OncoResponse

Interrogating for Cures™

Discovery and Development of Antibodies to Relieve Immunosuppression in the Tumor Microenvironment

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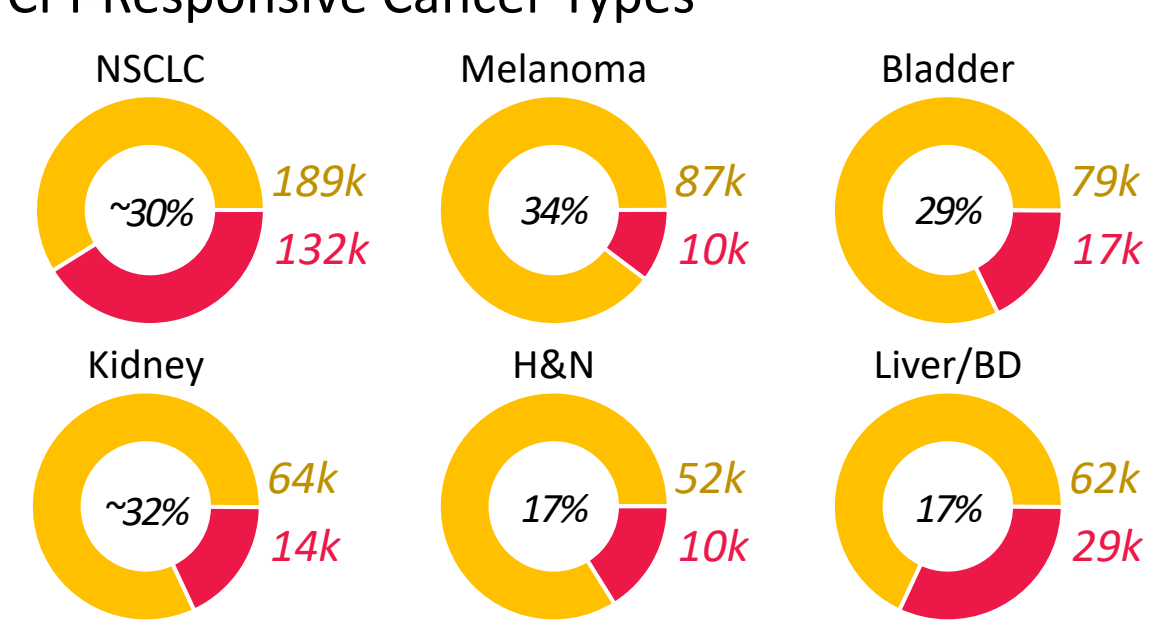
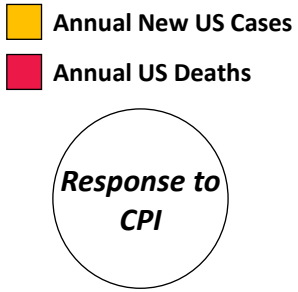
World Vaccine & Immunotherapy Congress

30 Nov – 2 Dec, 2021

The Immuno-Oncology (IO) opportunity

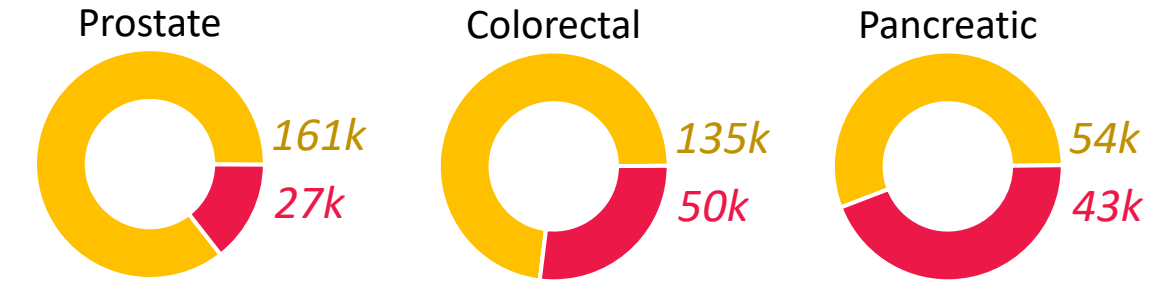
CPI-Responsive Cancer Types

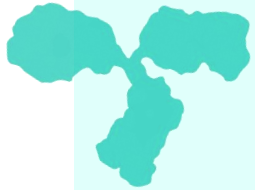




- Response rates from checkpoint inhibitors (CPI) continue to be low due in part to the suppressive Tumor Microenvironment (TME)
- There is a large unmet need to overcome immunosuppression of the TME to dramatically increase response rates and survival

CPI-Non-Responsive Cancer Types





OncoResponse leverages the power of the Elite Responder's immune system to discover antibodies that modulate immunosuppression in the TME

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

OncoResponse

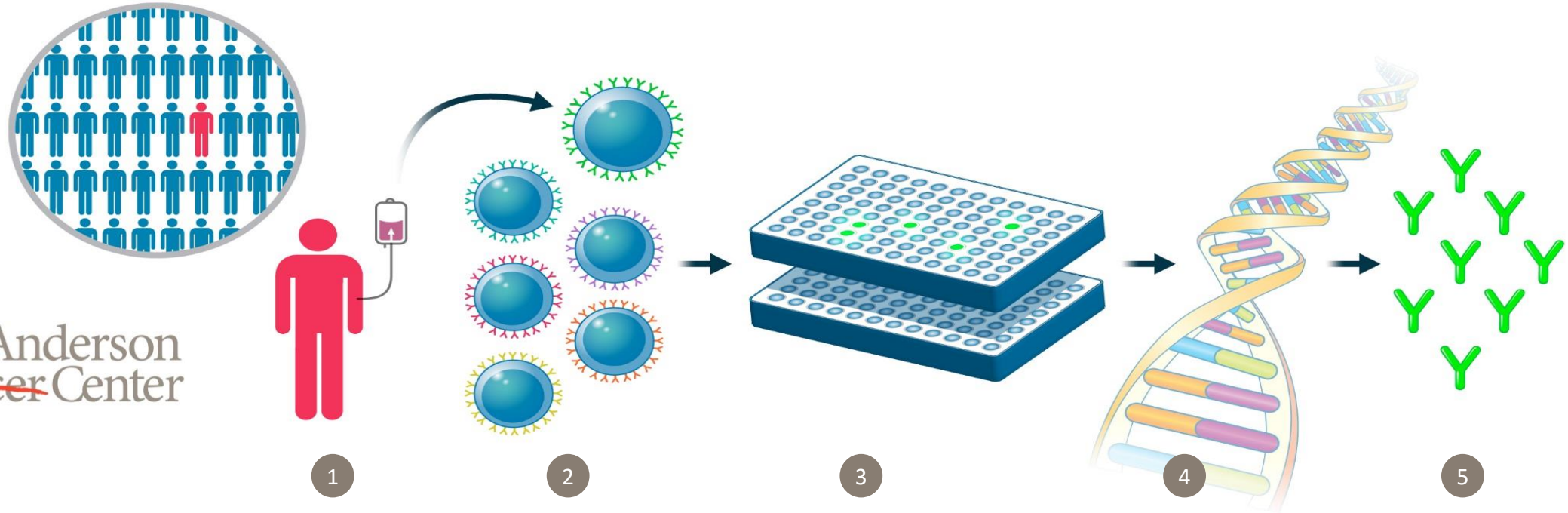
Our Mission

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

Immuno-Oncology experts focused on the Tumor Microenvironment

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

OncoResponse is product focused with a proven discovery platform

Antibody	Mechanism	Discovery	*In vitro*	*In vivo*	DDC	Phase 1
OR2805	Targets & reprograms TAMs/MDSCs					
Anti-Siglec-15	Reverse immunosuppression by TAMs					
Anti-LILRB2/ILT4	Reverse immunosuppression & reprogram TAMs					

- Strategic alliance with MD Anderson provides unique access to B cells and tissue from cancer patients
- Platform identifies, from Elite Responders, human antibodies with exceptional reactivity to immune cells
- Focus on human antibodies that modulate immune cell activity and enhance immunotherapy responses
  - Targeting TAMs/MDSCs to **relieve immunosuppression** in the tumor microenvironment
  - **Reverse immunosuppression** and **promote NK and CD8 T-cell killing** of tumor cells

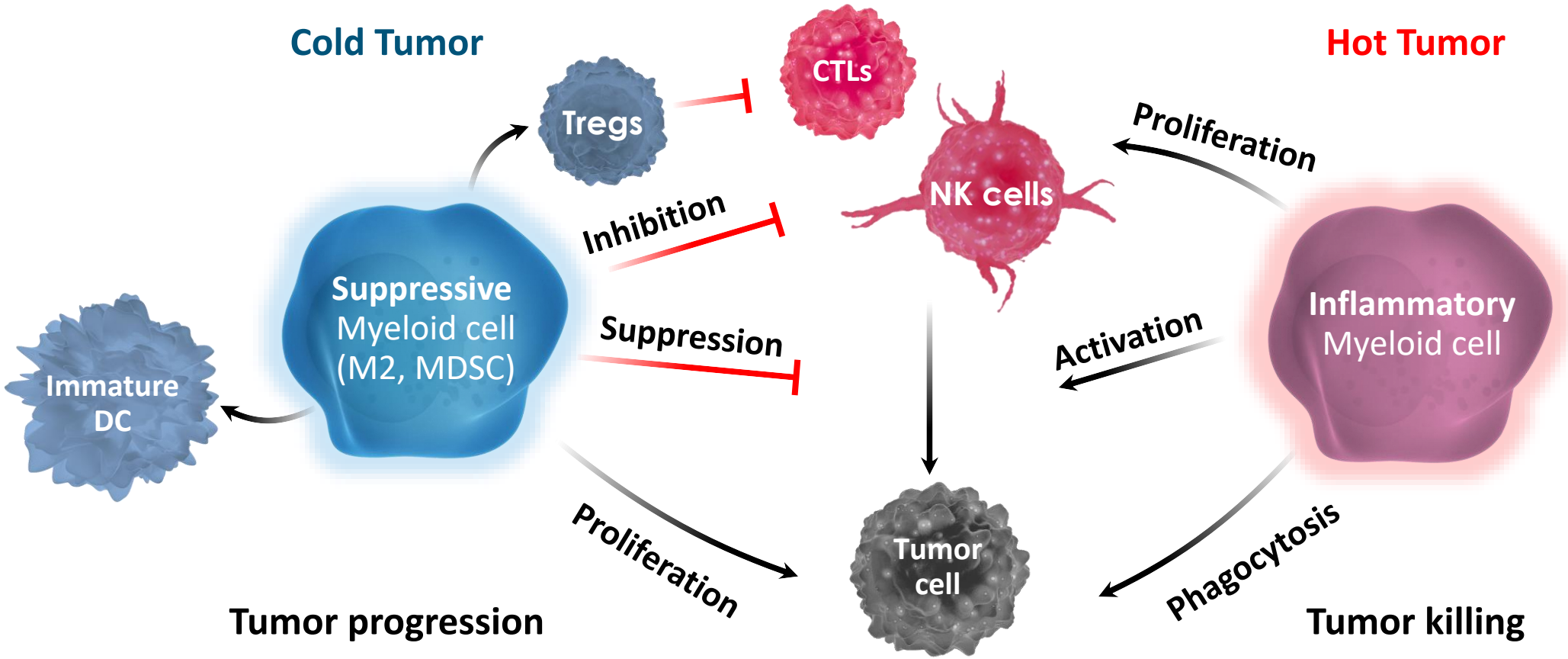
Abbreviations: Ab, antibody; CTL, cytotoxic T lymphocyte; MDSC, myeloid-derived suppressor cells; NK, natural killer; TAM, tumor-associated macrophages; DDC, drug development candidate

Rationale for targeting tumor associated macrophages (TAMs)

- **M2 TAMs** create a highly **immunosuppressive** environment promoting tumor growth
- Evidence shows that TAMs are central to treatment resistance
  - Presence of **M2 macrophages** correlates with **poor patient prognosis** in multiple tumor types
  - Presence of **M1 macrophages** correlates with **better patient outcomes** and response to immunotherapies
- **Repolarization** of M2 TAMs to M1 phenotype **relieves immunosuppression** and **enhances anti-tumor** activity
- Targeting TAMs has shown promising preclinical results
  - Siglec-15, LILRB2, CD47/SIRP-alpha, TREM1/2, Clever-1, MARCO, PI3Kγ
- Emerging clinical data support targeting TAMs for anti-cancer therapy
  - NC318 (anti-Siglec-15 mAb), MK-4830 (anti-LILRB2 mAb)

Nature Medicine 2015;21:938, Nat Rev Drug Discov. 2018;17:887, Cancer Cell 2019;35:885, Cell 2017;171:934, J Clin Invest. 2017;127:2930, J Clin Invest. 2018;128:5647, Nat Med. 2019;25:656, Nature Medicine 2015;21:117, ESMO 2020,

TAMs are critical regulators of the TME



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

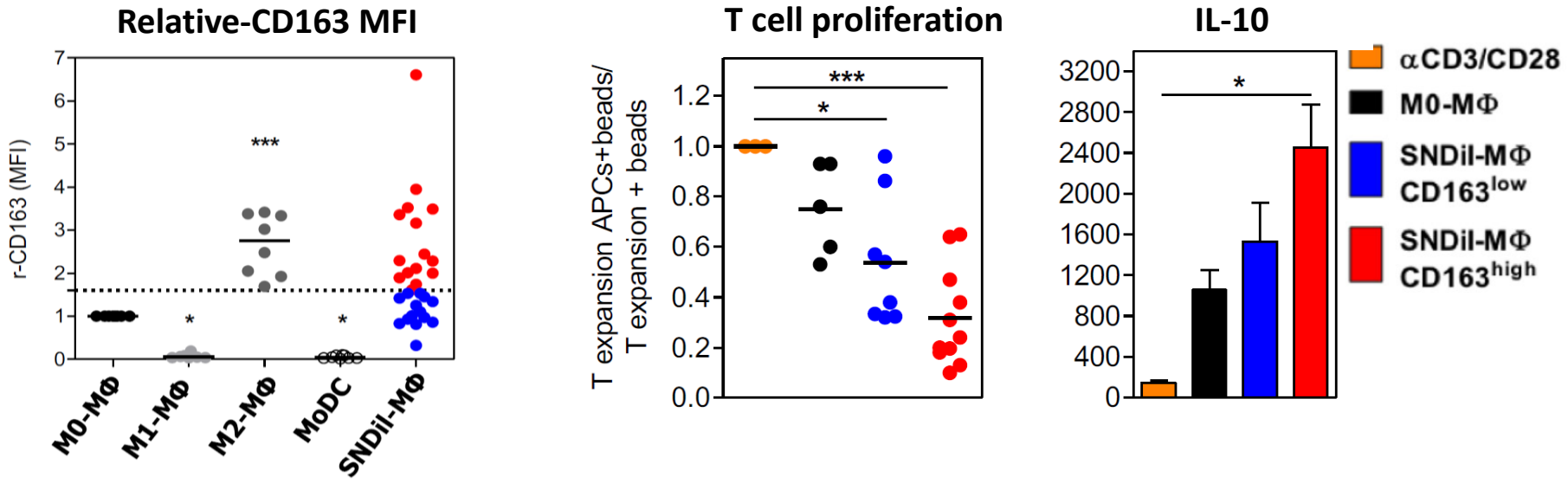
CD163 - Normal physiology and role in cancer

- 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]
  - In HNSCC, BC and GC, expression of CD163 correlated with decreased response to chemo
  - Higher levels of expression in melanoma predicts poor response to CPI
  - CD163 expression correlates with IL-10 expression in melanoma

[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.

TME factors force monocytes to differentiate into CD163^{high}CD86^{low}IL-10^{high} immunosuppressive macrophages (TAMs) in breast cancer

- High frequency of CD163^{+} TAMs correlates with higher risk of relapse in BC patients
- Tumor secreted factors differentiate monocytes towards M2-like macrophages
- Blood monocytes from breast cancer patients are refractory to M1-macrophage differentiation conditions, and secrete immunosuppressive, metastasis-related and angiogenic cytokines



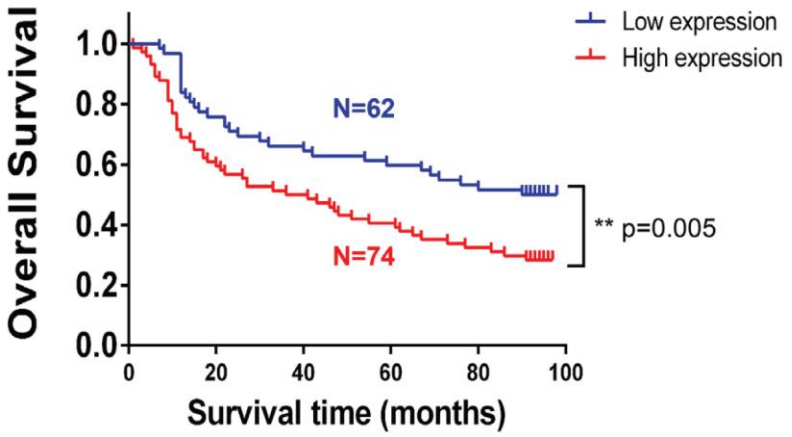
SNDil (supernatant from primary tumors)

Clin Transl Immunology. 2020;9:e1108

CD163 is a negative prognostic marker in cancer

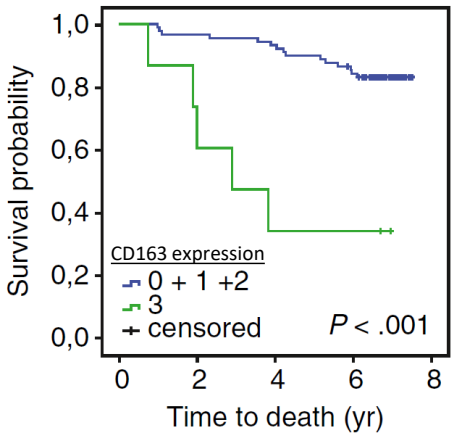
Gastric Cancer[12]

Overall survival



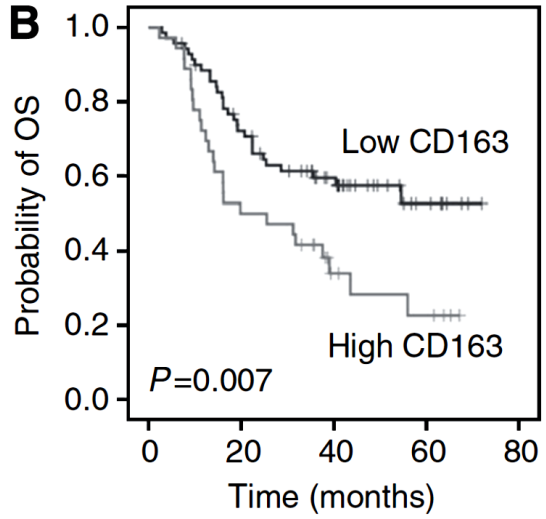
Breast Cancer[13]

Survival probability

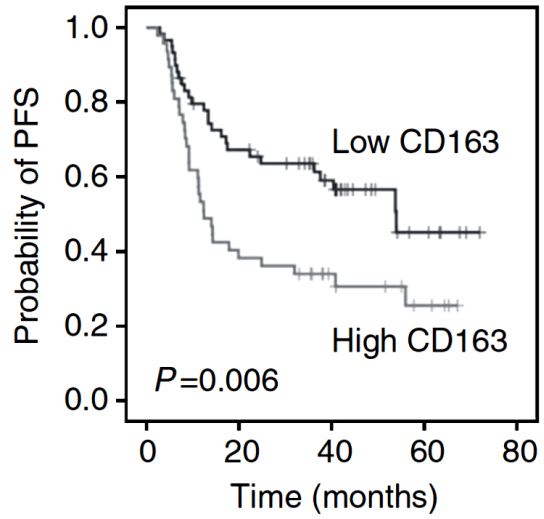


Head and Neck Cancer[14]

Overall survival

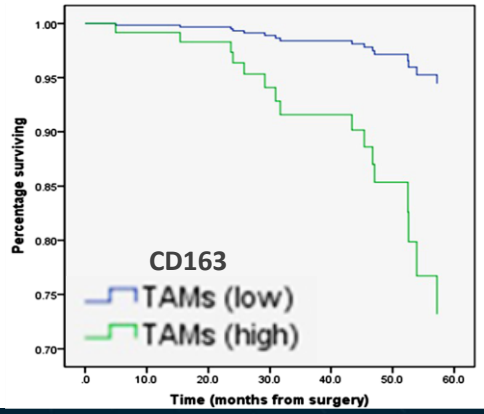


Progression-free survival

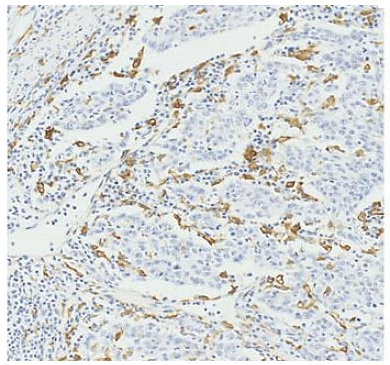


Colorectal Cancer[16]

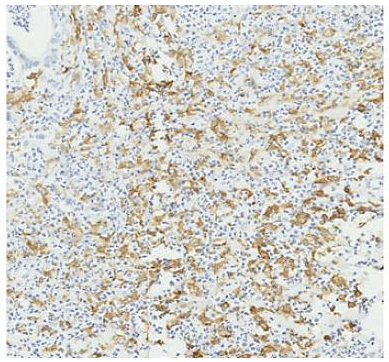
Overall Survival



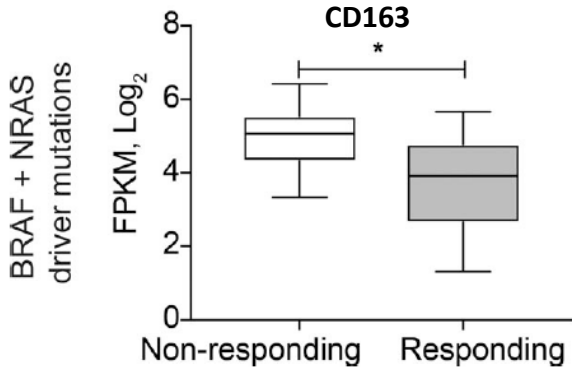
Low TAM Infiltration

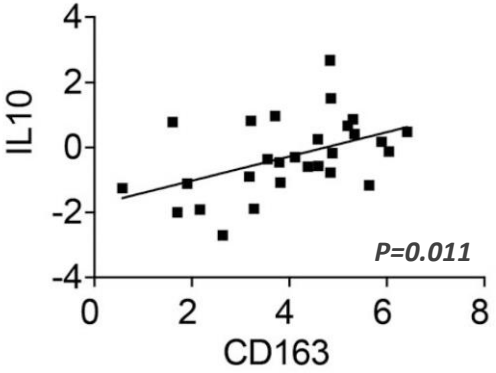


High TAM Infiltration



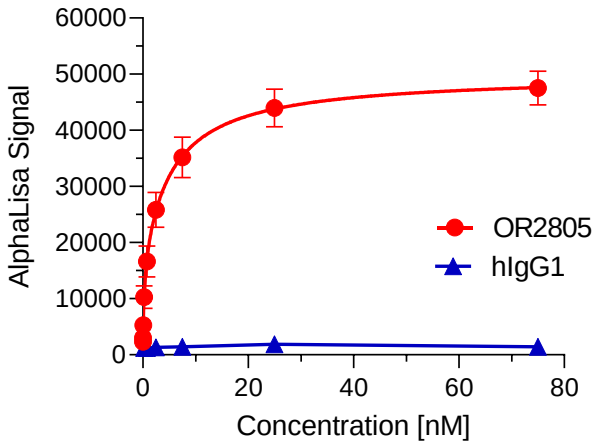
Melanoma patients on anti-PD-1 therapy[15,38]



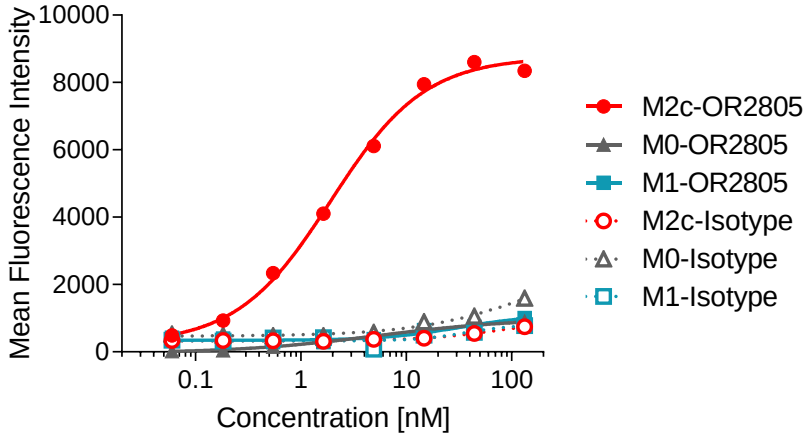


OR2805 demonstrates specific binding to immunosuppressive myeloid cells

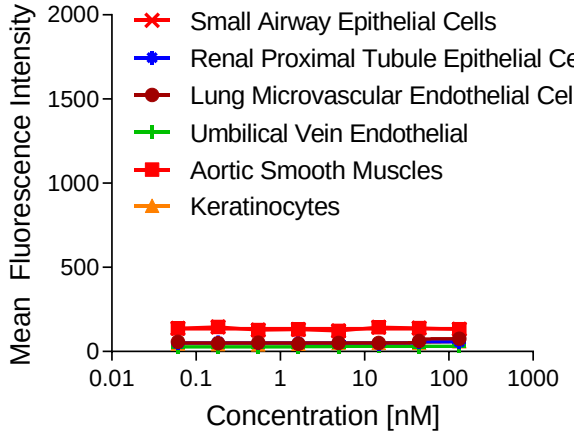
OR2805 binds to human CD163



Specific binding to human immunosuppressive myeloid cells



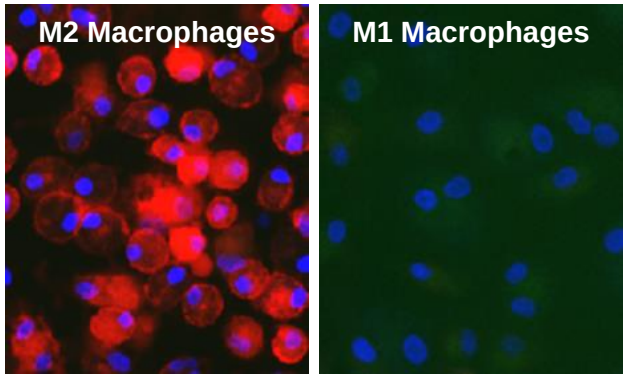
No binding to a panel of human primary immune and non-immune cells

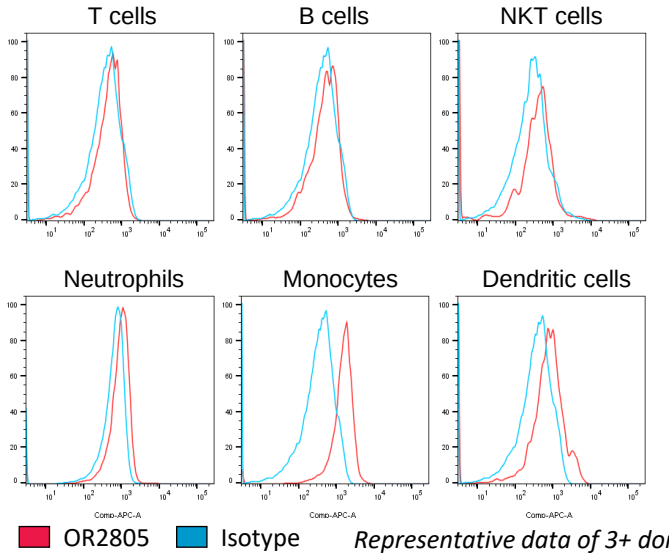


OR2805 binds to TAMs in dissociated NSCLC tumors

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

OR2805 staining



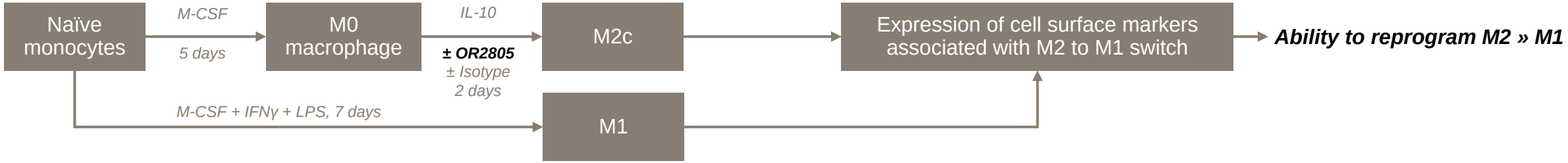


Representative data of 3+ donor

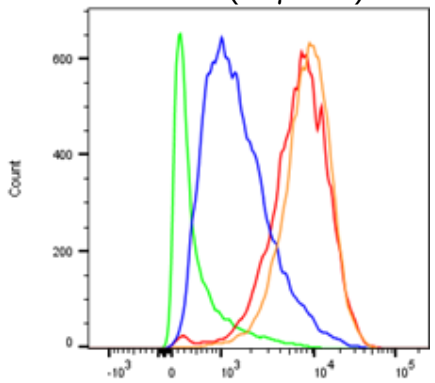
OR2805 has a potential to target immunosuppressive myeloid cells in the TME without impacting other cells

OncoResponse

OR2805 reduces expression of M2c macrophage surface markers

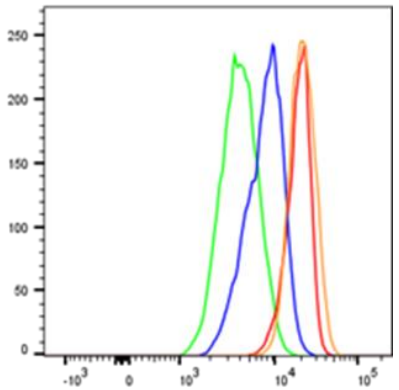


CD16 (FcγRIIIa)



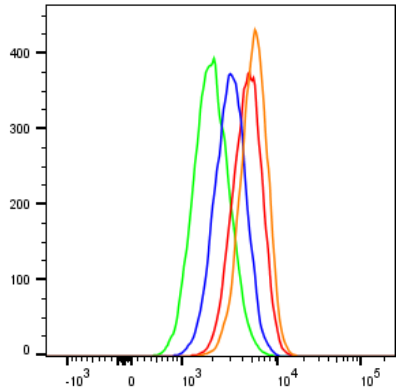
Low affinity IgG receptor. Highly expressed on M2cs.

CD64 (FcγRI)



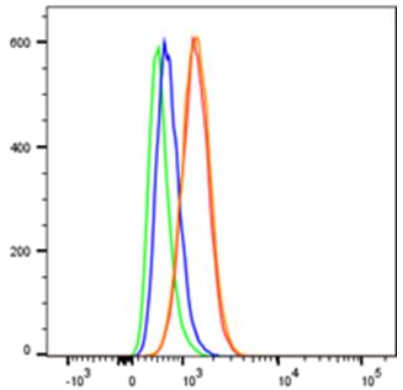
High affinity IgG receptor. Highly expressed on M2cs.

TLR2



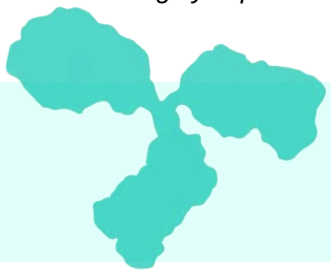
Innate immune receptor involved in immune modulation. Highly expressed on M2cs.

Siglec-15



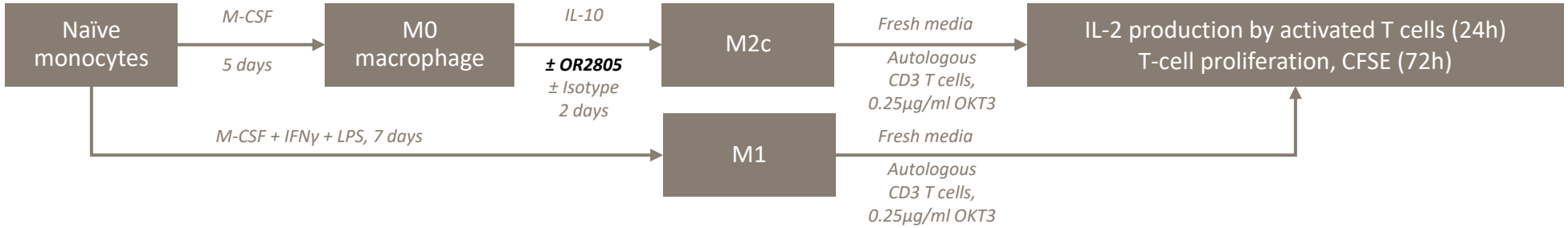
Transmembrane protein involved in immune suppression. Specific expression on M2c.

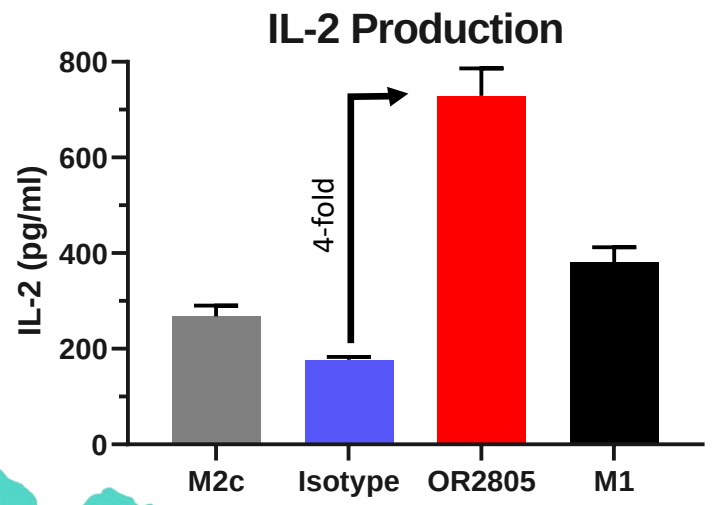
Representative data of 3+ donors

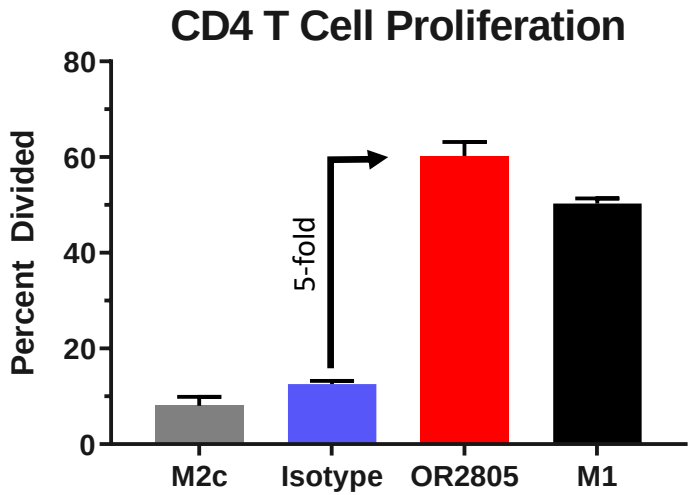


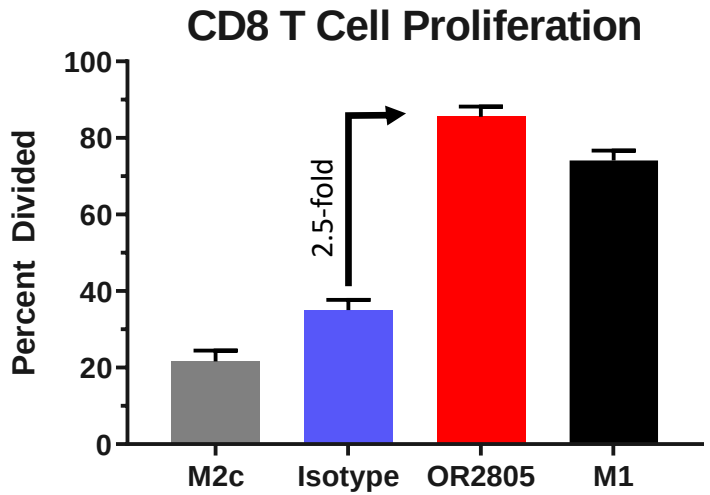
OR2805 treatment reduces expression of cell-surface markers associated with tumor-promoting M2c macrophages

OR2805 treated M2c macrophages promote T-cell activation and proliferation









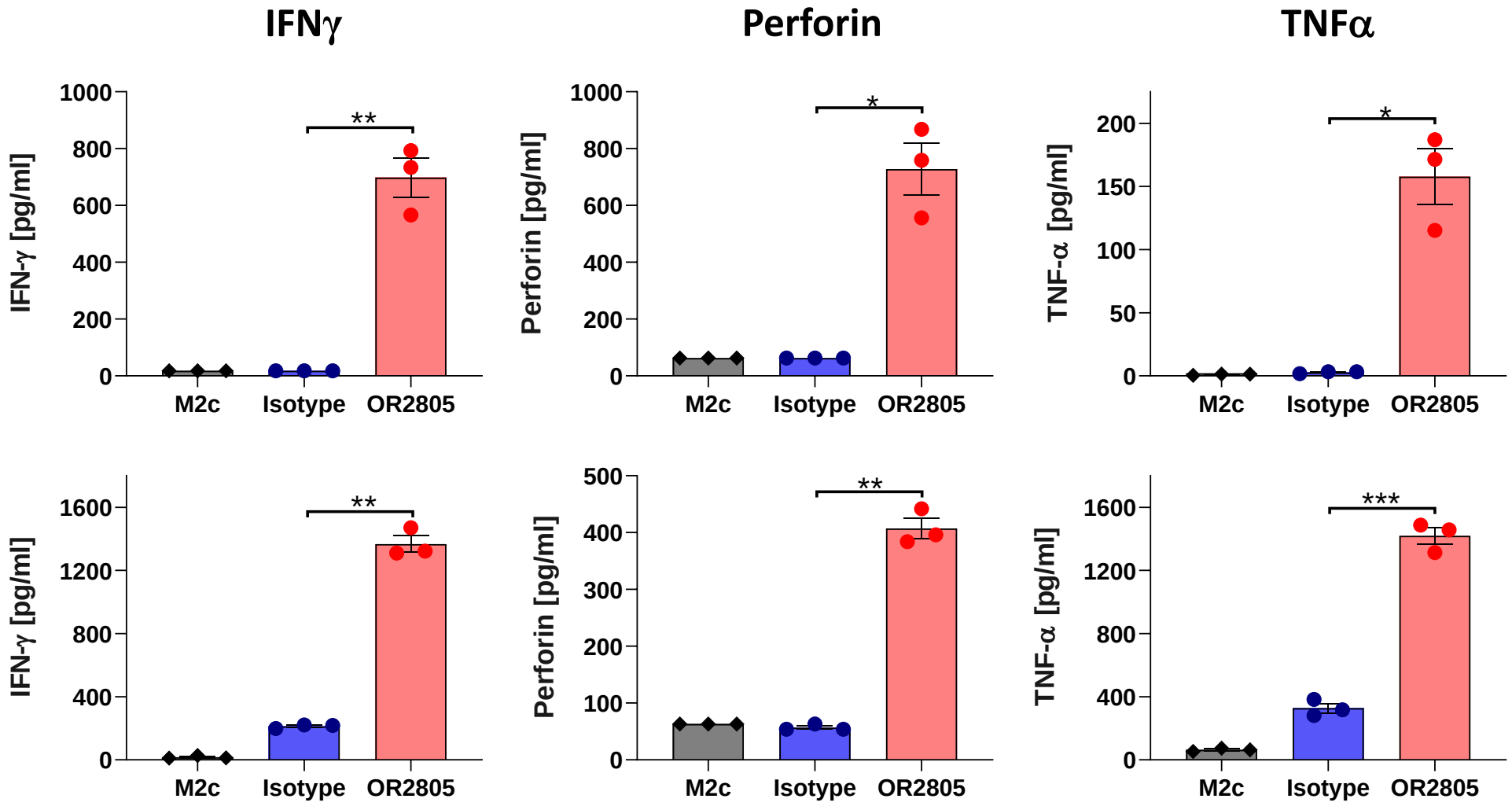
Representative data of 12+ donors

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 promote T-cell activation

M2c/CD8 coculture

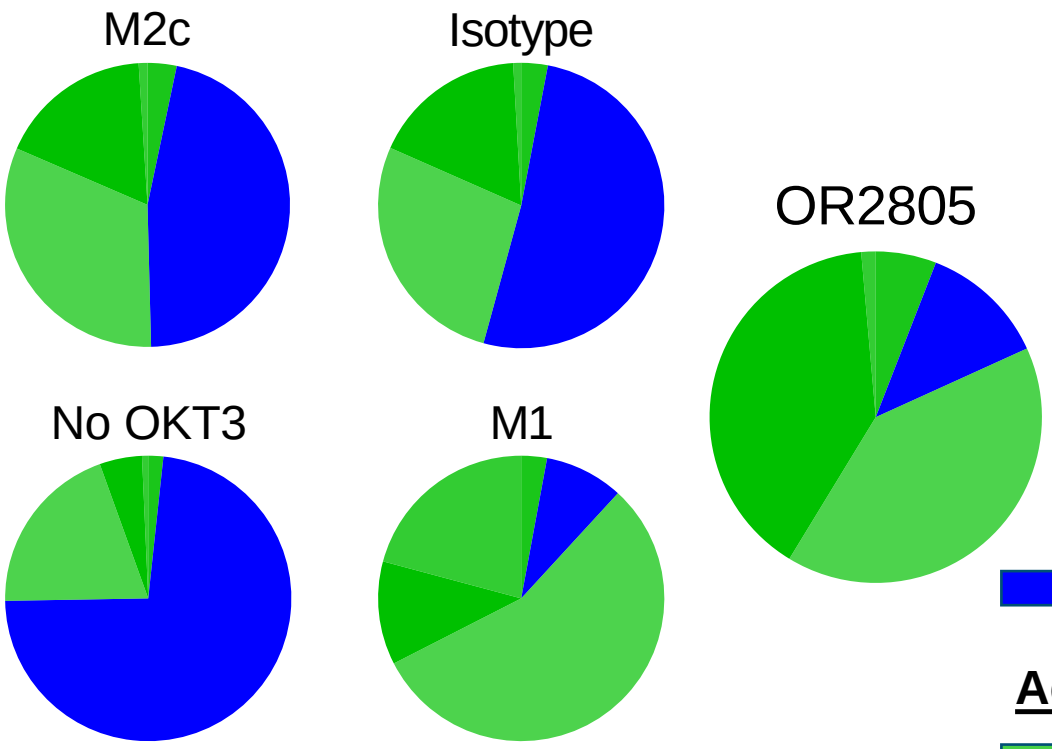
M2c/CD4 coculture



Representative data from n=3 donors

OR2805-treated M2c macrophages skew T cells towards activated Th1-like phenotype

Distribution of CD4$^+$ T cells phenotypes



- CXCR3 is preferentially expressed on Th1 cells
- IFNγ production within the TME enhances CXCR3-mediated T-cell recruitment to the tumor site
- CXCR3 signaling promotes CD8$^+$ T-cell infiltration
- CXCR3 expressing CD8$^+$ T-cell populations display enhanced cytotoxicity against tumor cells

Resting T cells

CXCR3$^-$ CD69$^-$ CD25$^-$

Activated CXCR3$^-$ T cells

CXCR3$^-$ CD69$^+$ CD25$^+$

Activated CXCR3$^+$ T cells

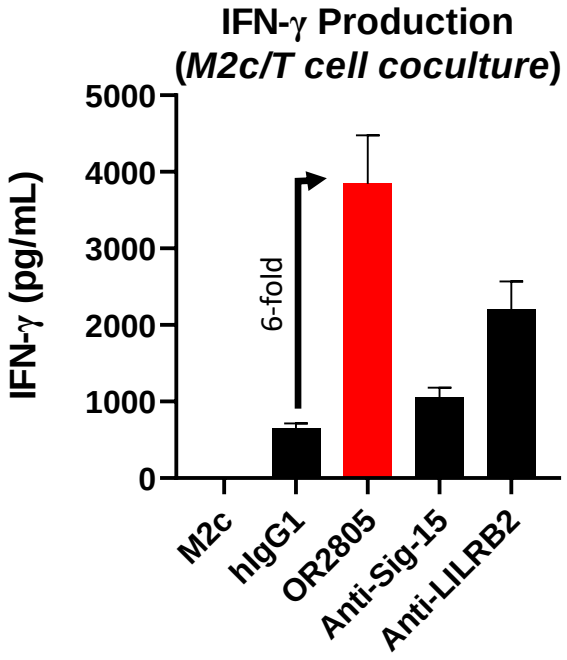
CXCR3$^+$ CD69$^+$ CD25$^+$

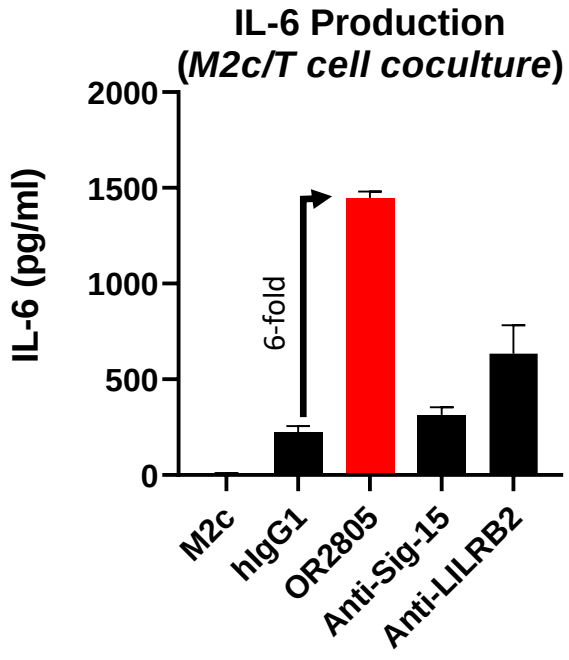
CXCR3$^+$ CD69$^+$ CD25$^-$

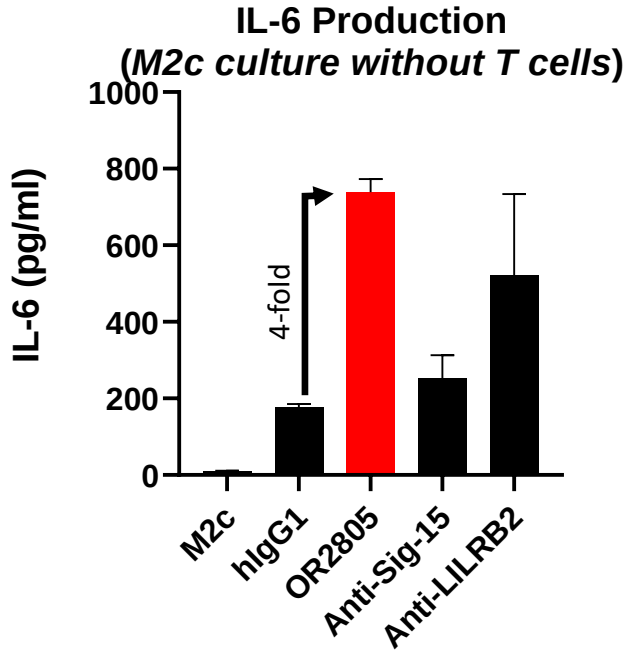
CXCR3$^+$ CD69$^-$ CD25$^+$

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

OR2805 is superior to other myeloid targeting agents in clinic



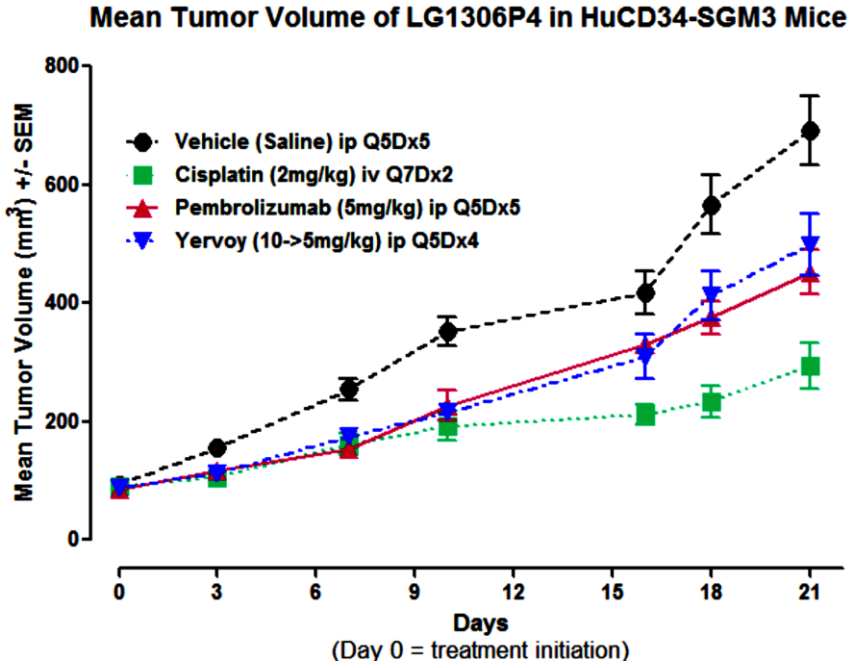




Representative data of 3+ donors

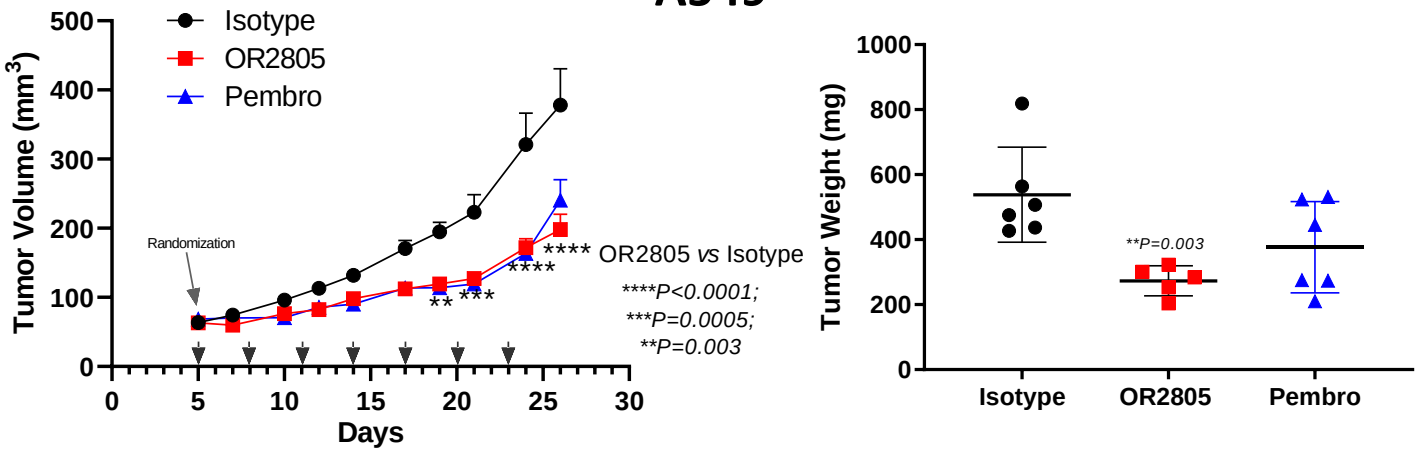
OR2805 induces anti-tumor activity in humanized NSG-SGM3 mice

NSCLC



The Jackson Laboratory

A549



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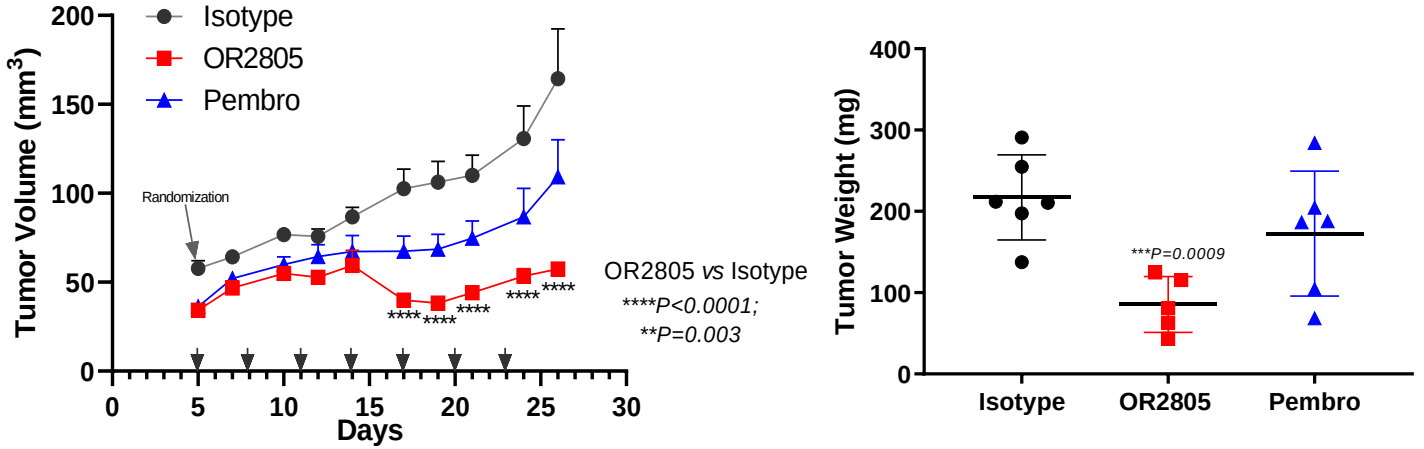
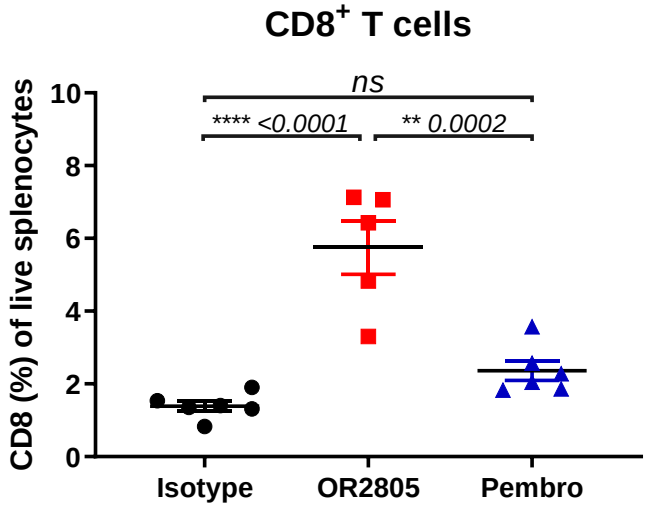
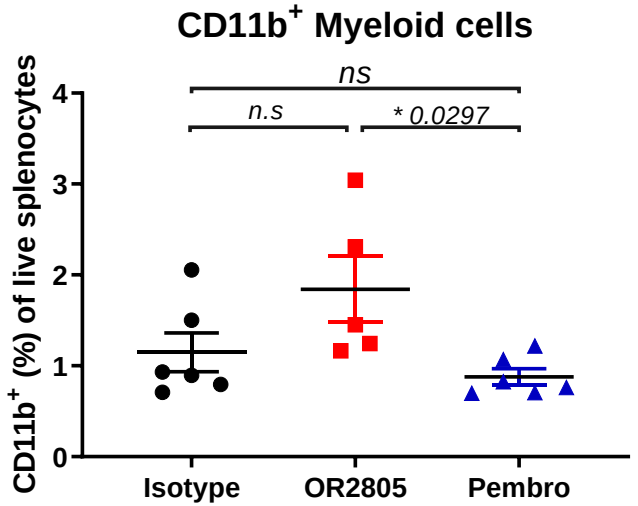


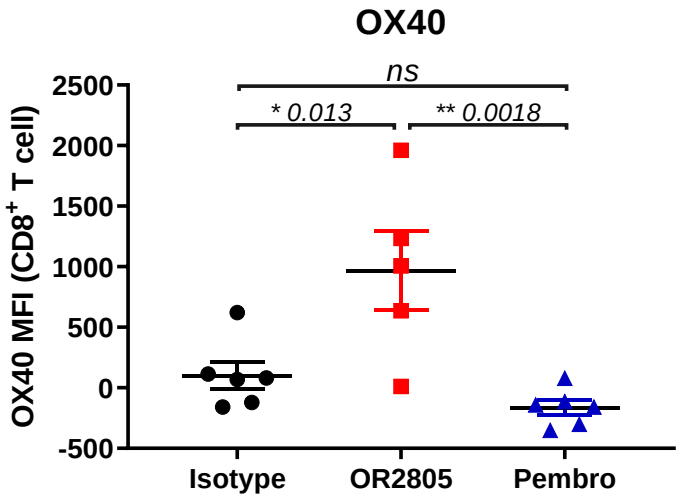
OR2805 treatment increases proportions of activated CD8+ T cells and myeloid cells in humanized NSG-SGM3 model

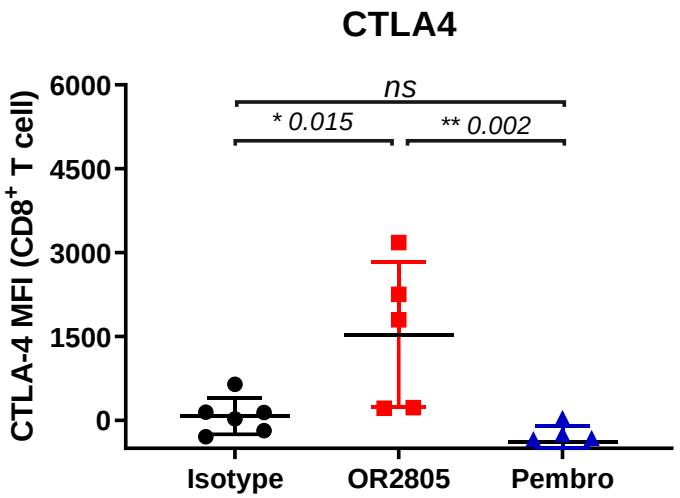
Proportions of human T and myeloid cells in spleen



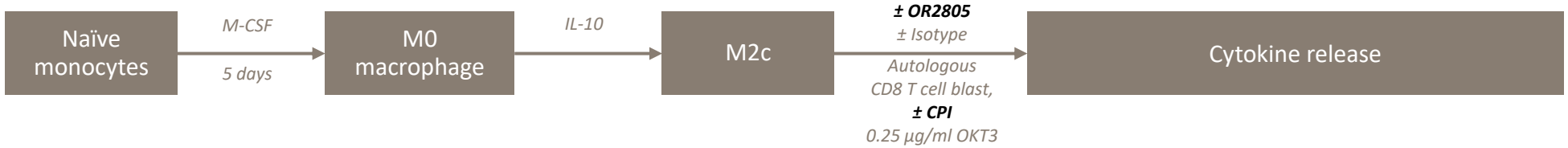


Expression of activation and proliferation markers on human CD8+ T cells in spleen

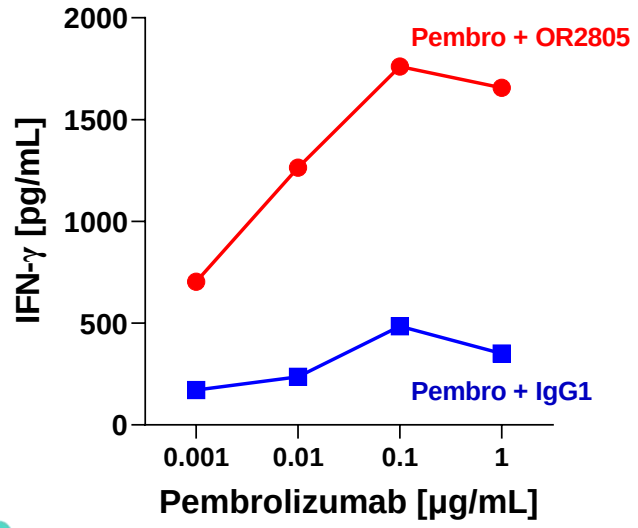




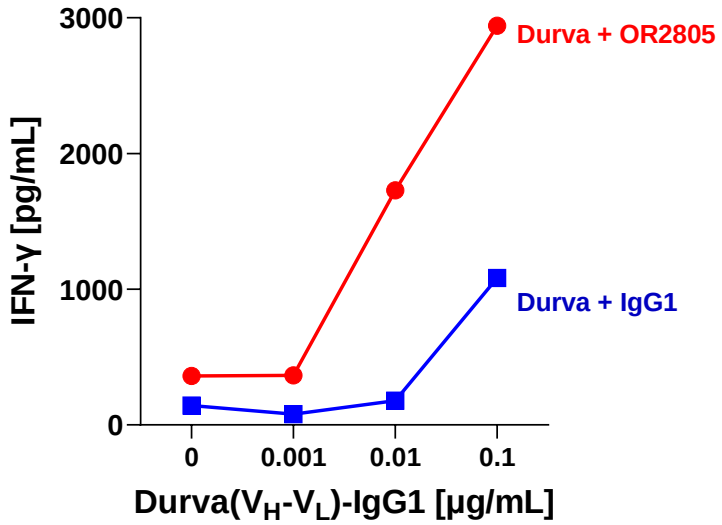
Combination with OR2805 enhances activity of anti-PD-1 and anti-PD-L1 in M2c/T cell blast coculture assays



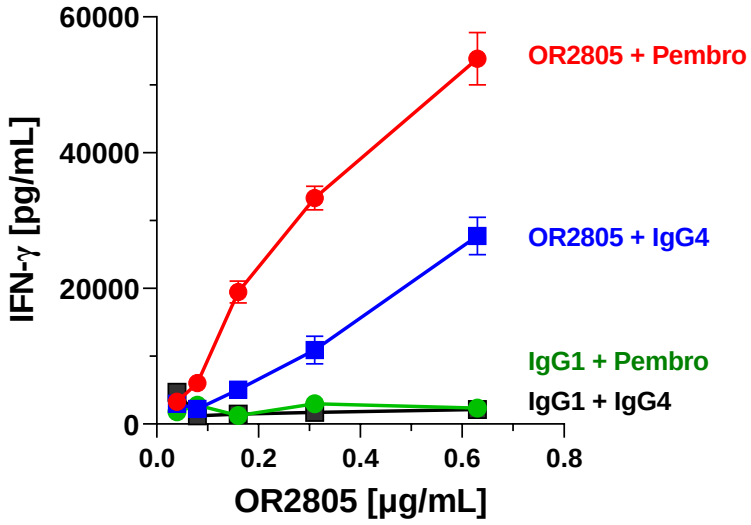
OR2805 + anti-PD-1



OR2805 + anti-PD-L1

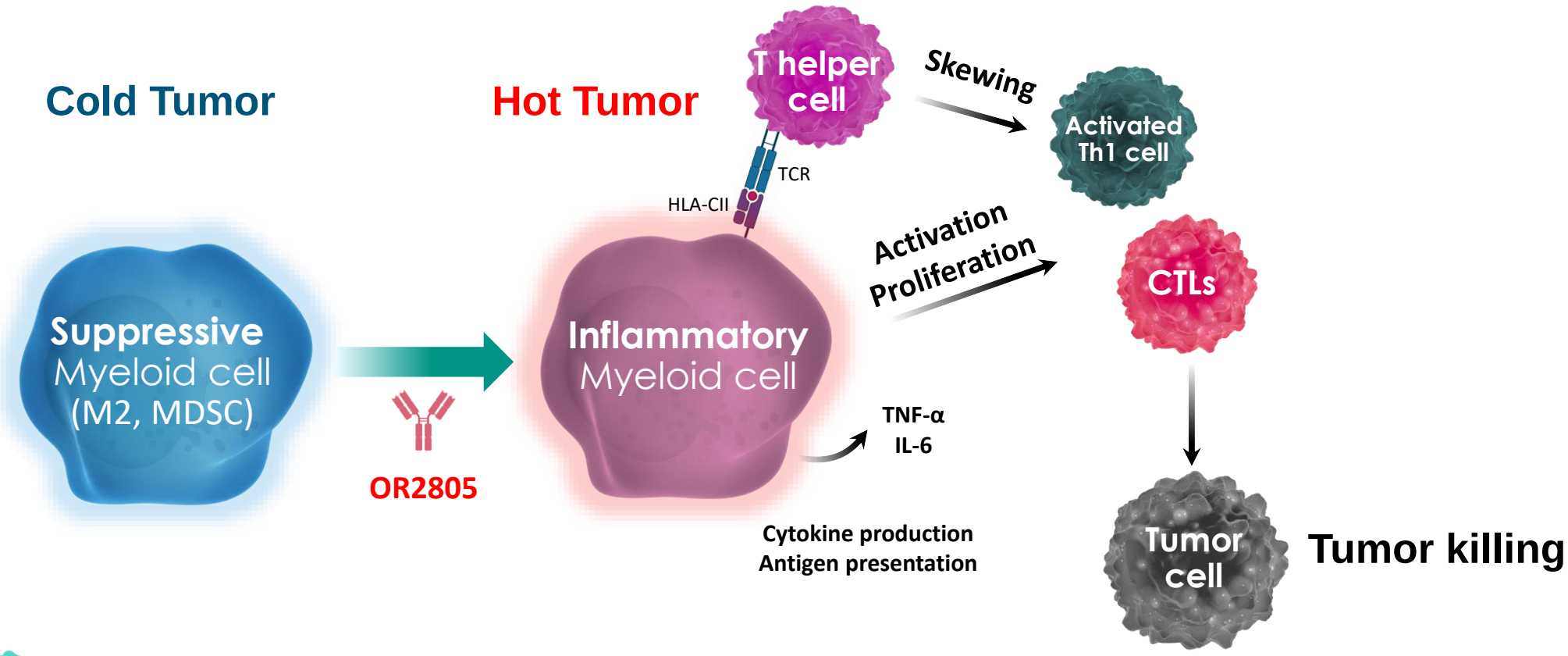


Anti-PD-1 + OR2805



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

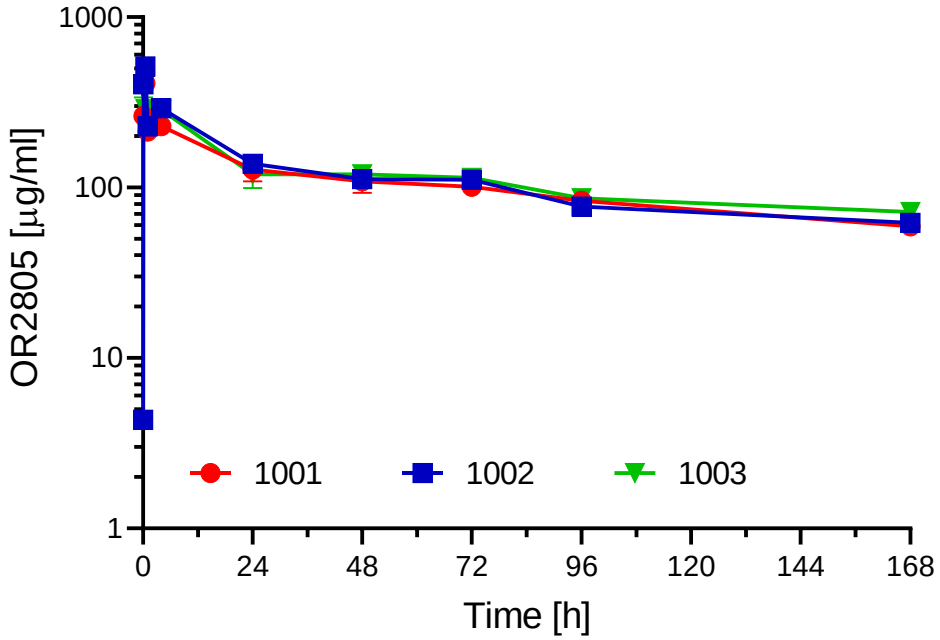
OR2805 relieves immunosuppression caused by myeloid cells in the TME



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

OR2805 toxicology predicts tolerable safety profile

OR2805 serum levels in cynomolgus monkeys



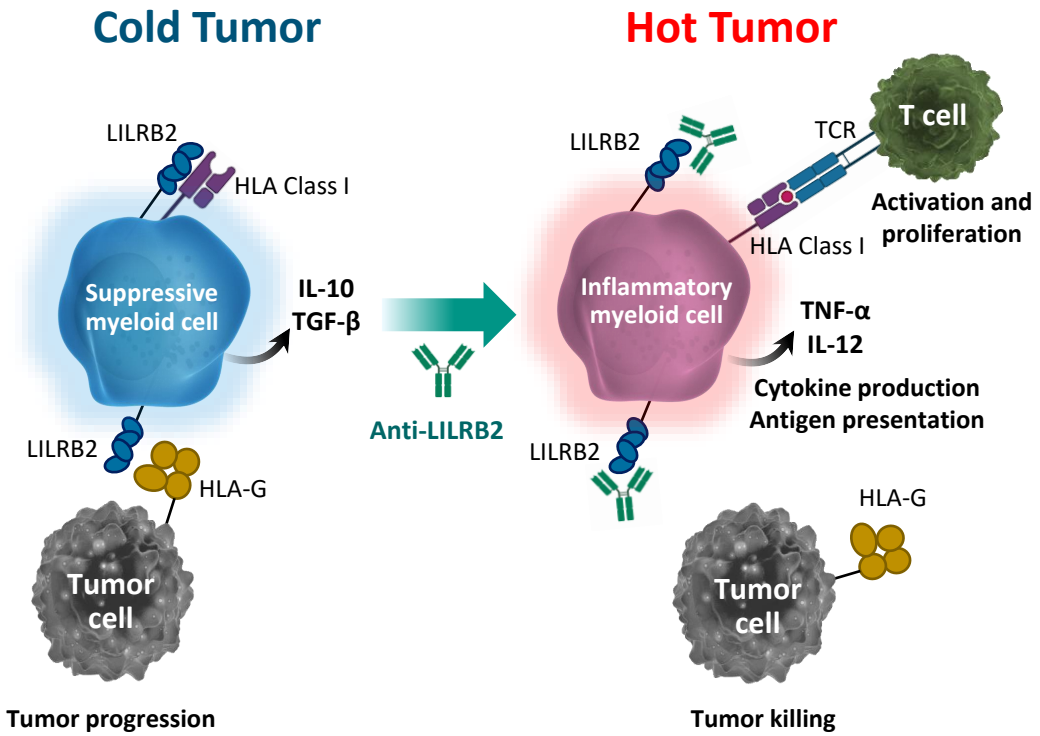
- Completed pilot, dose-range finding and GLP tox studies up to 100 mg/kg
- Observed OR2805 half-life in cynomolgus monkeys is about 5.8 days
- No in-life toxicity observed
- No abnormalities on pathological exam
- Normal serum chemistries and hematology
- No changes in immune cell subsets
- Slight elevation in serum IL-6 suggesting biological activity
- Ph1 study ongoing

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



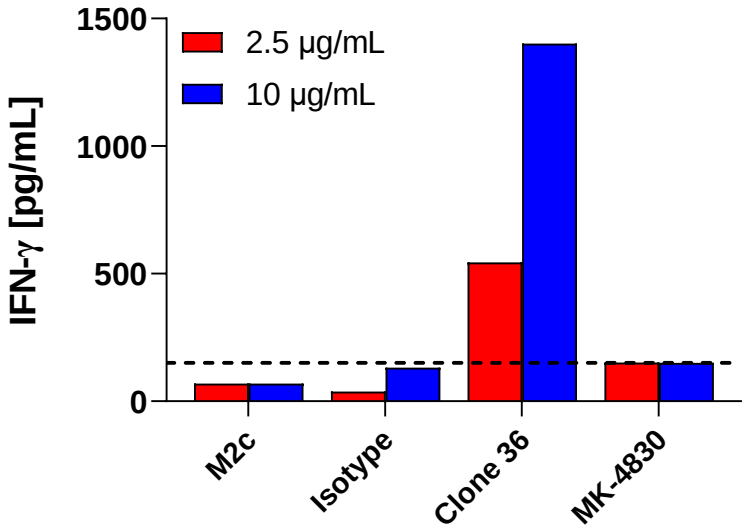
- LILRB2 is highly expressed on dendritic cells (DCs) and MDSCs of the TME and some tumor cells
- Upregulates HLA-G expression and secretion by tumor cells and promotes suppressive macrophage phenotype
- LILRB2 on DCs diminishes the killing ability of CTLs by competitive binding to MHC-class I with CD8 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

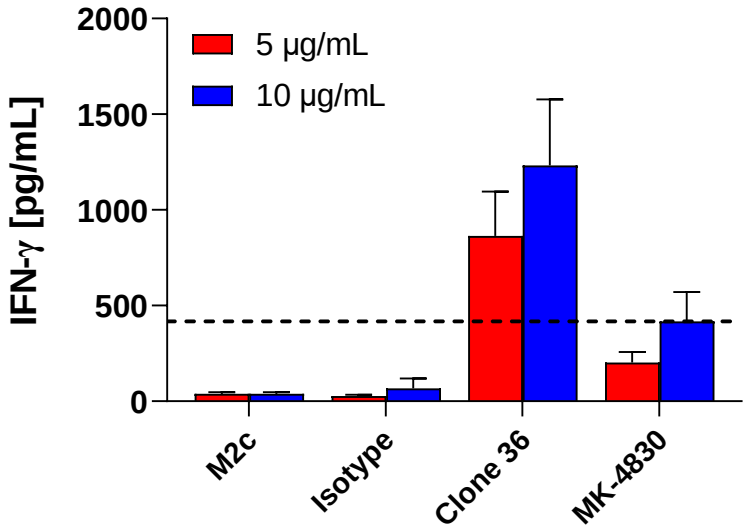
M2c/T cell blast coculture

IFNγ production

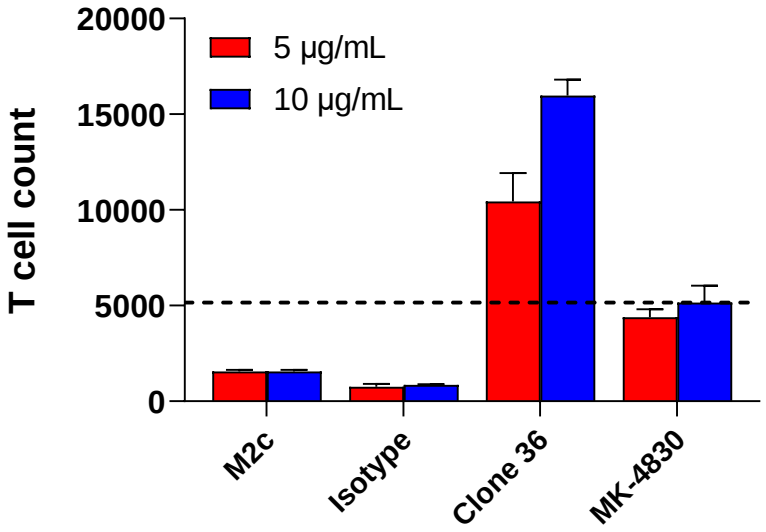


M2c/CD8⁺ T cell coculture

IFNγ production



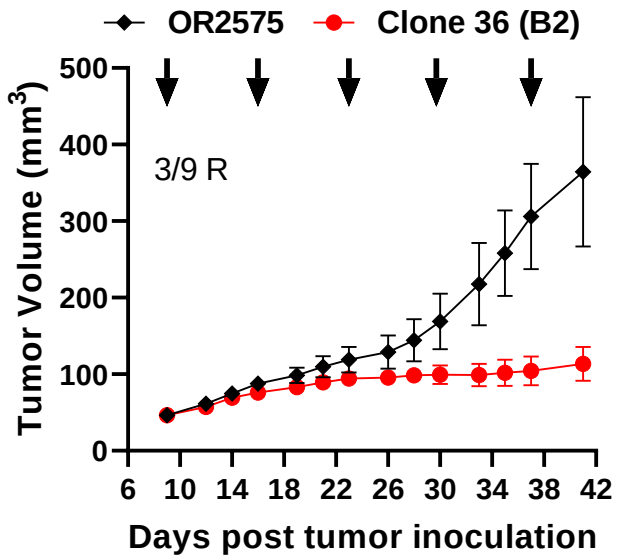
CD8⁺ T cell proliferation



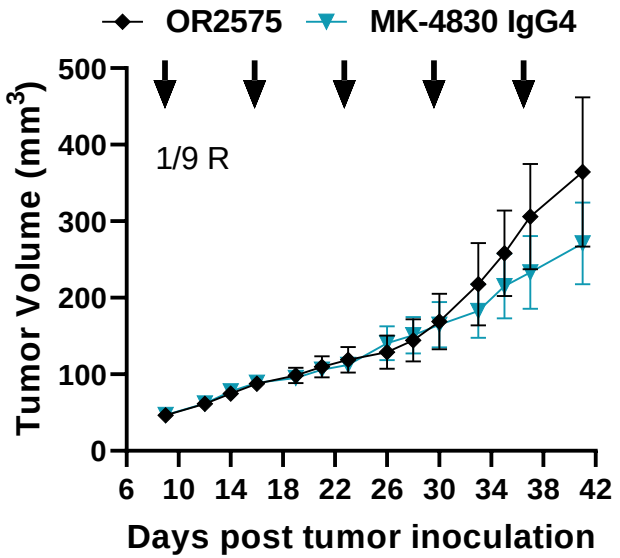
OncoResponse antibody outperforms MK-4830 in M2/T cell coculture assay

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

Clone 36 (OncoResponse)



MK-4830 (Merck)

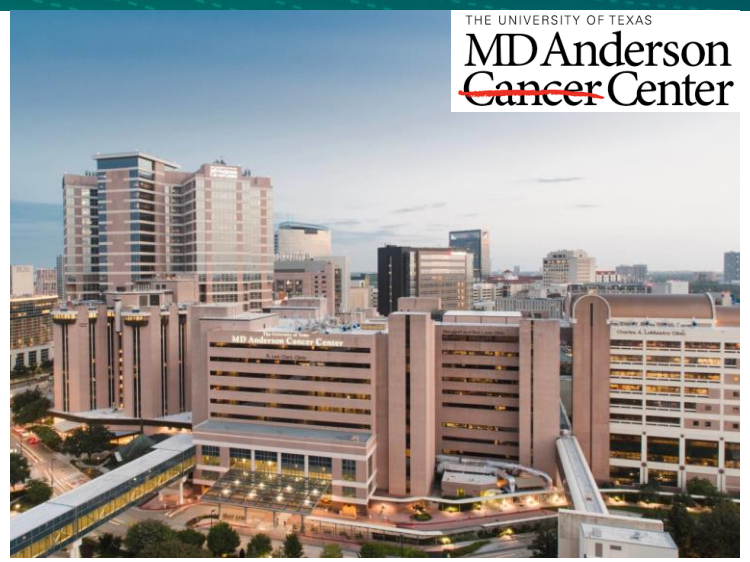


- Dosing: 20 mg/kg i.p.
- Dosing Days: 9, 16, 23, 30, 37

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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