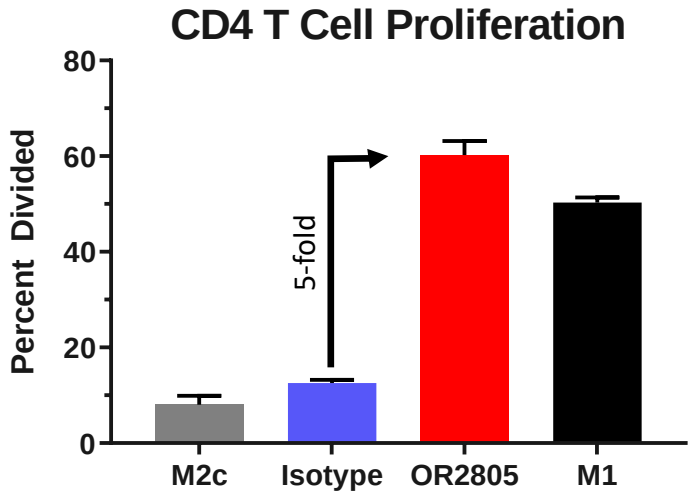


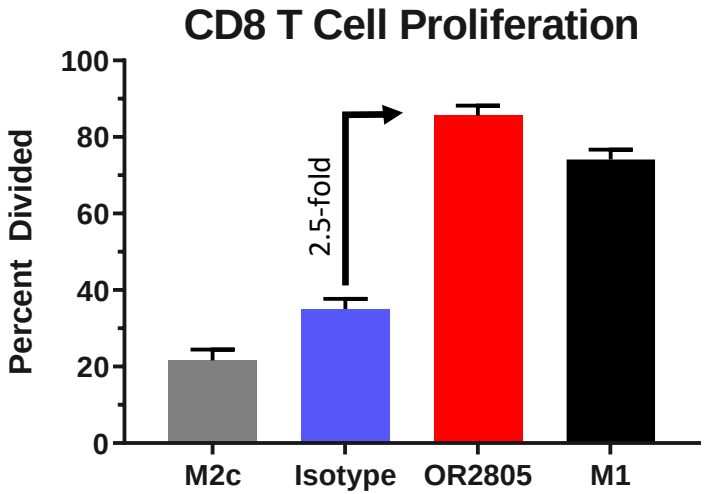
OR2805 targets CD163 and reprograms the immune suppressive functions of tumor-associated macrophages (TAMs)

OR2805-treated M2c macrophages promote T-cell activation & proliferation







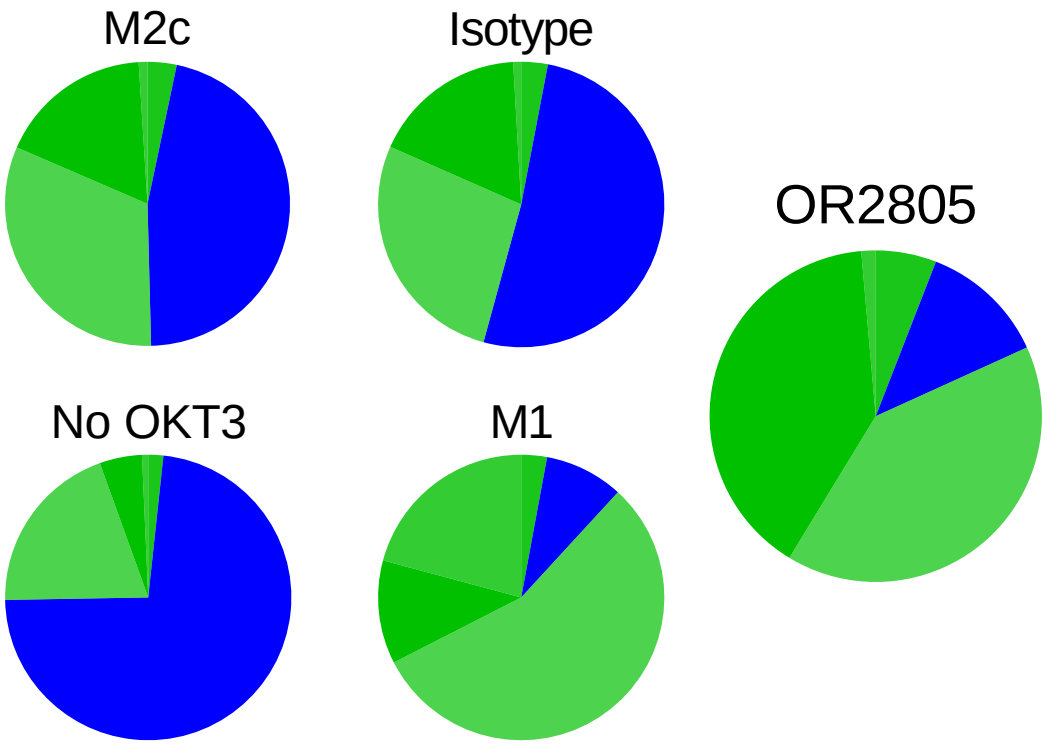


Representative data of 12+ donors

OR2805-treatment reduces the ability of M2c to suppress T-cell activation leading to greater T-cell stimulation (IL-2, IL-1β, IFNγ, TNFα, CCL4 & perforin production) and both $CD4^+$ and $CD8^+$ T-cell proliferation

OR2805-treated M2c macrophages skew T cells to activated Th1 phenotype

Distribution of CD4⁺ T cells phenotypes



- CXCR3 expression promotes $CD8^+$ infiltration
- IFNγ enhances CXCR3-mediated T-cell recruitment
- CXCR3-expressing $CD8^+$ T cells show enhanced anti-tumor cytotoxicity

Resting T cells

$CXCR3^- CD69^- CD25^-$

Activated $CXCR3^-$ T cells

$CXCR3^- CD69^+ CD25^+$

Activated $CXCR3^+$ T cells

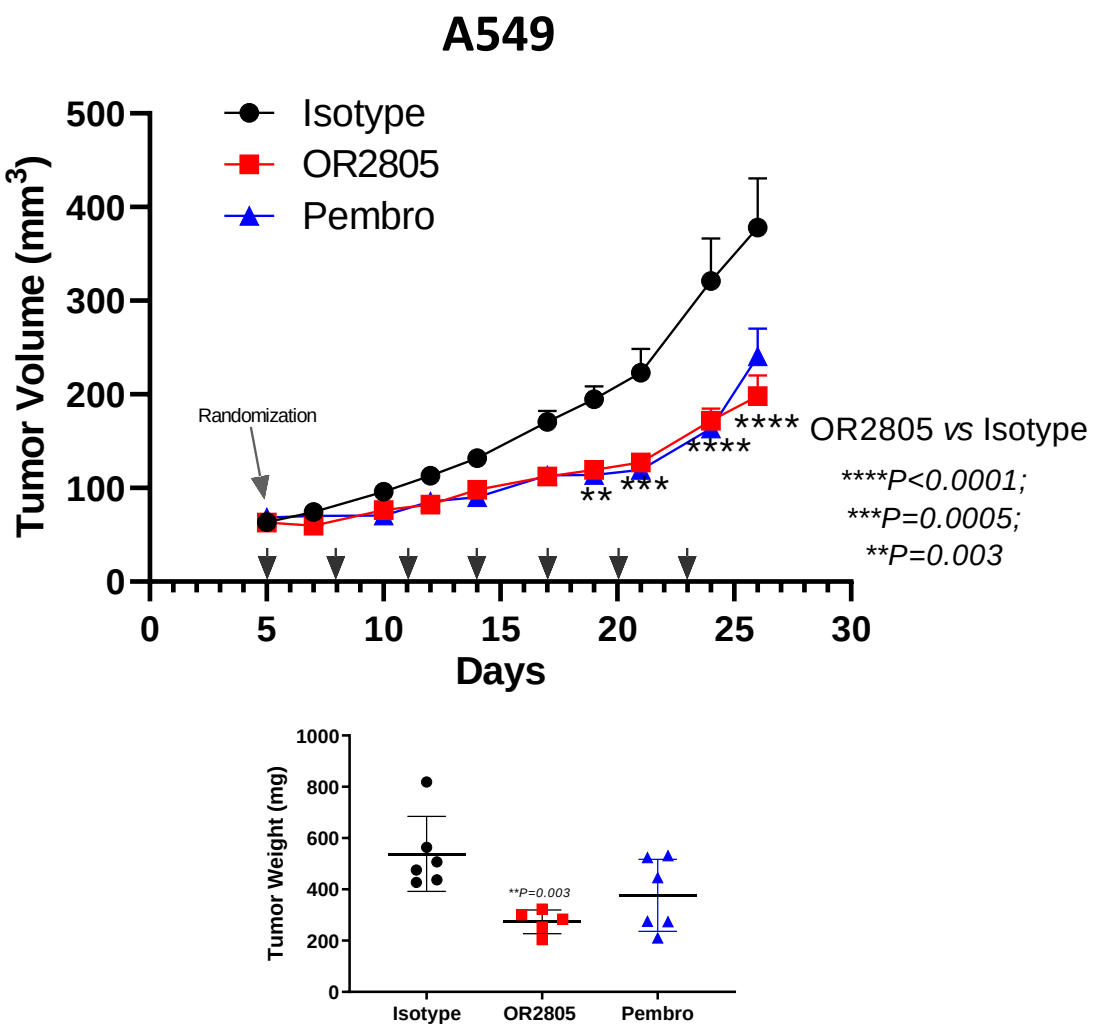
$CXCR3^+ CD69^+ CD25^+$

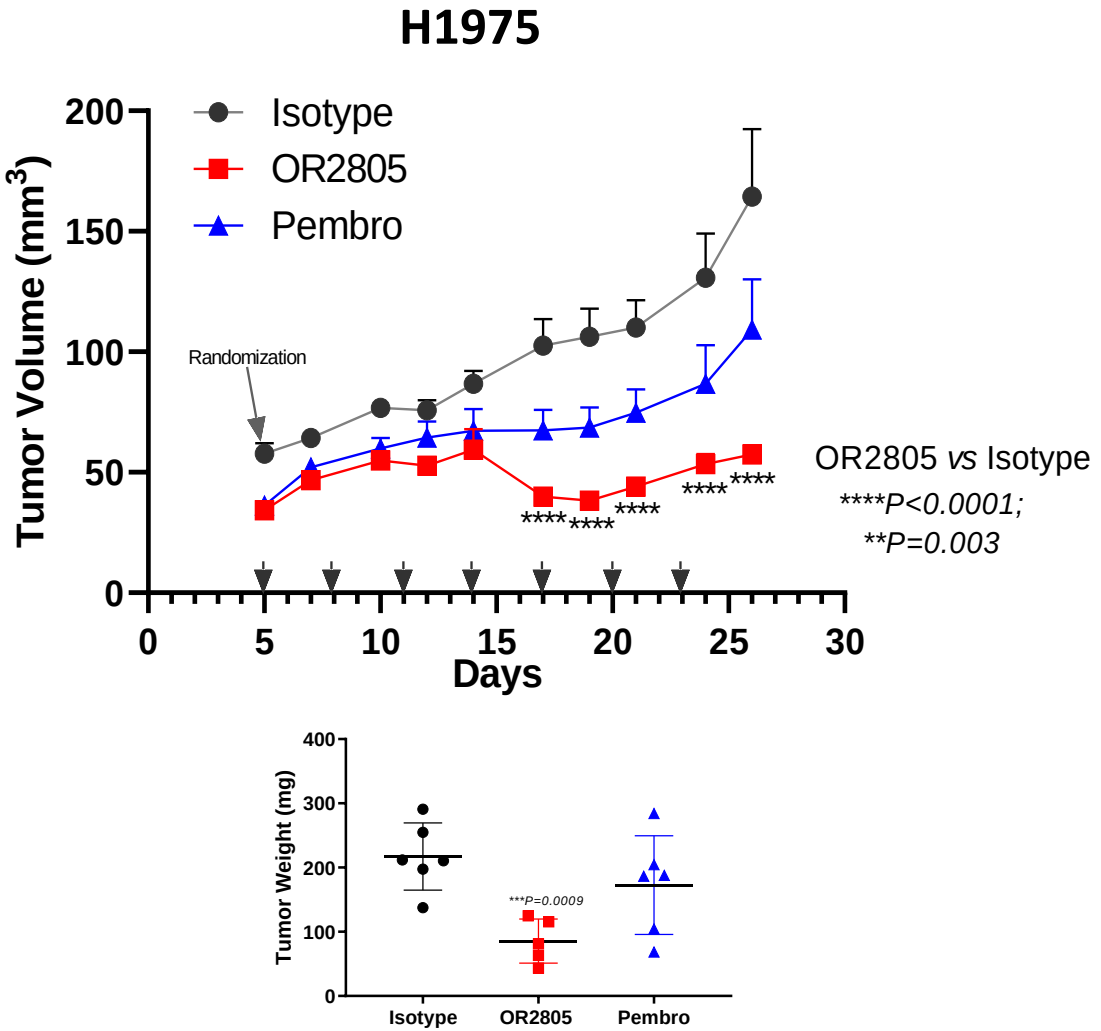
$CXCR3^+ CD69^+ CD25^-$

$CXCR3^+ CD69^- CD25^+$

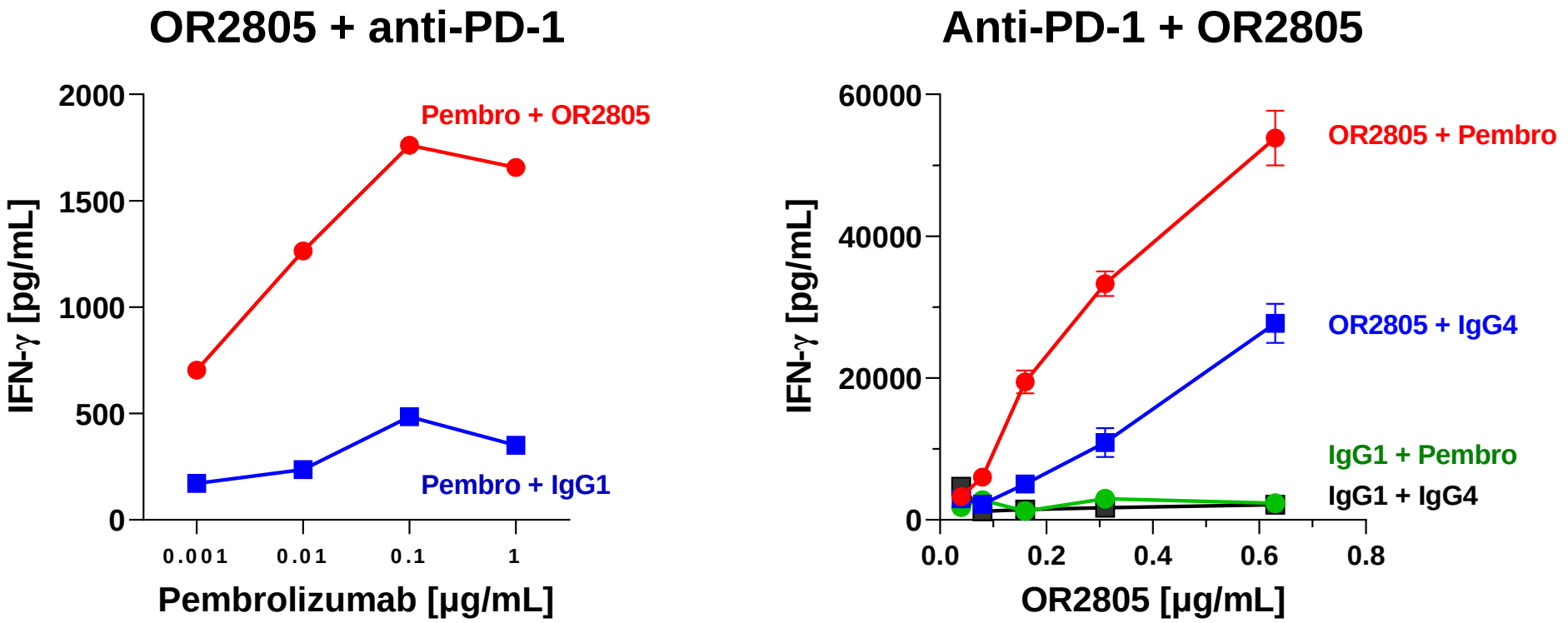
OR2805-treated macrophages promote T-cell activation leading to greater expression of T-cell activation markers (CD69, ICOS, OX40)

OR2805 induces anti-tumor activity in humanized NSG-SGM3 mice





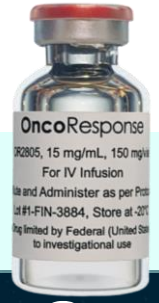
Combination with OR2805 enhances activity of anti-PD-1 and anti-PD-L1 in M2c/Exhausted T cell coculture assays



IFN-γ production is enhanced by combination of OR2805 with anti-PD-1 or anti-PD-L1 antibody in M2c/Exhausted T cell coculture assays

Summary: OR2805 relieves immunosuppression caused by myeloid cells in the tumor microenvironment

- Binds with high specificity to M2 TAMs
- Minimizes M2 suppressive effect on T-cell activation and proliferation and skews T cells towards anti-tumor Th1 phenotype
- Shows enhanced expression of activation markers and cancer-killing ability in cocultured T cells
- Demonstrates robust anti-tumor activity in lung cancer xenograft models
- Combination with OR2805 amplifies anti-PD-1 activity in coculture assays
- A phase 1-2 study of OR2805 alone or in combination in subjects with advanced solid tumors is ongoing (NCT05094804)



OR2805 has therapeutic potential as a single agent or in combination with checkpoint inhibitors

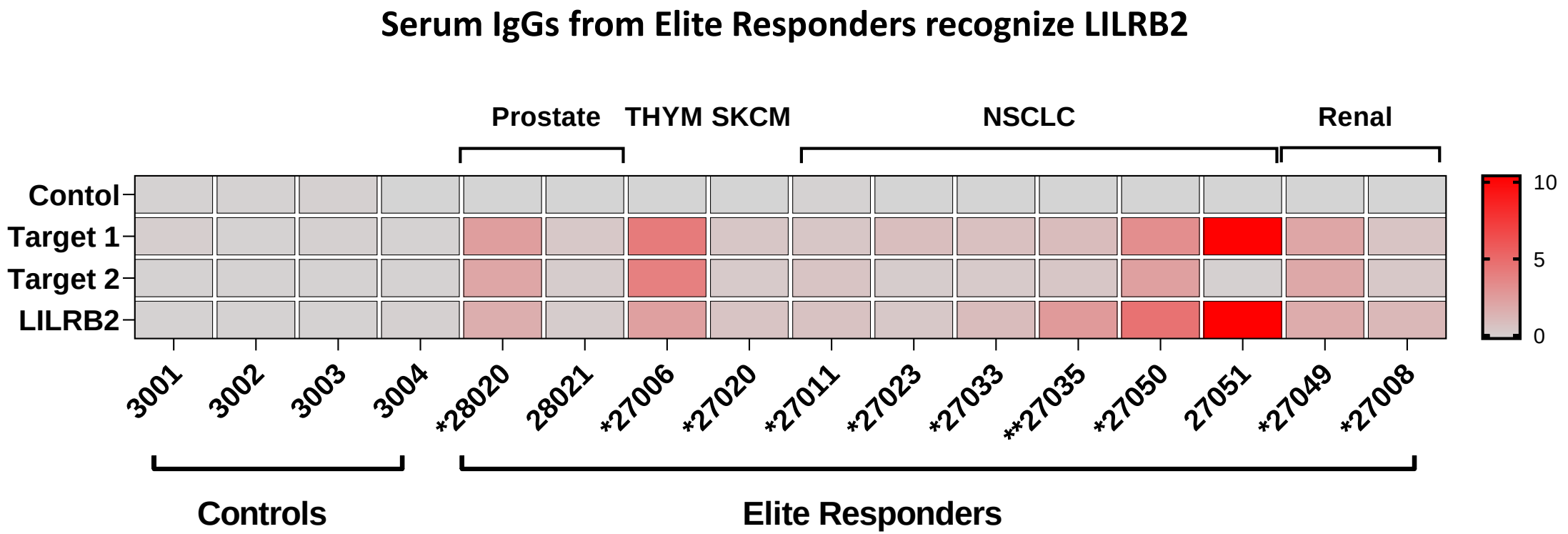
OncoResponse

OR502

Anti-Leukocyte Immunoglobulin Like Receptor B2 (LILRB2)

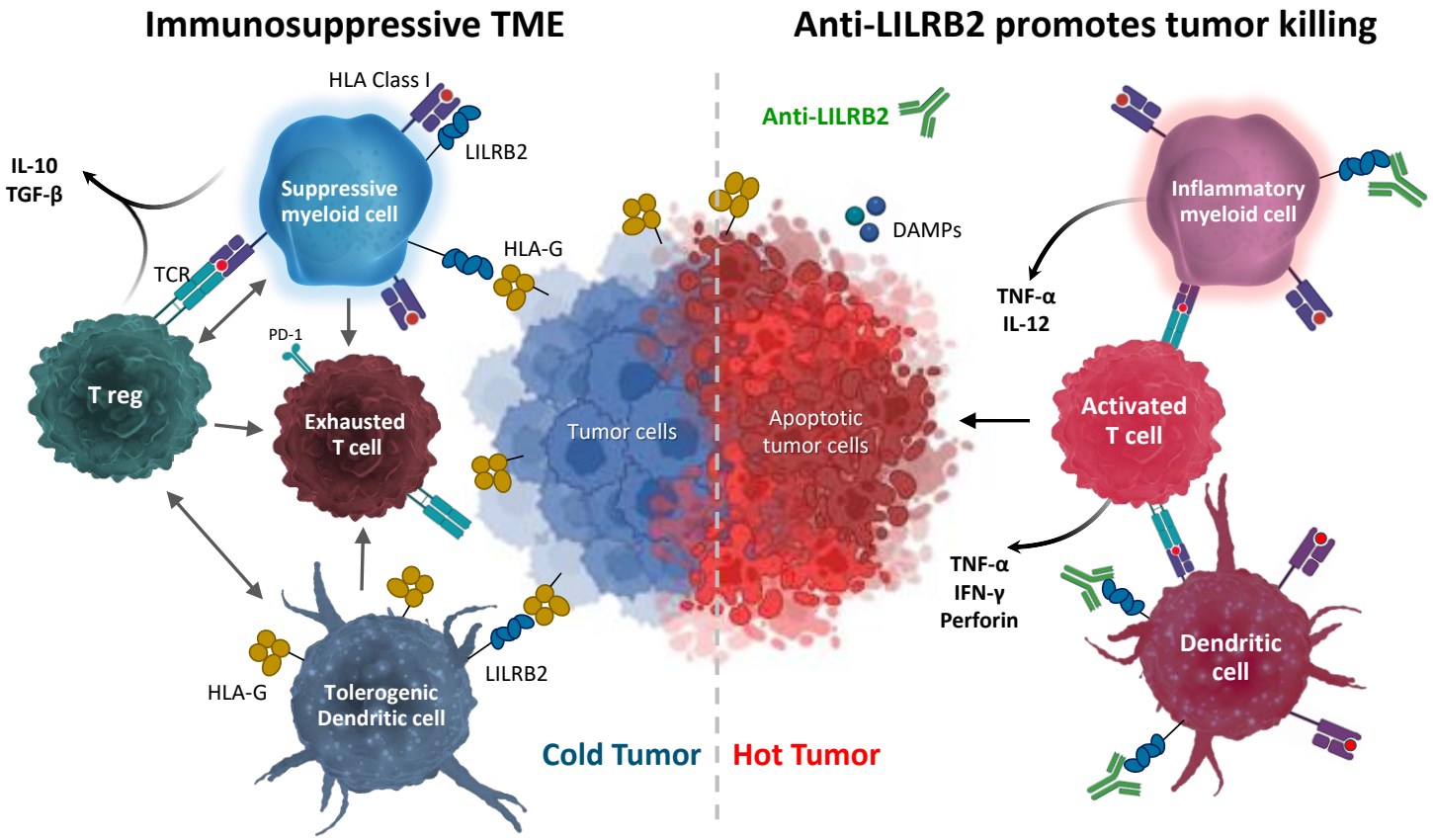
Targeting LILRB2–HLA-G binding to reverse immunosuppression in cancer

Presence of anti-LILRB2 antibodies in Elite Responders sera



- Serum IgGs from Elite Responders recognize targets involved in immunosuppression
- OncoResponse is building a “Seromics” database for discovery of novel targets, epitopes, and potential biomarkers

LILRB2 promotes immunosuppression and blockade drives anti-tumor activity



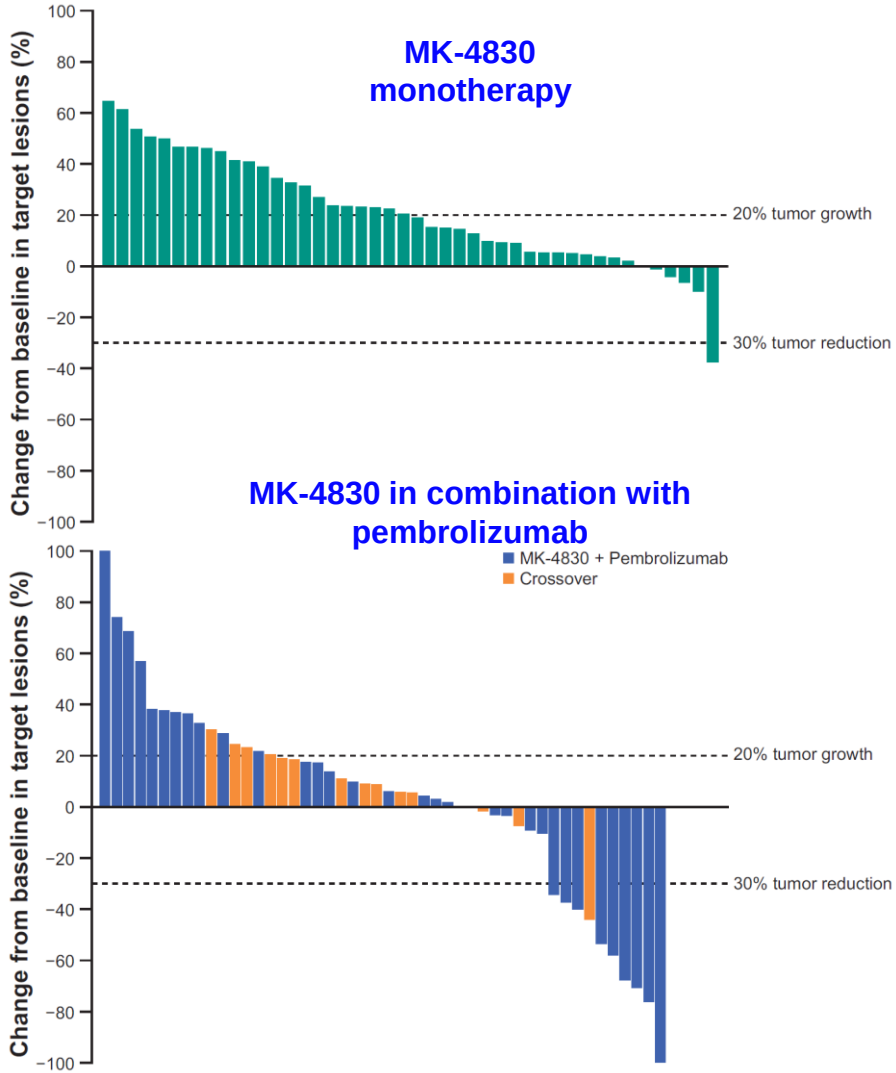
- ITIM-containing inhibitory receptor mostly expressed on myeloid cells
- Expression correlates with poor survival in multiple cancers
- Expression contributes to anti-PD-1 resistance
- Receptor with multiple immune inhibitory activities
  - Inhibits Ca^{++} signaling through SHP-1 recruitment
  - Competes with cytotoxic T lymphocytes for MHC class I binding and diminishes their killing ability
  - Promotes suppressive macrophage phenotype
  - Inhibits FcR mediated activation of monocytes
  - Impairs DC maturation leading to induction of immunosuppressive Treg and Th2 cell phenotypes
  - Promotes immune evasion by upregulating HLA-G expression and secretion by tumor cells
- LILRB2 blockade reverses anti-PD-(L)1 resistance

J Clin Invest. 2018;128:5647, Biochim Biophys Acta. 2018;1869:278, Clin. Cancer Res. 2021;28:57-70, J Immunol. 1998;160:3096-3100, Eur. J. Immunol. 1998;28:3423-34., Nat Immunol., 2002;3:237-43, PNAS 2003;100:8856-61

LILRB2 is a clinically validated target

Anti-LILRB2 restores anti-PD-1 response in patients with advanced solid tumors

- Phase 1 study of anti-LILRB2 antibody MK-4830 validates LILRB2 as an immunotherapy target
- 50 monotherapy subjects
  - One confirmed PR (2% ORR)
  - One confirmed PR after crossover to MK-4830 + pembrolizumab
- 34 subjects MK-4830 + pembrolizumab
  - One CR, 7 PRs (ORR 24%)
  - 5 of 11 subjects with prior anti-PD-1 responded
  - Responses occurred in patients who lacked predictive biomarkers associated with response to pembrolizumab monotherapy
- MK-4830 monotherapy and in combination with pembrolizumab was well tolerated with no unexpected toxicities

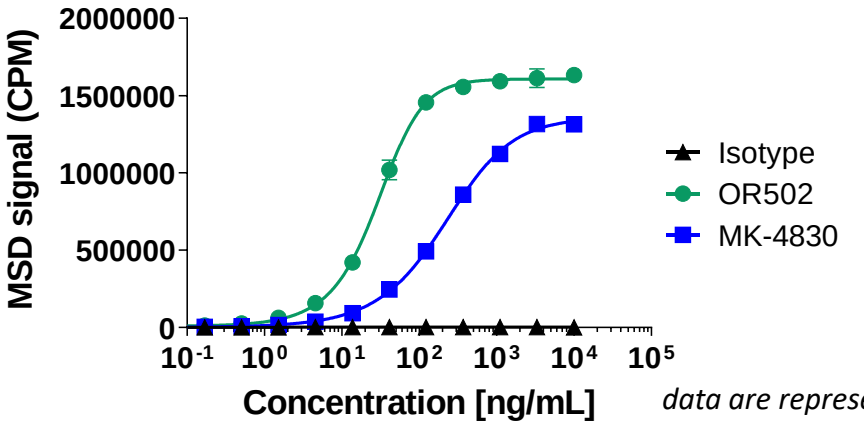


Clin Cancer Res. 2022;28:57-70

OR502 demonstrates specific, high-affinity binding to LILRB2

Binding to LILRB2 by MSD

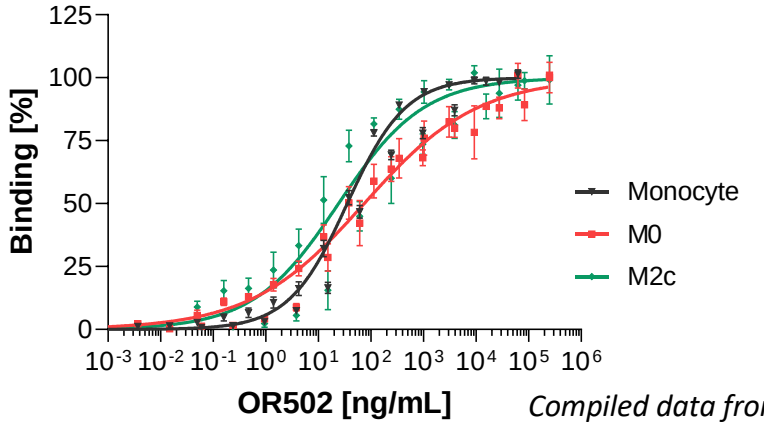
(High-affinity binding to LILRB2 protein)



data are representative of 4 experiments

Binding to Monocytes, M0 and M2c

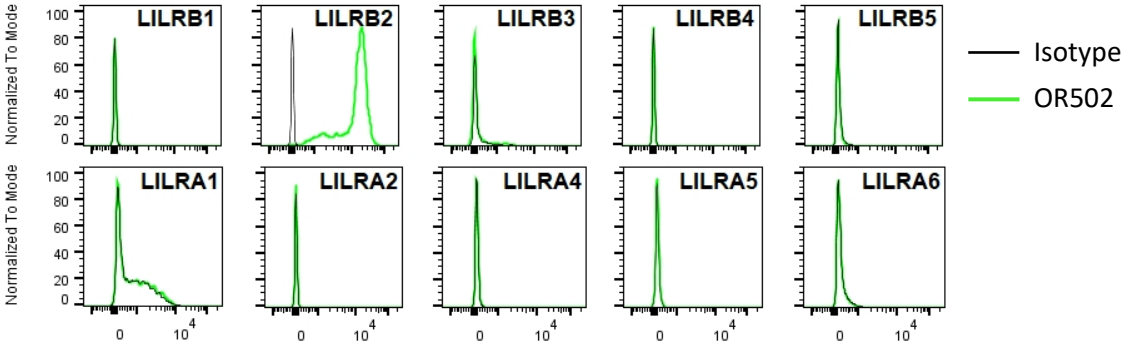
(High-affinity binding to LILRB2 on myeloid cells)



Compiled data from 6-15 subjects

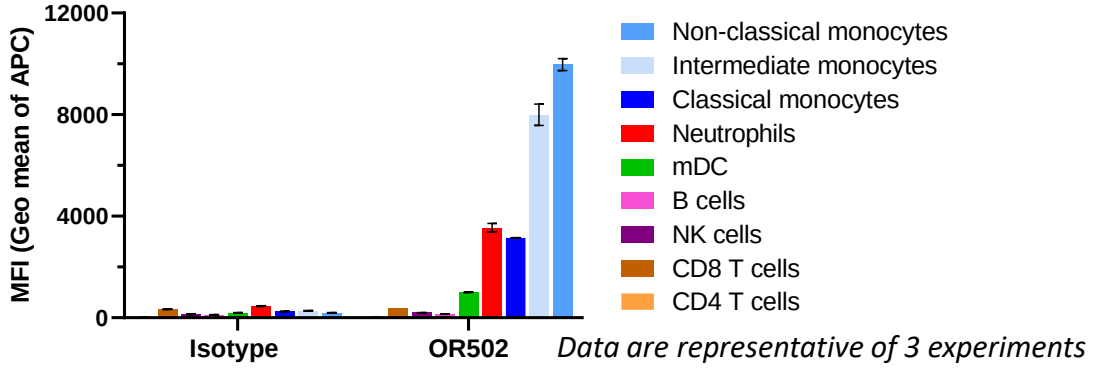
Counter-screen

(No detectable binding to other family members)



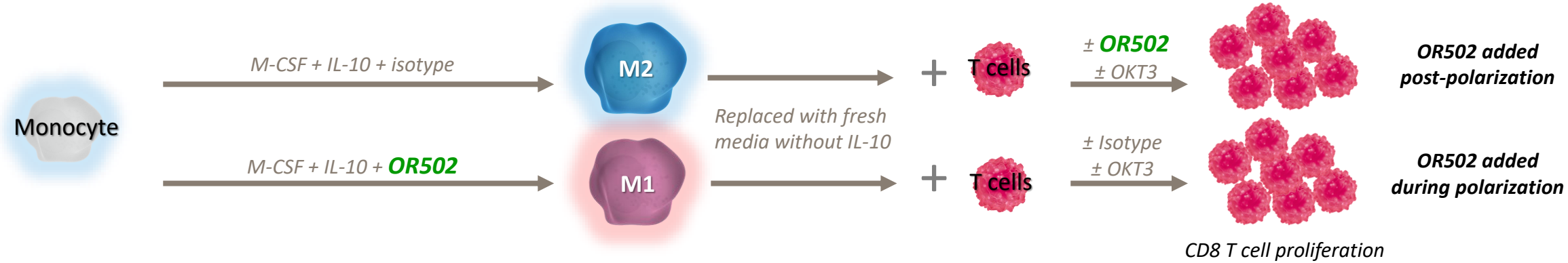
Whole blood immunophenotyping

(Specific binding to LILRB2 positive myeloid cells)

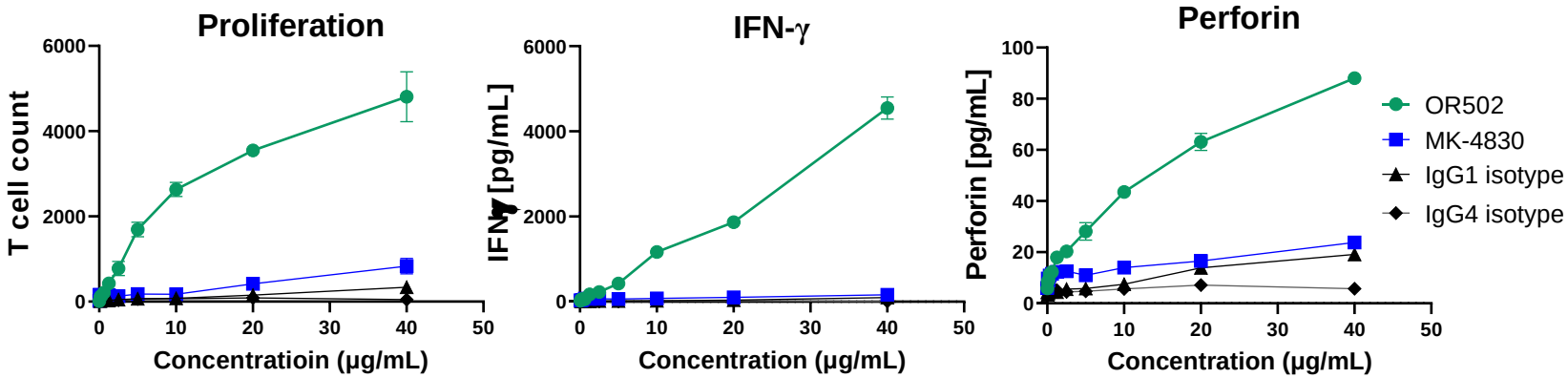


Data are representative of 3 experiments

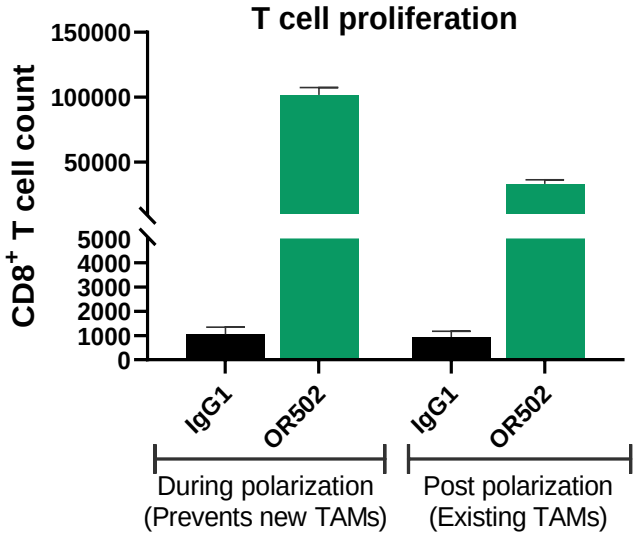
OR502 reverses and prevents the immunosuppressive phenotype of existing and new macrophages and restores anti-cancer T cell responses



Rescues T cell proliferation and activation



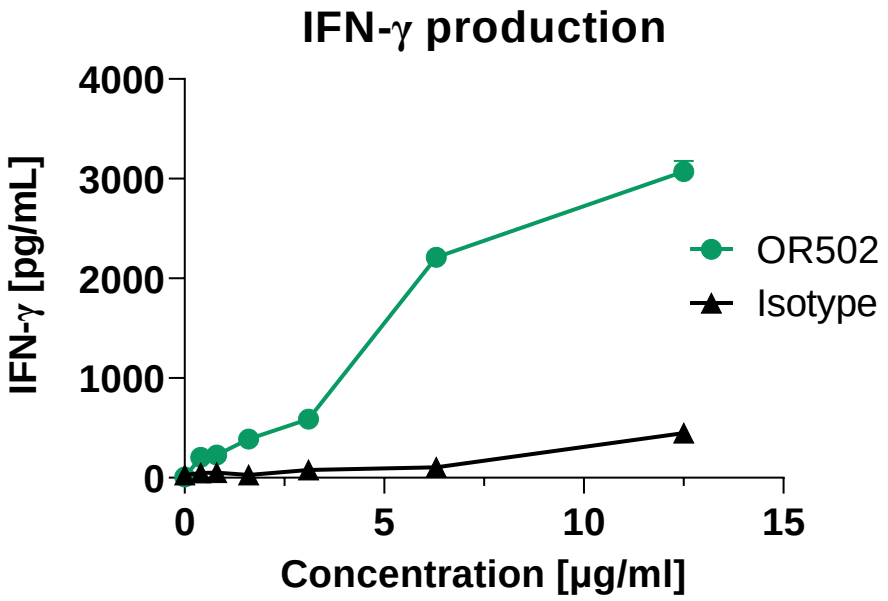
Reduces and prevents immunosuppressive phenotype of existing and new TAMs



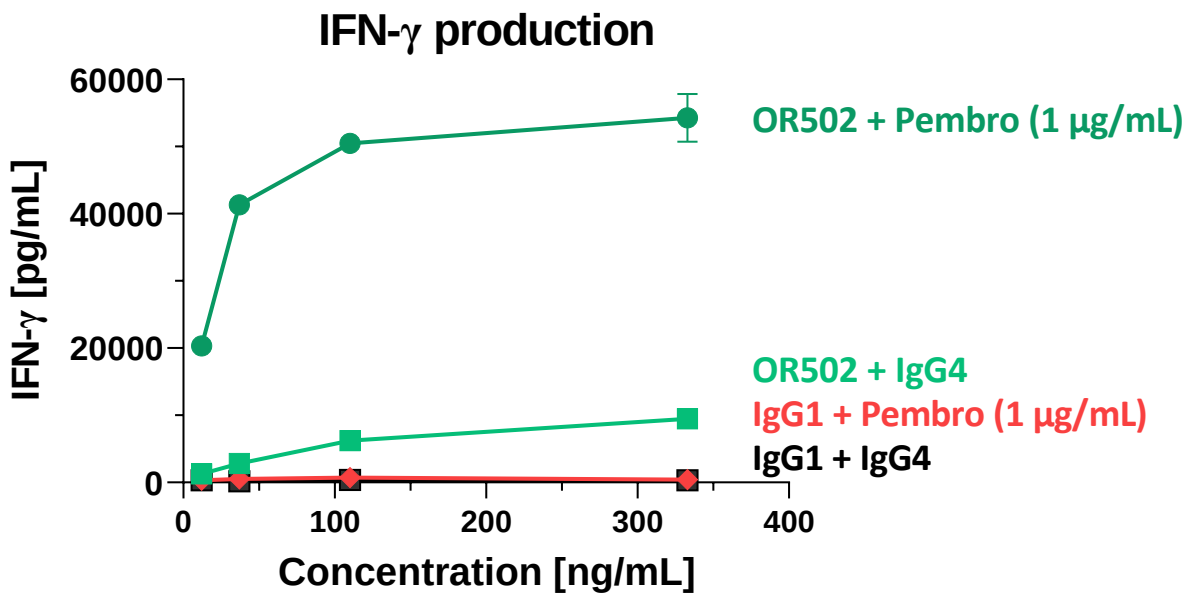
OR502 amplifies anti-PD-1 activity in M2/Exhausted T cell coculture assays

M2c/Exhausted T cell coculture

(Rescues IFN-γ production)

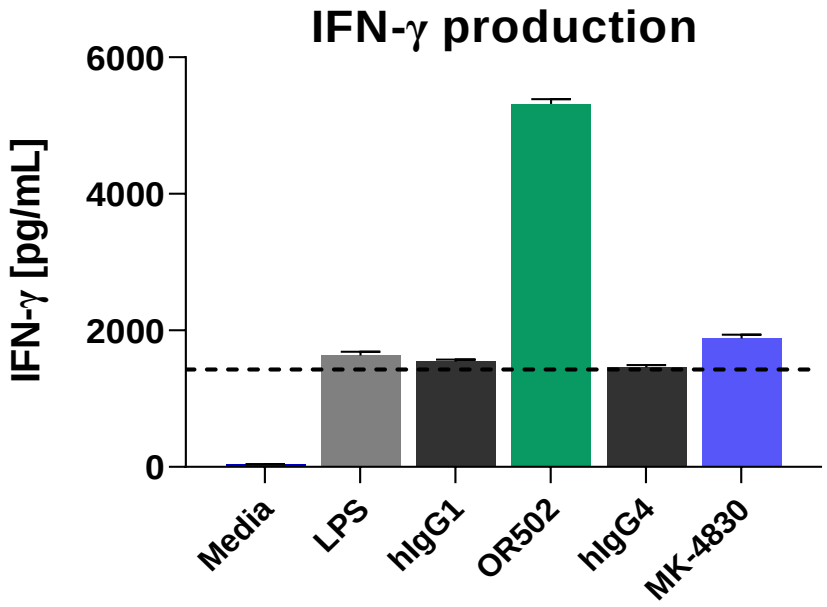


(Amplifies anti-PD-1 activity)

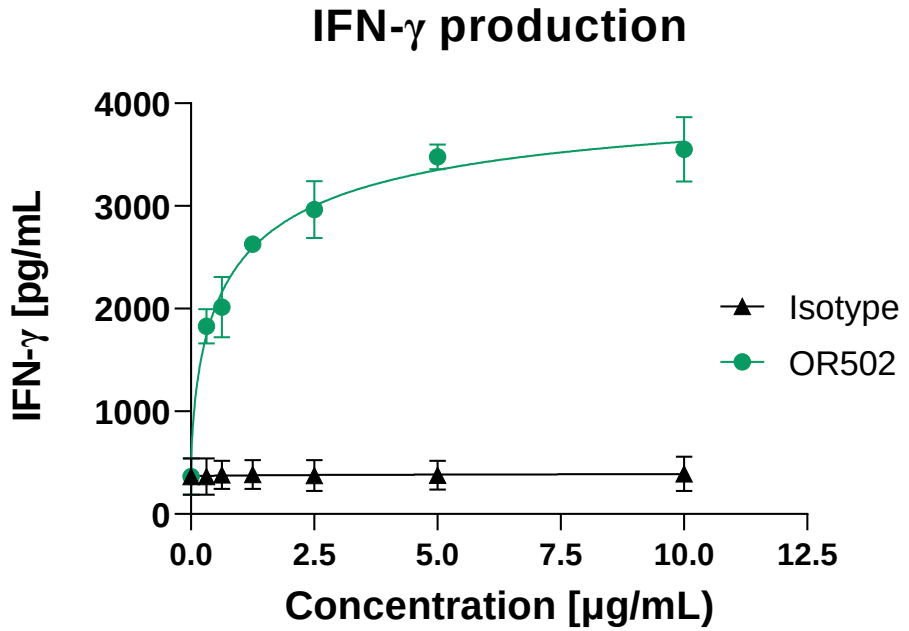


- IFNγ production is enhanced by combination of OR502 with pembrolizumab in M2c/Exhausted T-cell coculture assay
- MK-4830 demonstrates no significant activity in this assay

OR502 boosts LPS-induced IFN-γ secretion by huPBMCs better than MK-4830



Data are representative of >3 experiments

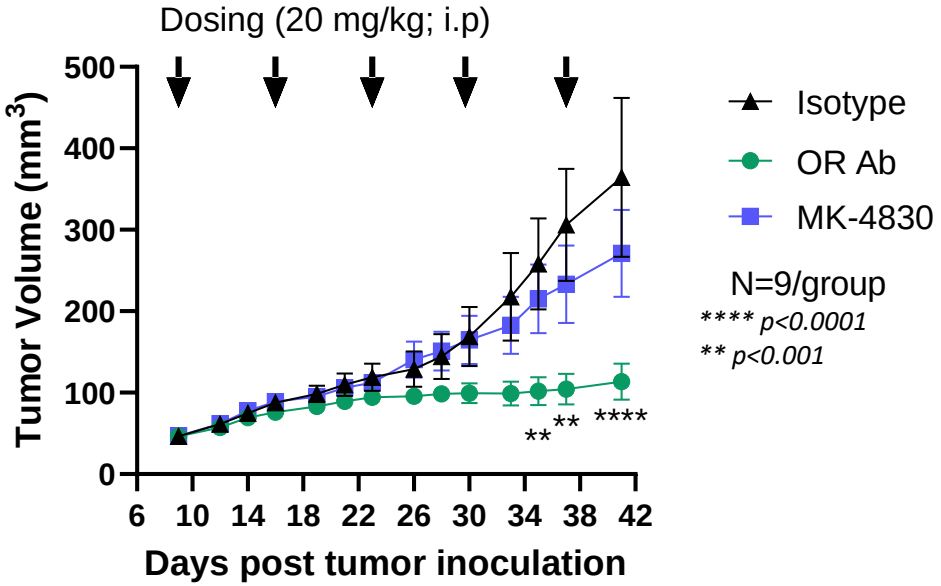


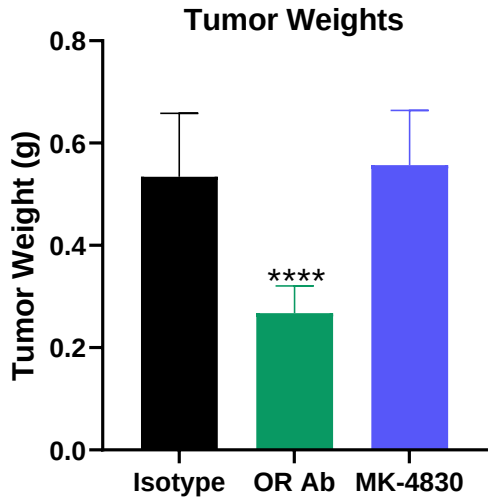
Data are representative of 2 experiments

- OR502 outperforms MK-4830 by inducing a stronger LPS-mediated IFN-γ response by human PBMCs
- Activity is dependent on OR502's ability to block LILRB2 interactions with HLA-class I

OR502 parent antibody demonstrates significant anti-tumor activity

OncoResponse anti-LILRB2 antibody significantly inhibits growth of SK-MEL-5 melanoma in NSG-SGM3 mice



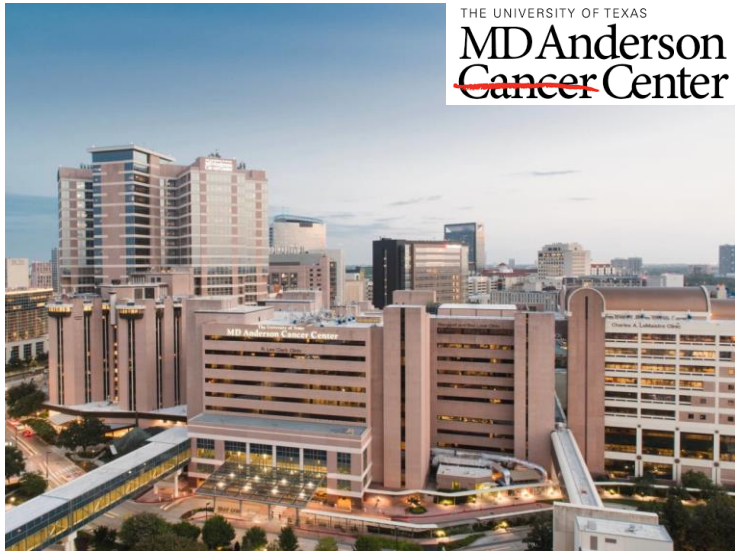


	Tumor Growth Inhibition (%)						Regression (%)
Group	***d28***	***d30***	***d33***	***d35***	***d37***	***d41***	***d41***
Anti-LILRB2 (OncoResponse)	47	57	69	74	78	79	33
MK-4830 (Merck)	-5	3	16	17	24	26	11

OR502 restores innate and adaptive immune responses by modulating immunosuppressive myeloid cells and can reverse unresponsiveness to anti-PD-1

- Robust anti-tumor activity in SK-MEL-5 tumor model
- Modulates the immunosuppressive function of TAMs and enhances adaptive anti-tumor responses
- Boosts LPS-induced IFNγ production by human PBMCs
- Reduces and prevents immunosuppressive phenotype of existing and new TAMs
- Amplifies anti-PD-1 activity in M2/T cell coculture assays
- High-affinity binding to a distinct epitope compared to other clinical candidates
- Typical human IgG PK profile in humanized FcRn mice
- Superior preclinical profile compared to benchmark

Acknowledgements



Bob Lechleider
Clifford Stocks
Darbie Whitman
Doug Spicer
Francisco Zapata
Gajendra Naika
Huyen Dinh
Jacob Heit
Kate Harrop
Kevin Green
Lauren Loh
Meghan Zuck
Meilyn Sylvestre
Myriam Bouchlaka
Peter Probst
Phil Hammond
Ramya Chandrasekaran
Ray Fox
Stephen Willingham
Tatyana Pisarenko
Tiffany Feist
Tom Graddis
Xin Wu

<u>Scientific Advisors</u>

Anil Singhal
David DeNardo
David Hong
James Welsh
Michael Curran
Mike Gallatin
Miriam Merad

Patients who provided precious tissue samples for this study

OncoResponse

Interrogating for **Cures**™

ThankYou.

For more information, please visit
www.OncoResponse.com