OncoResponse

Interrogating for Cures™

Reprogramming human macrophages to relieve immunosuppression in the tumor microenvironment

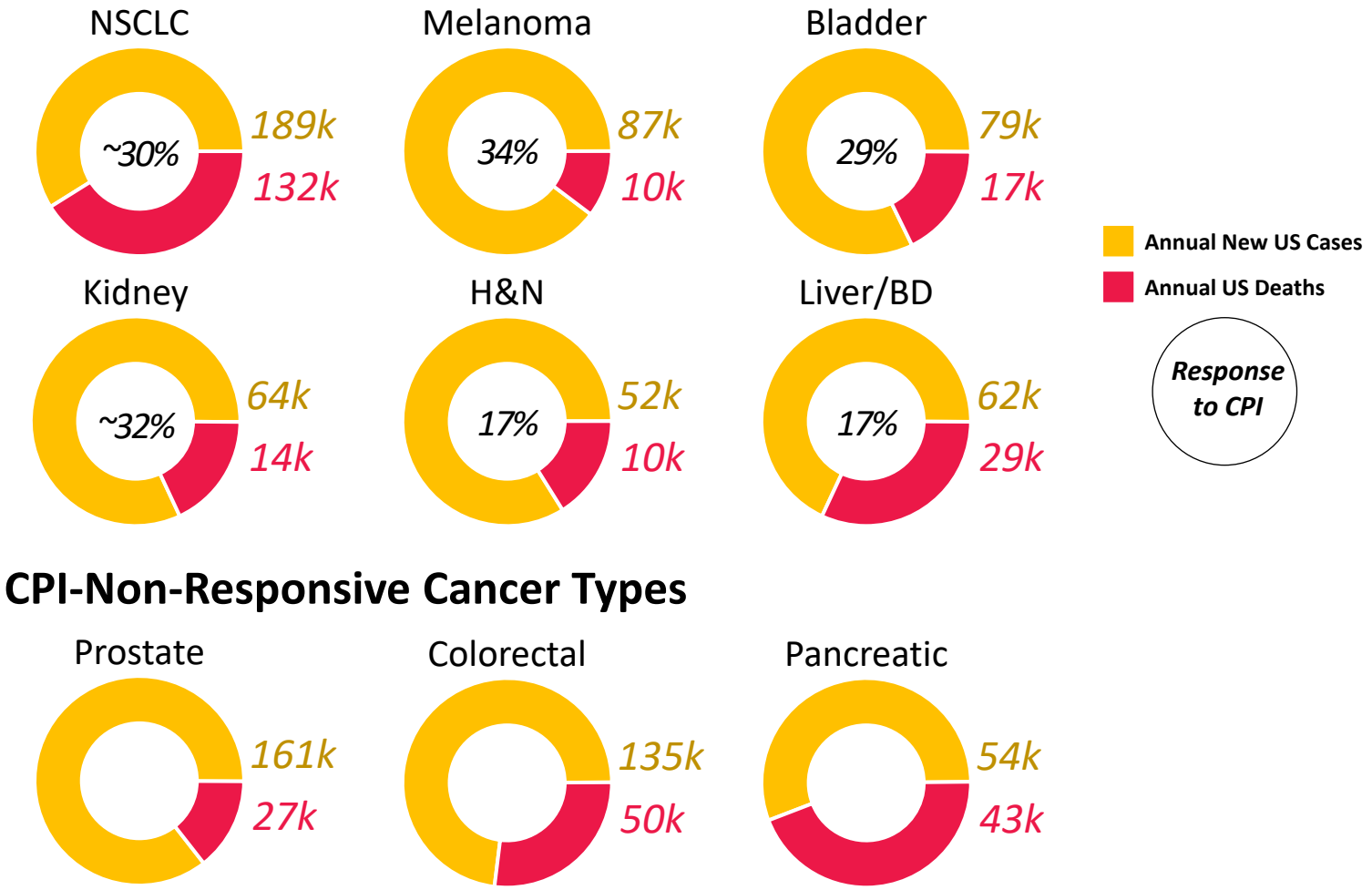
Kamal D. Puri

Festival of Biologics

March 9-11, 2022

The Immuno-Oncology (IO) opportunity

CPI-Responsive Cancer Types



CPI-Non-Responsive Cancer Types

Abbreviations: CPI, checkpoint inhibitor; IO, immuno-oncology; TME, tumor microenvironment

- Response to checkpoint inhibitors (CPI) continue to be low due in part to the suppressive Tumor Microenvironment (TME)
- Large unmet need to overcome immunosuppression of the TME to increase response and survival

- **OncoResponse: Discover new therapies that leverage the immune system to attack cancer**
  - **Rare antibodies from Elite Responders that modulate immunosuppression in the TME**
  - **Used as single agent or in combination with CPI to improve patient outcomes**

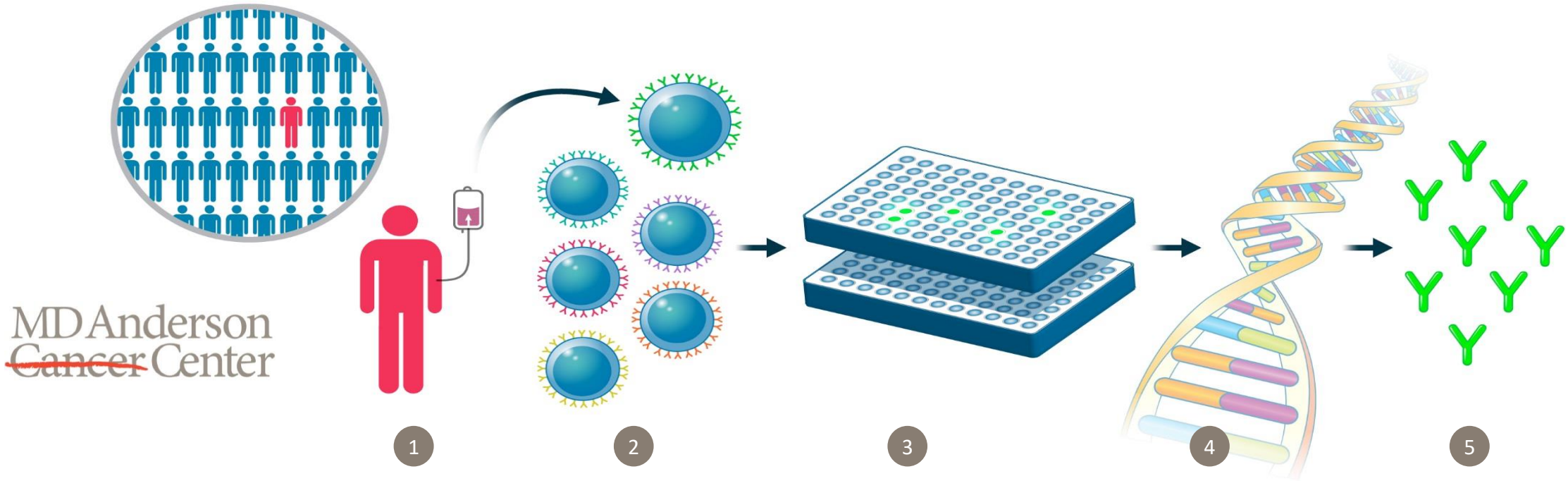
OncoResponse

Our Mission

Attack cancer based on clues offered by the immune systems of Elite Cancer Responders

OncoResponse platform interrogates the entire B-cell repertoire

Access to Elite Responders → Identify rare Abs inaccessible to other Ab discovery platforms → Develop therapeutic mAb candidates

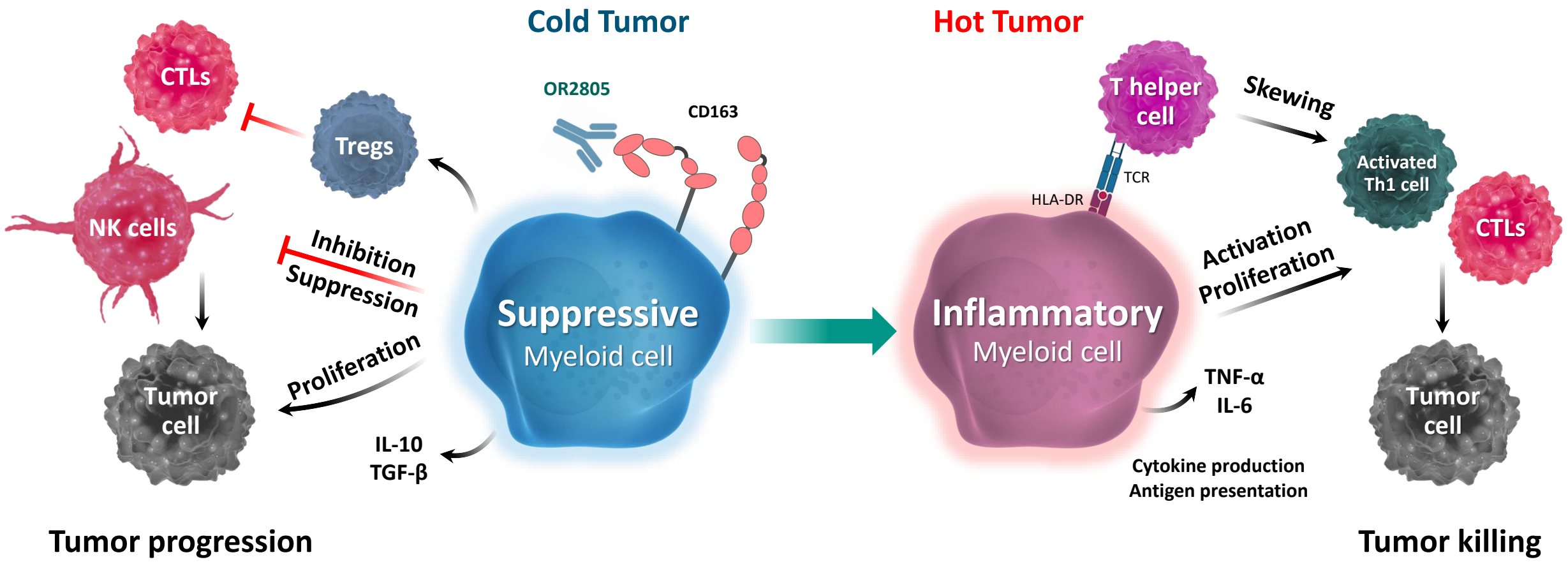


MD Anderson Cancer Center

1. Blood/PBMC collection
2. IgG/A^{+} memory B cell activation
3. Rapid functional screening identifies clones with desired properties
4. Deep sequencing of positive clones
5. Recombinant antibodies

Validated antibody platform delivered preclinical and clinical stage antibodies

OR2805 relieves immunosuppression caused by myeloid cells in the TME



OR2805 targets CD163 and reprograms M2 macrophages resulting in the loss of M2 cell-mediated immune-suppression

CD163 - Normal physiology and role in cancer

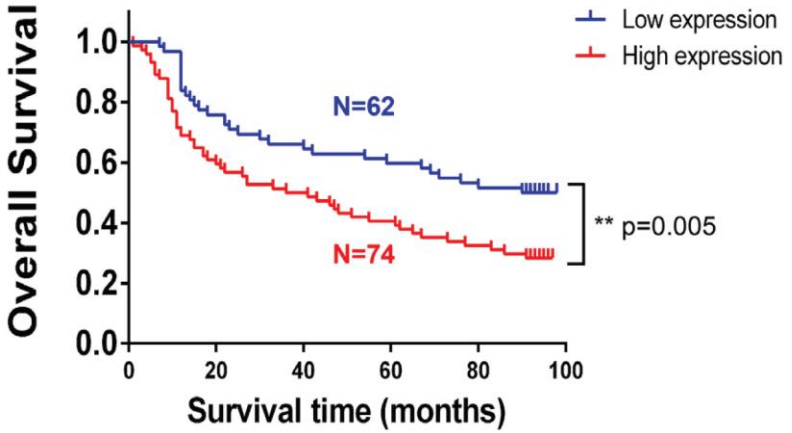
- Expression predominantly limited to and upregulated on immunosuppressive macrophages[1]
- Binding by its ligands induces secretion of immunosuppressive cytokines [2,3]
- Inhibits T-cell proliferation [4,5]
- Overexpression in human macrophages results in an M2 phenotype[6]
- Knockout mice develop normally but have impaired tumor implantation[7]
- Expression in tumors correlates with poor survival [8-11]

[1]Genomics Institute of the Novartis Research Foundation, [2]Molecular Immunology 2010;47:1650, [3]JCI Insight. 2016;1:e85375, [4]Biochem Biophys Res Commun. 2001;288:841,[5]Scientific Reports 2017;7:12940, [6]Immunobiology 2017;222:900, [7]Cancer Res 2018;78:3255, [8]Clin Transl Immunology 2020;9:e1108, [9]Cancer Management and Research 2020;12:5831, [10]Cell 2016;165:35, [11]J Exp Med. 2019;216:2394.

CD163 is a negative prognostic marker in cancer

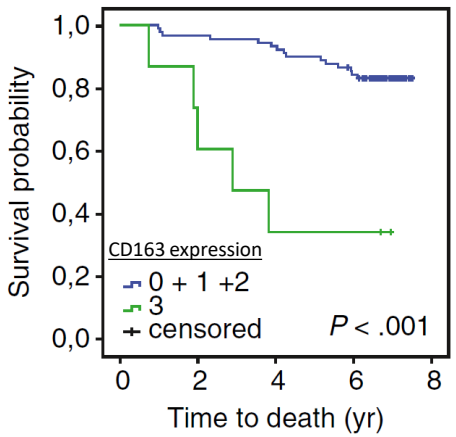
Gastric Cancer[12]

Overall survival



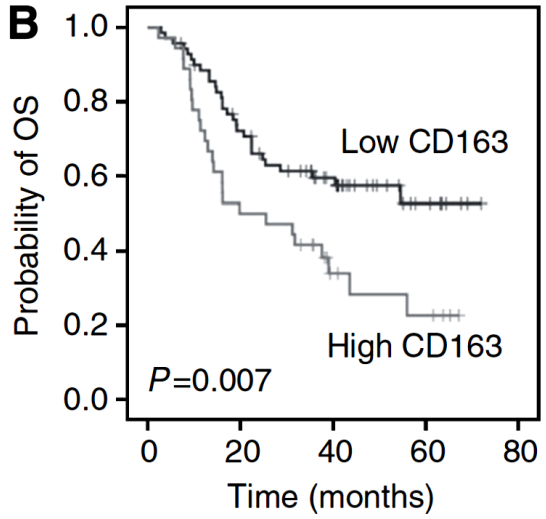
Breast Cancer[13]

Survival probability

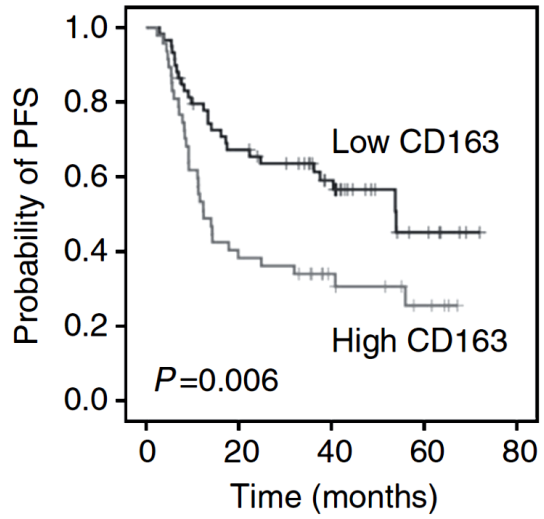


Head and Neck Cancer[14]

Overall survival

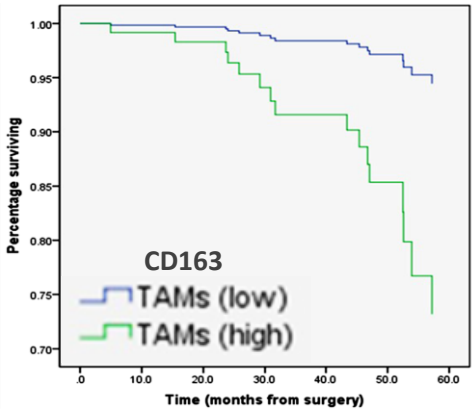


Progression-free survival

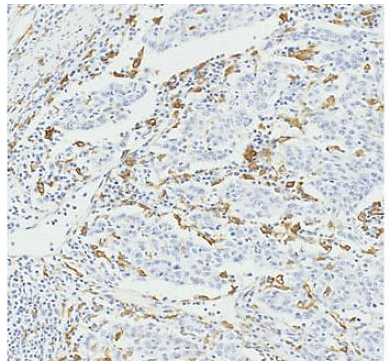


Colorectal Cancer[16]

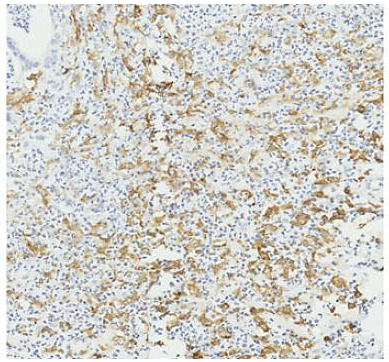
Overall Survival



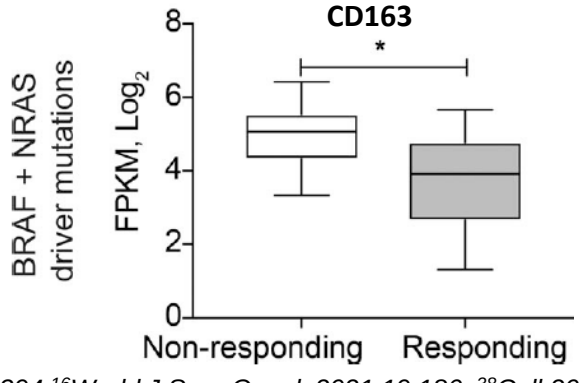
Low TAM Infiltration

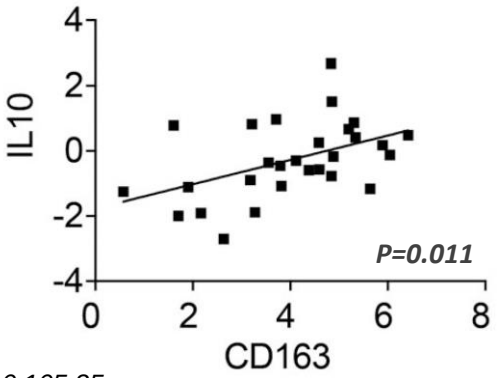


High TAM Infiltration



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

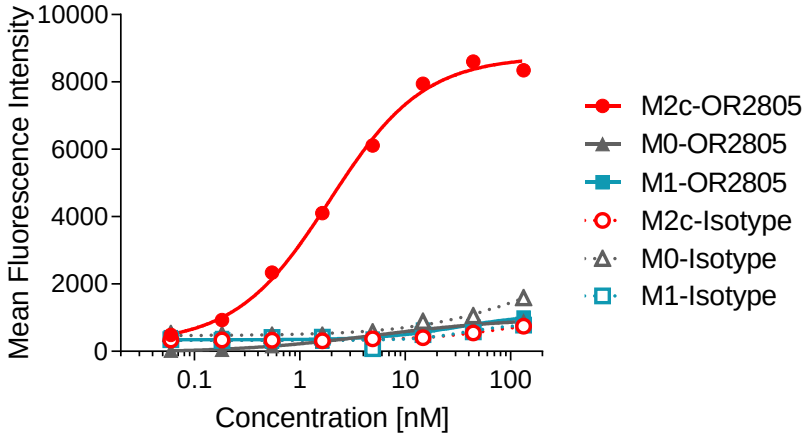


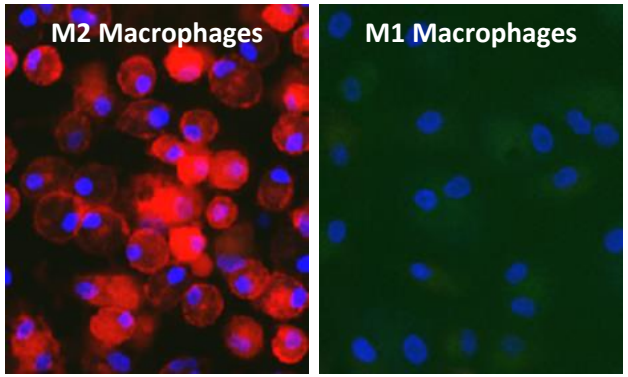


[12]Oncotarget 2017;8:87244, [13]BMC Cancer 2012;12:306, [14]Br J Cancer 2014;111:1509,[15]J Exp Med. 2019;216:2394,[16]World J Surg Oncol. 2021;19:186, [38]Cell 2016;165:35.

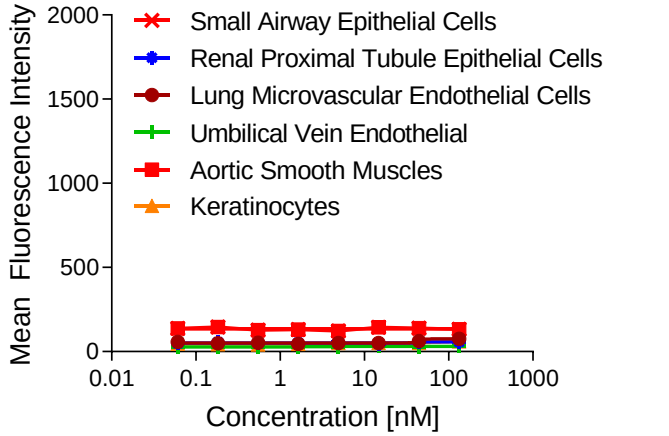
OR2805 demonstrates specific binding to immunosuppressive myeloid cells

Specific binding to human immunosuppressive myeloid cells



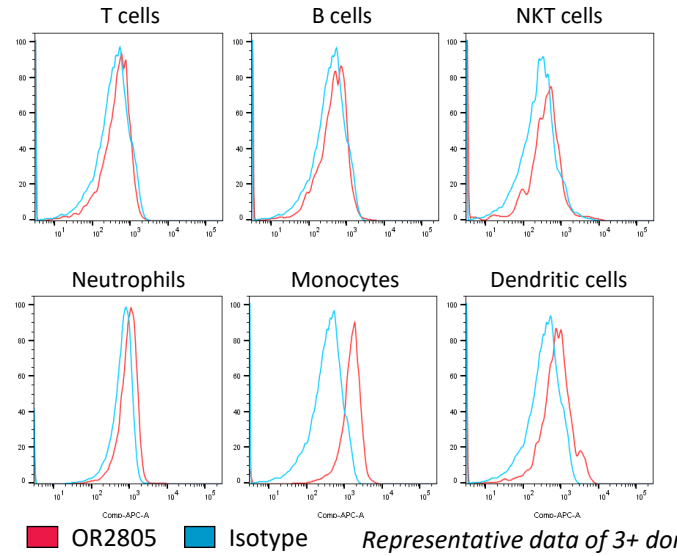


No binding to a panel of human cell types



Binding to TAMs in dissociated NSCLC tumors

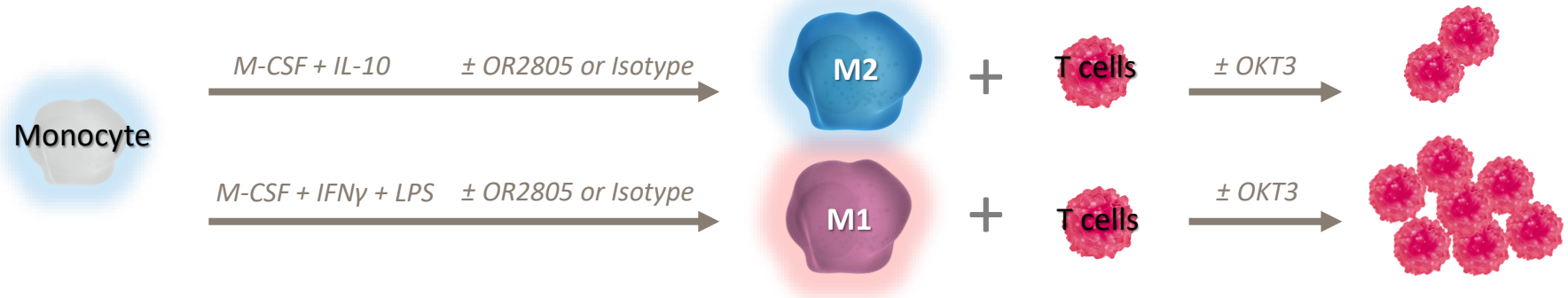
Cell surface markers	Patient 1 cells (%)	Patient 2 cells (%)
Total $CD14^+$ (monocytes)	26	30
$CD163^+$ of $CD14^+$ (M2c)	69	88
$OR2805^+$ of M2c	**82**	**77**
$CD163^-$ $CD80^+$ of $CD14^+$	20	11
$OR2805^+$ of $CD163^-$ TAMs	11	9

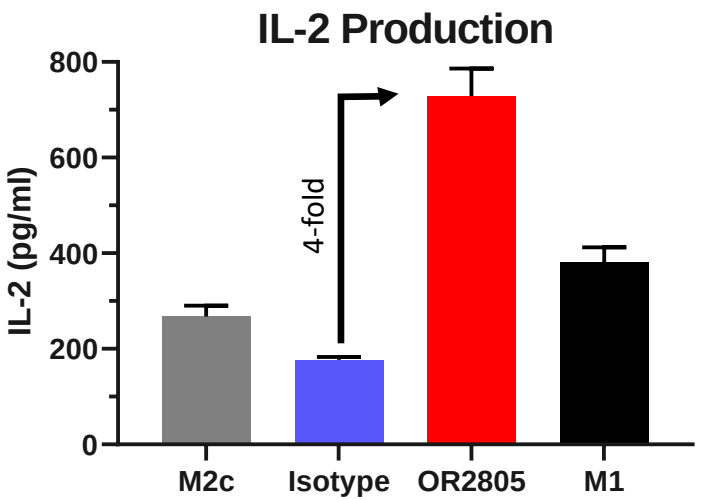


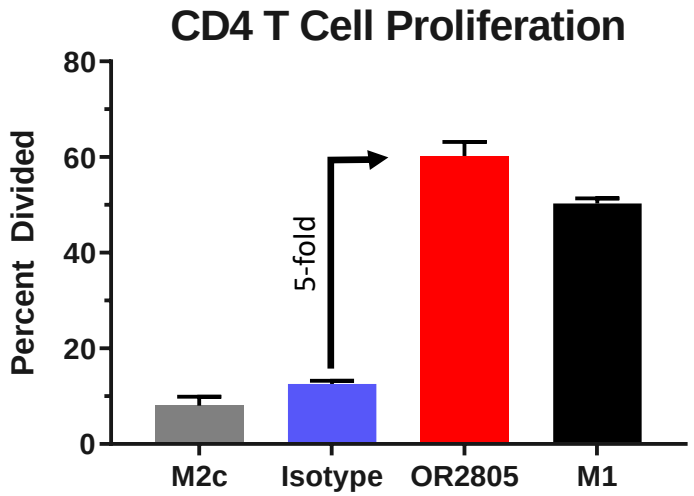
Representative data of 3+ donor

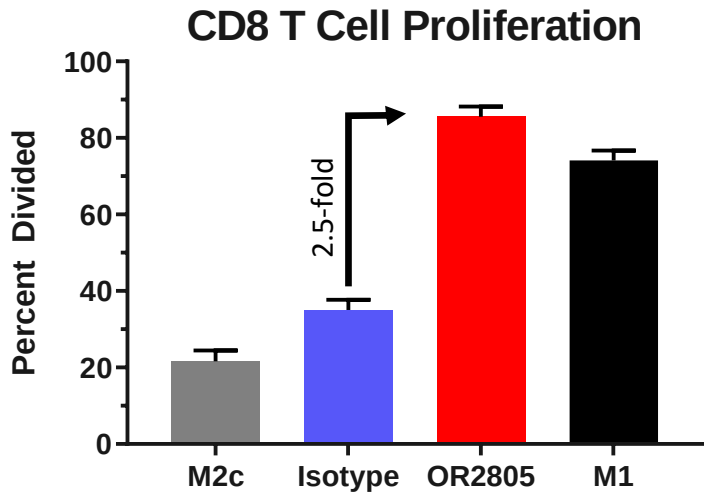
OR2805 has a potential to target immunosuppressive myeloid cells in the TME without impacting other cells

OR2805 treated M2c macrophages promote T-cell activation & proliferation







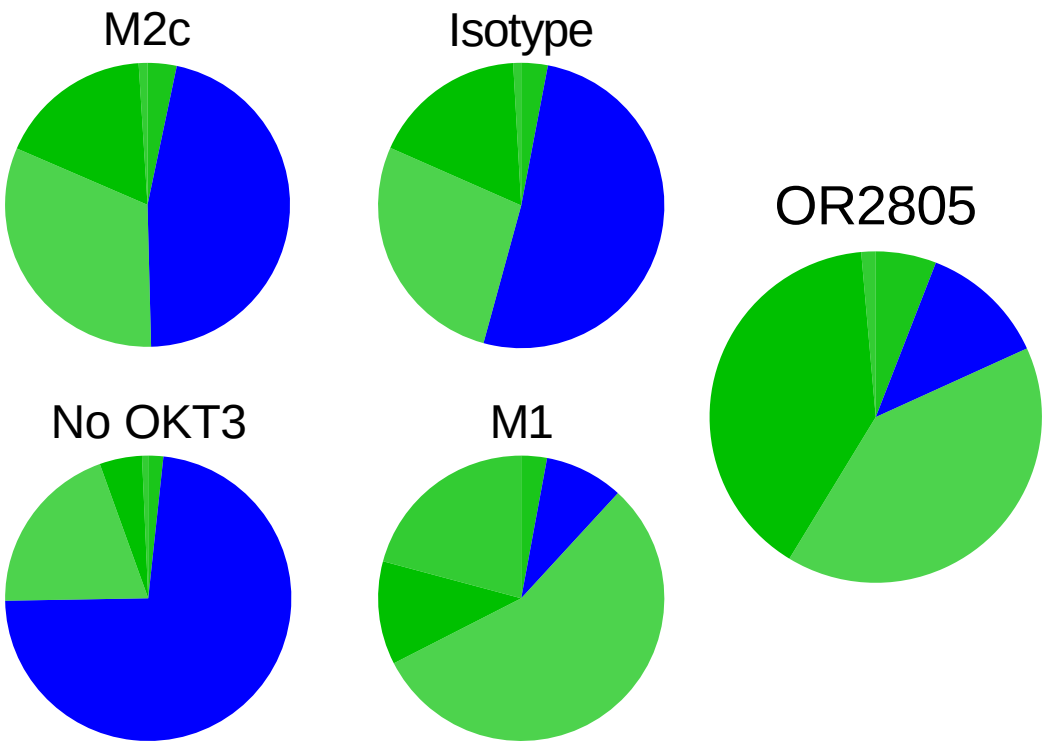


Representative data of 12+ donors

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⁺

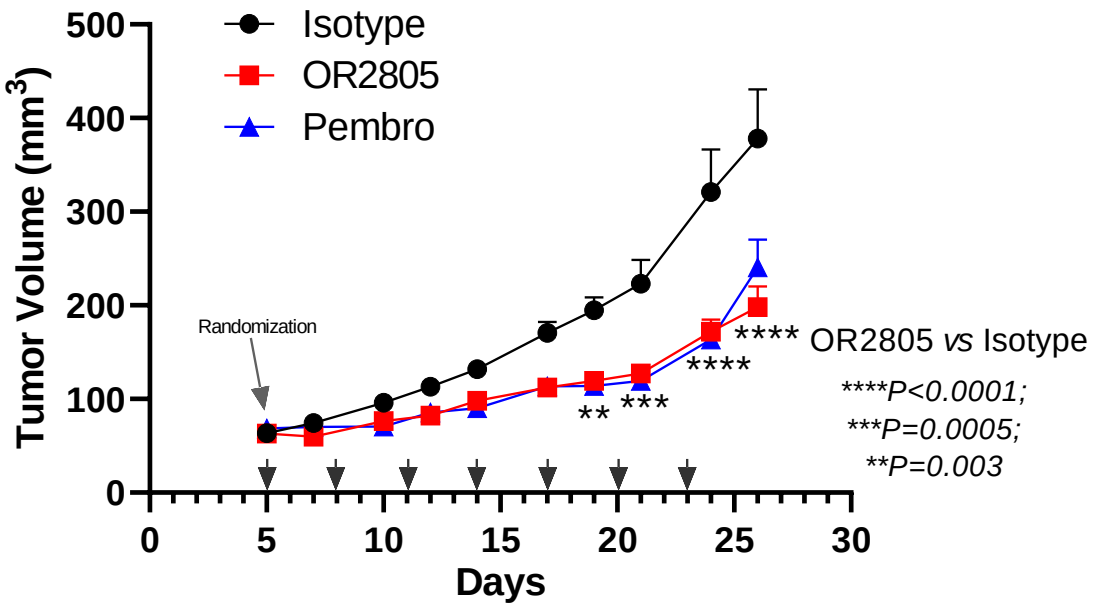
CXCR3⁺ CD69⁺ CD25⁻

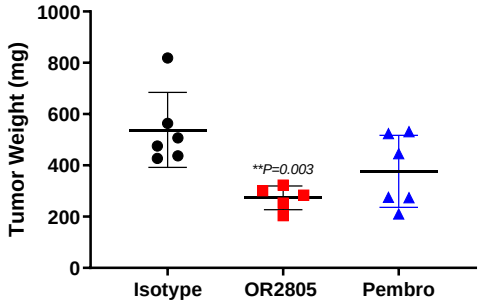
CXCR3⁺ CD69⁻ CD25⁺

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

A549





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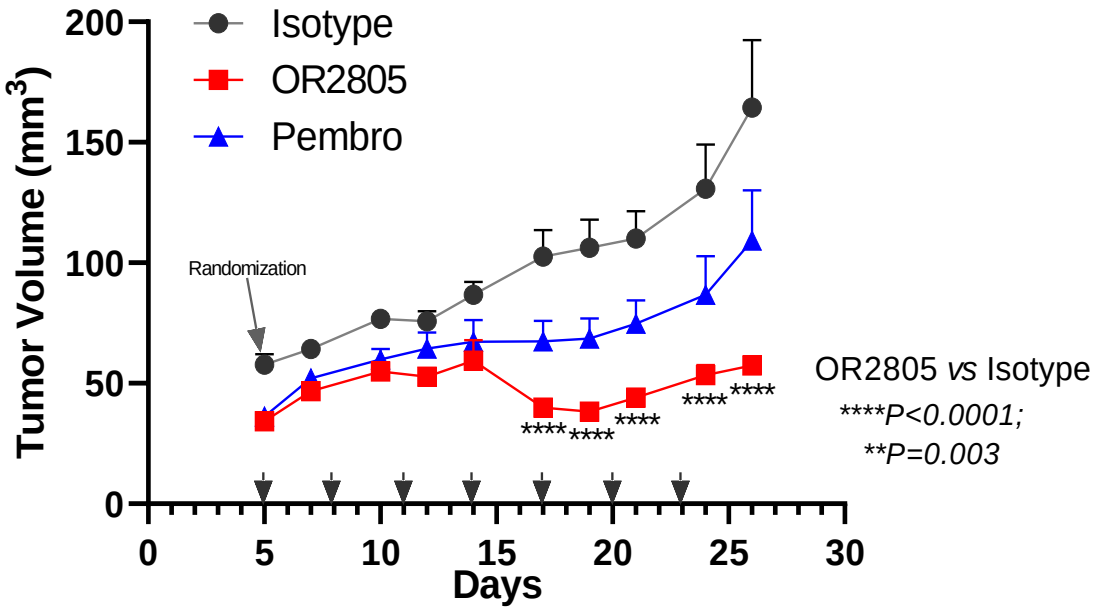
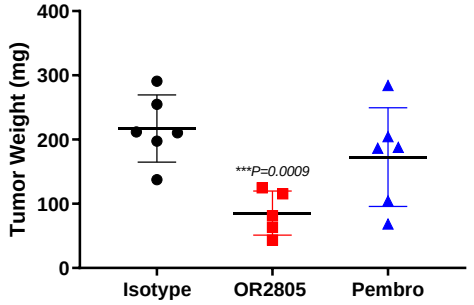
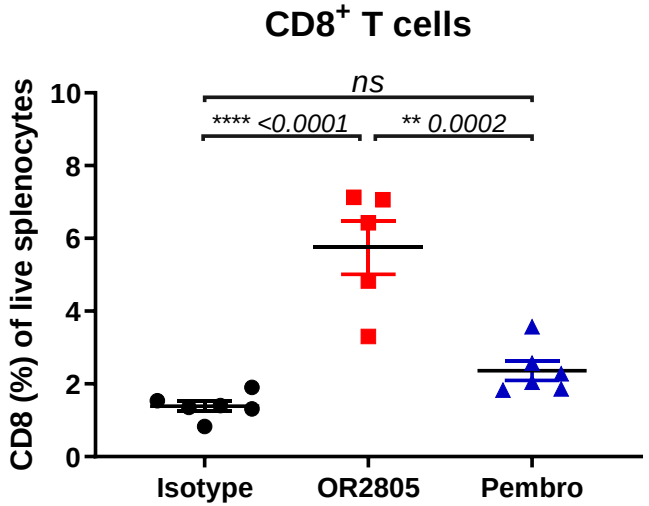
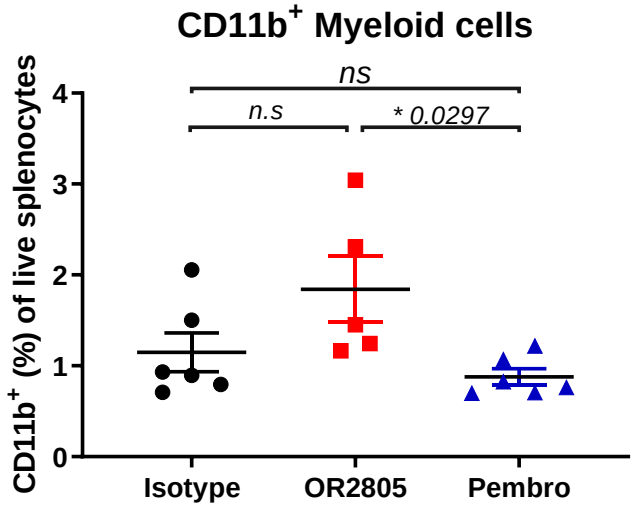




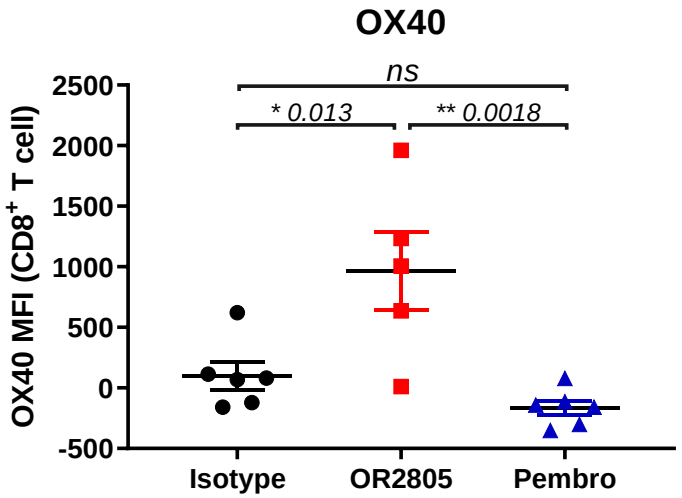
OR2805 treatment increases proportions of activated CD8+ T cells and myeloid cells in humanized NSG-SGM3 model

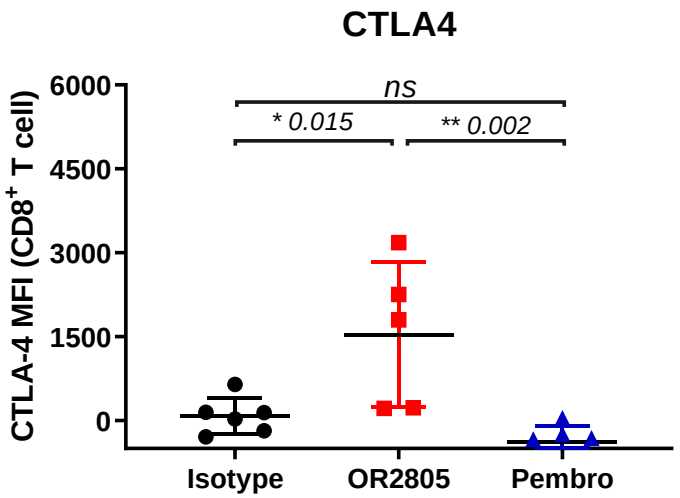
Proportions of human T and myeloid cells in spleen



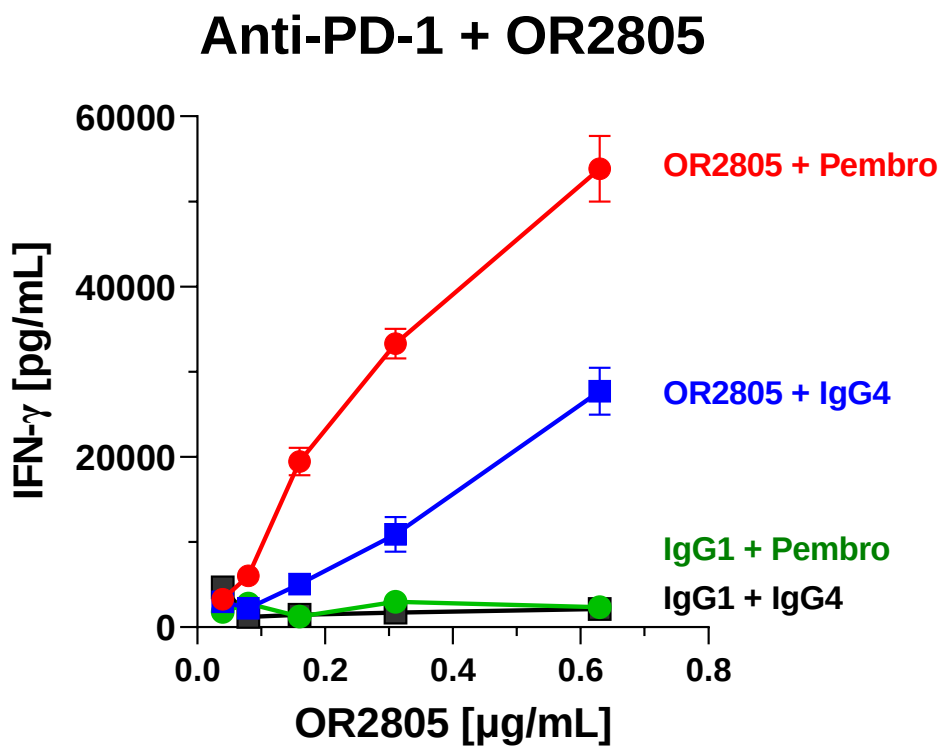


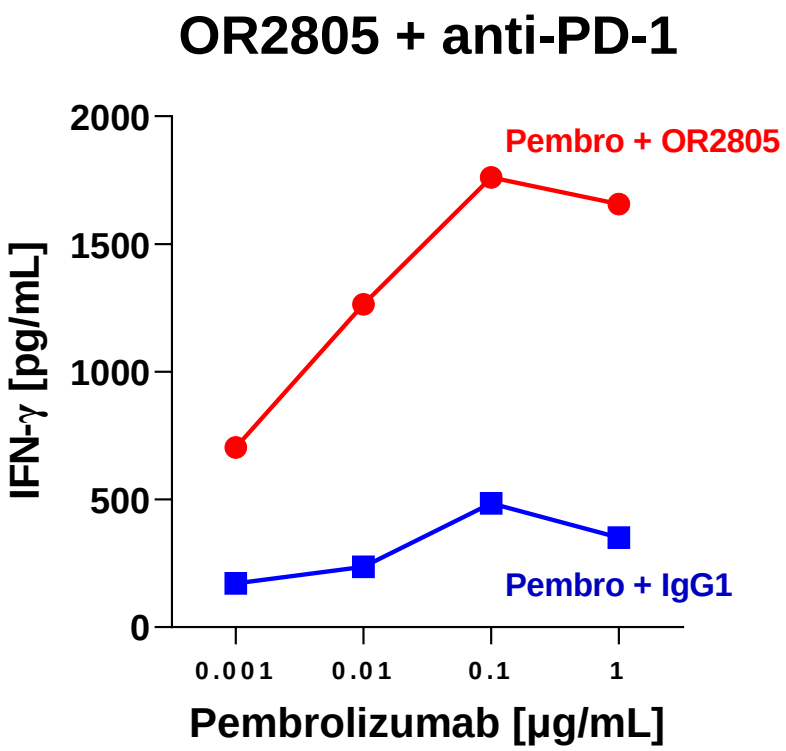
Activation and proliferation markers on human CD8+ T cells in spleen





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

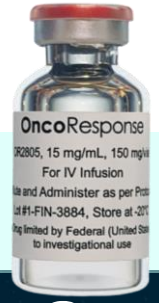




OR2805 has the potential as a single agent or in combination with CPI to increase the number of patients who may benefit from immunotherapy

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 dose escalation-expansion study of OR2805 alone or in combination in subjects with advanced solid tumors is ongoing (NCT05094804)



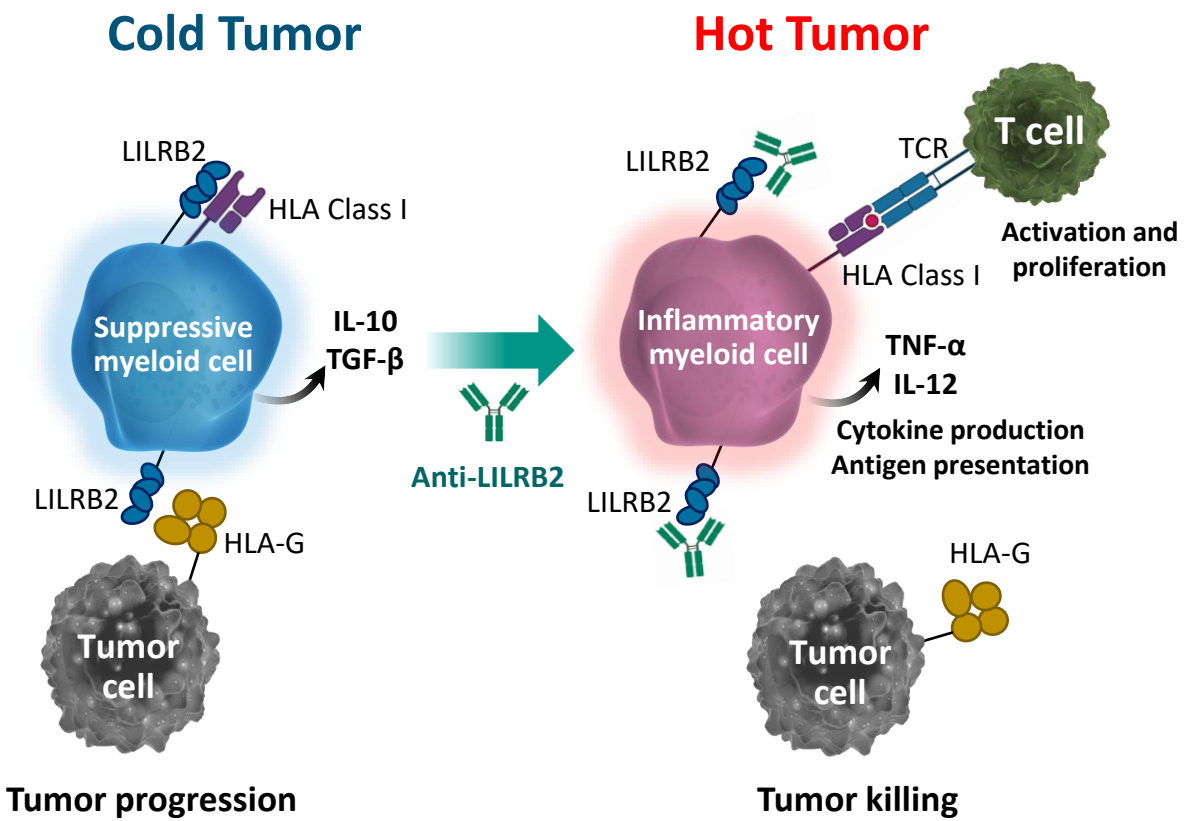
OR2805 has therapeutic potential as a single agent or in combination with checkpoint inhibitors

OncoResponse

Leukocyte Immunoglobulin-Like Receptor B2 (LILRB2/ILT4)

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

LILRB2 antagonism reprograms TAMs and promotes anti-tumor immunity in the TME



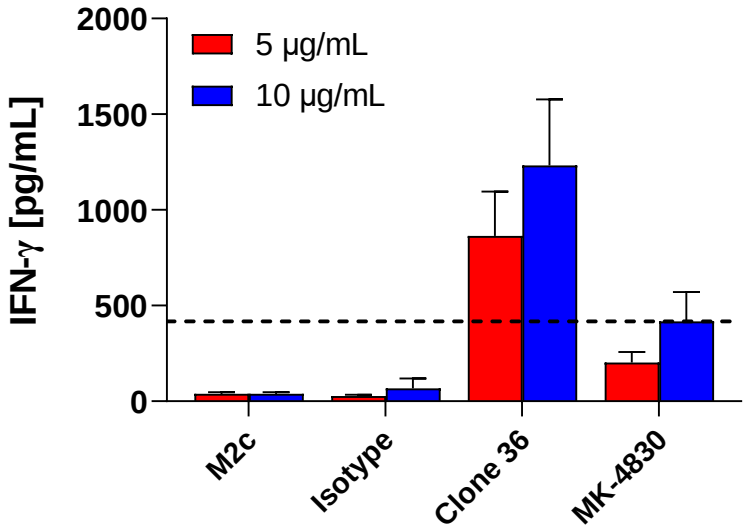
- Highly expressed on dendritic cells (DCs) and MDSCs of the TME and some tumor cells
- Upregulates HLA-G expression and secretion by tumor cells
- Promotes suppressive macrophage phenotype
- Diminishes killing ability of CTLs by competitive binding to MHC-class I with CD8 and/or upregulation of HLA-G in CTLs
- Impairs DC maturation to induce Th1 cell anergy and promotes Treg and Th2 differentiation

J Clin Invest. 2018;128:5647, Biochim Biophys Acta. 2018;1869:278

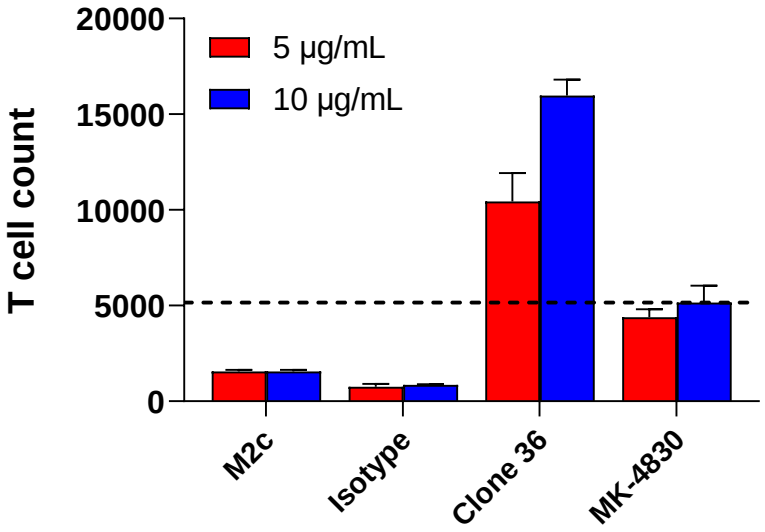
OncoResponse antibody enhances CD8⁺ T cell proliferation and IFNγ production in M2c/T cell coculture assay

M2c/CD8⁺ T cell coculture

IFNγ production

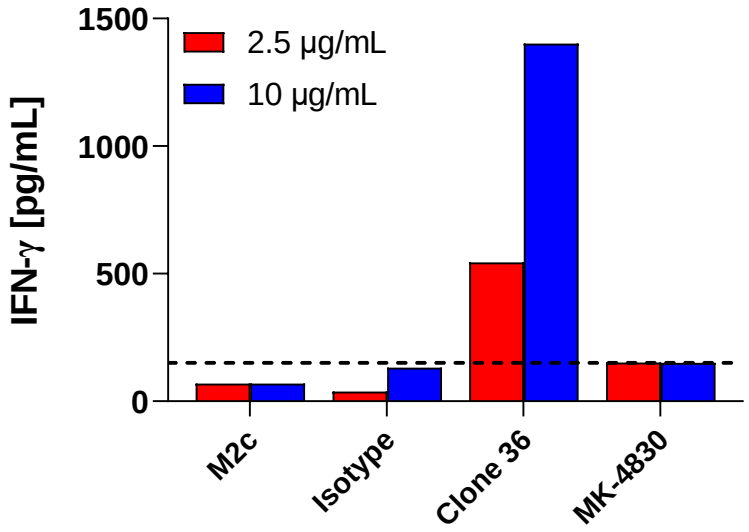


CD8⁺ T cell proliferation



M2c/Exhausted T cell coculture

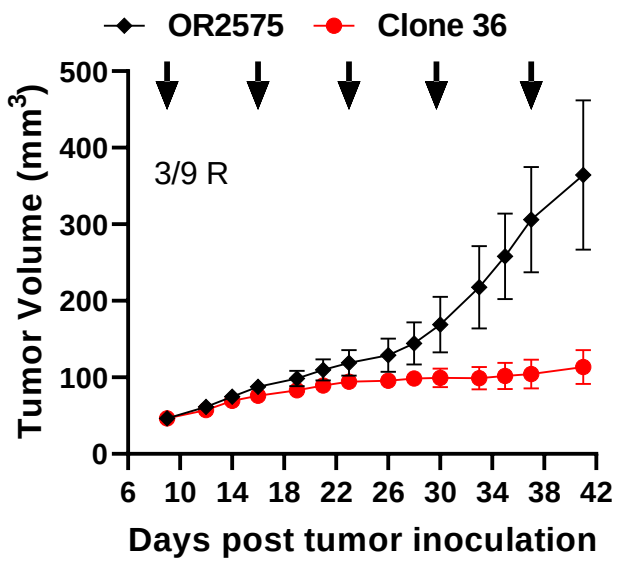
IFNγ production



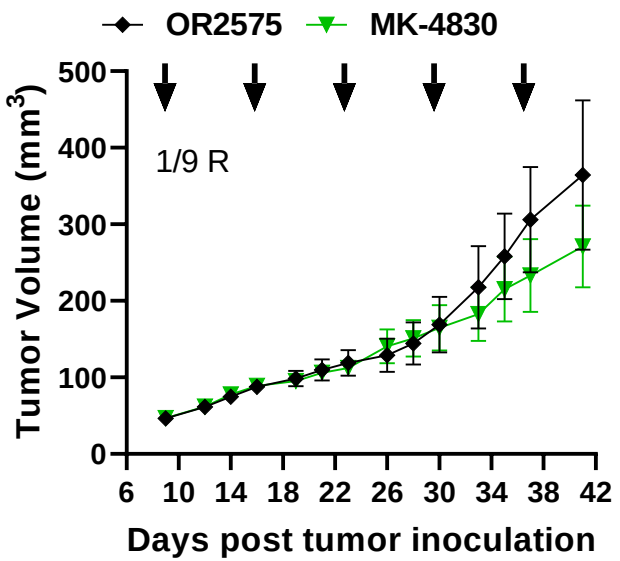
OncoResponse antibody outperforms MK-4830 in M2/T cell coculture assay

OncoResponse antibody induces anti-tumor response in SK-MEL-5 tumor model in humanized NSG-SGM3 mice

Clone 36 (OncoResponse)



MK-4830 (Merck)

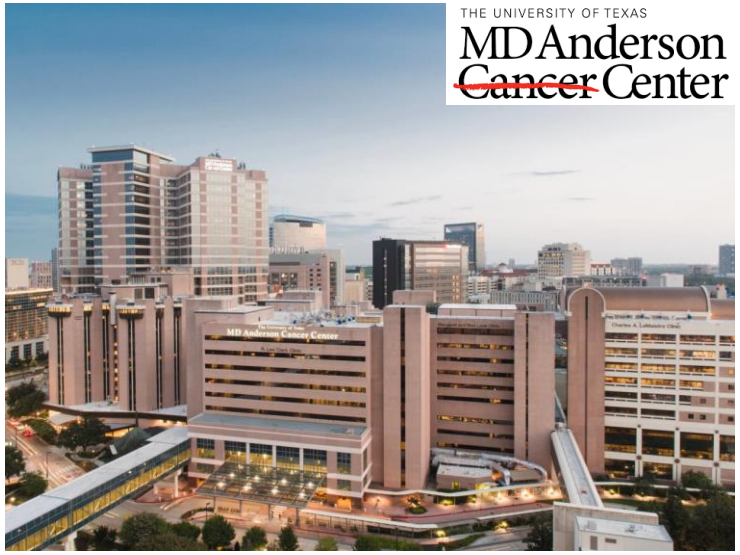


- Dosing: 20 mg/kg i.p.
- Dosing Days: 9, 16, 23, 30, 37

All groups N=9

	Tumor Growth Inhibition (%)						Regression (%)
Group	***d28***	***d30***	***d33***	***d35***	***d37***	***d41***	***d41***
Clone 36 (OncoResponse)	47	57	69	74	78	79	33
MK-4830 (Merck)	-5	3	16	17	24	26	11

Acknowledgements



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Mike Gallatin

Miriam Merad

Patients who provided precious tissue samples for this study

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Interrogating for **Cures**™

ThankYou.

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