OncoResponse

Interrogating for **Cures**™

Using the Human Immune System to Identify Antibodies that Modulate the Tumor Microenvironment

- Discovery of OR2805 from a Cancer Elite Responder that Relieves Immunosuppression Caused by TAMs

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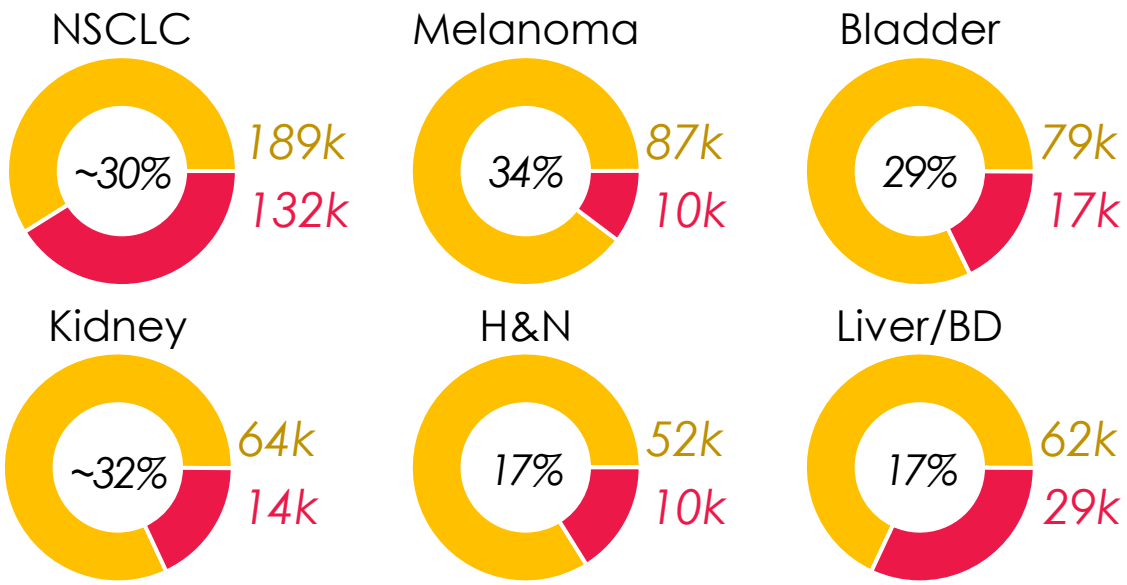
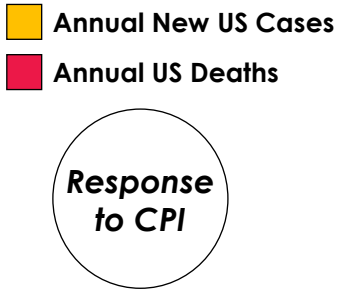
Festival of Biologics

March 31, 2021

The Immuno-Oncology (IO) opportunity

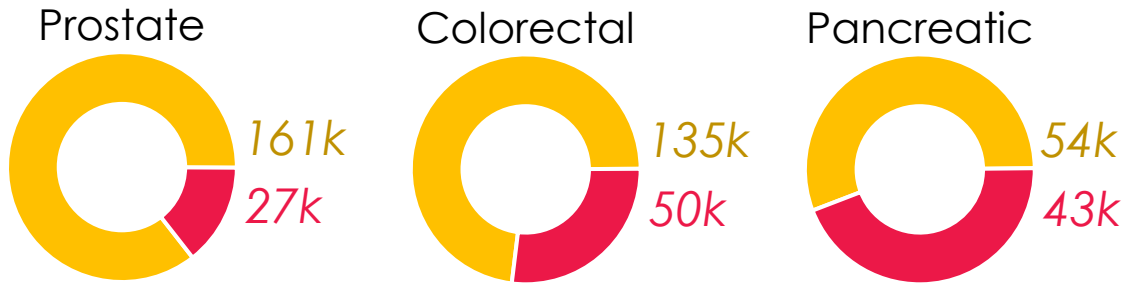
CPI-Responsive Cancer Types

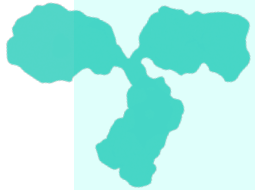




- Response rates from CPI continue to be low due in part to the suppressive Tumor Microenvironment (TME)
- There is a large unmet need to overcome immunosuppression of the TME to dramatically increase response rates and overall survival

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

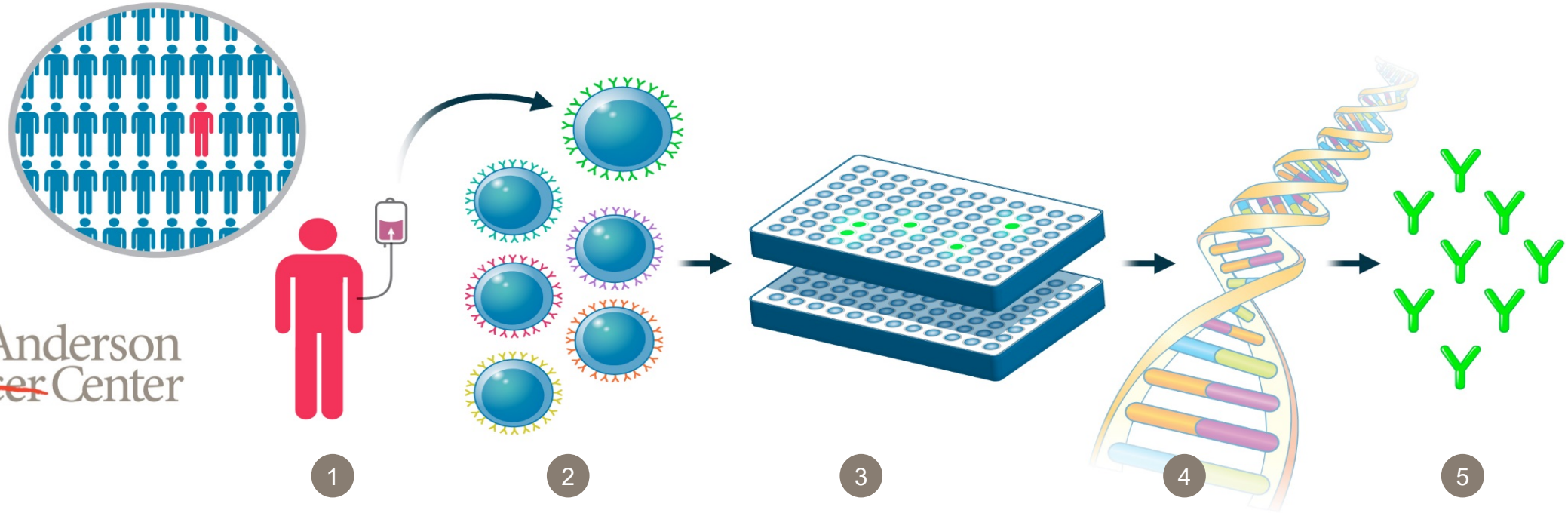
Our Mission

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

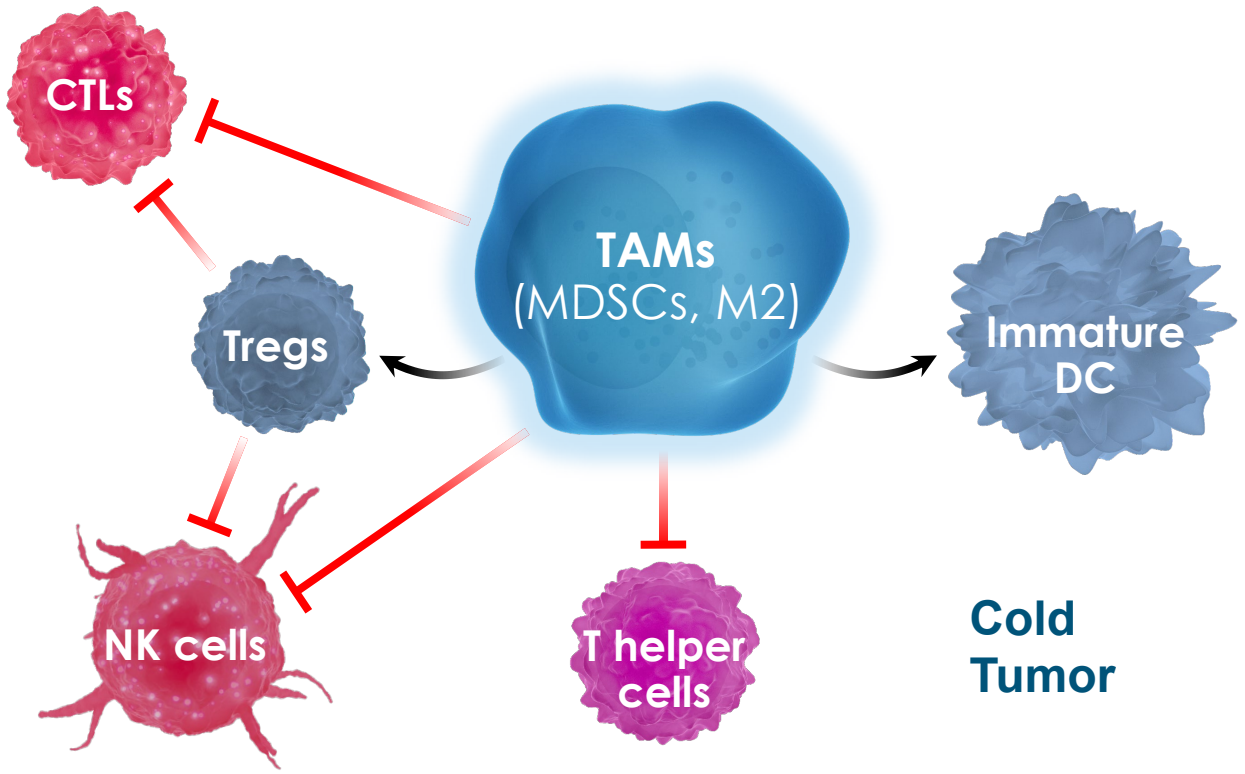
OR2805 targets TAMs in the TME to broaden and deepen responses

CTLs
- ↑T-cell anergy
- ↑T-cell exhaustion

NK cells
- ↓ADCC
- ↓NK cytotoxicity
- ↑NK cell exhaustion

T helper cells
- ↑T-cell anergy
- ↑T-cell exhaustion

TAMs
- ↑Treg cells
- ↑Tumor evasion
- ↑Efferocytosis
- ↓NK cytotoxicity
- ↓T-cell activation



Tregs
- ↓Teff cell function
- ↓NK cytotoxicity
- ↑Tolerance induction

Immature DCs
- Induction of Tregs
- Impaired maturation
- Defective antigen presentation
- Lack of co-stim for T-cells

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

CD163 - Normal physiology and role in cancer

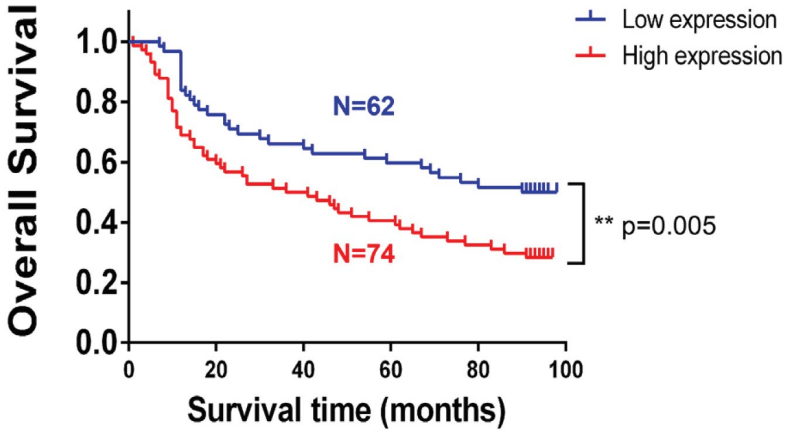
- Expression predominantly limited to immunosuppressive macrophages[1]
- Hemoglobin scavenger receptor upregulated on immunosuppressive macrophages
- Binding by its ligands induces secretion of immunosuppressive cytokines[2,3]
- Inhibits T-cell proliferation[4,5]
- Overexpression in human macrophages 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 predicted 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.

CD163 expression correlates with poor clinical outcome in cancer

Gastric Cancer

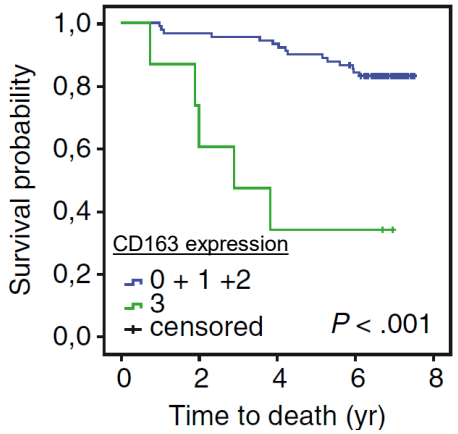
Overall survival



DOI: 10.18632/oncotarget.20244

Breast Cancer

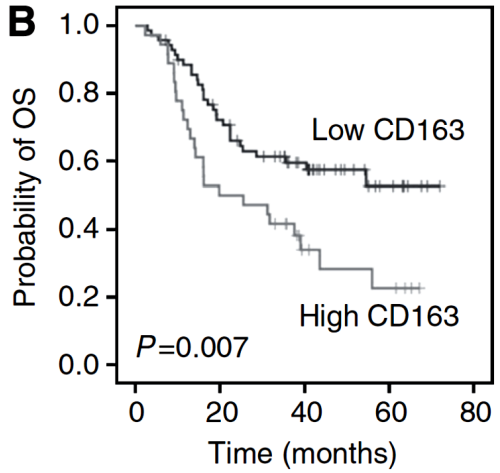
Survival probability



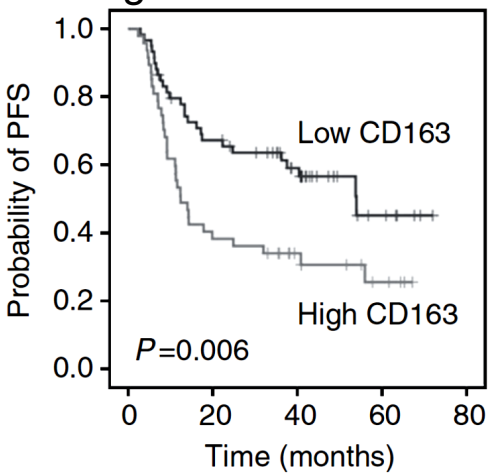
DOI: 10.1186/1471-2407-12-306

Head and Neck Cancer

Overall survival

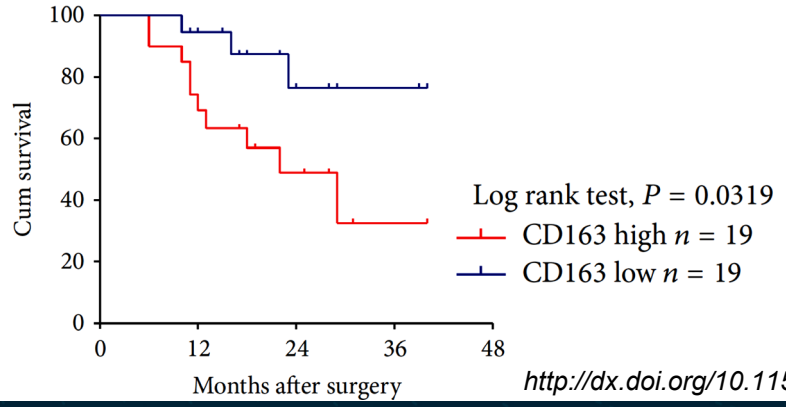


Progression-free survival



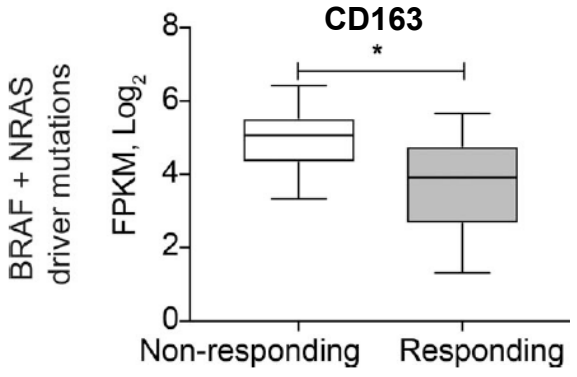
DOI:10.1038/bjc.2014.446

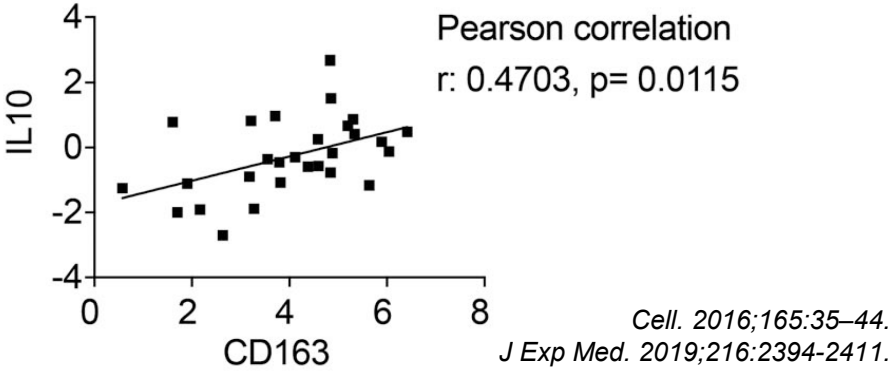
Oral Squamous Cell Carcinoma



http://dx.doi.org/10.1155/2014/838632

Melanoma patients on anti–PD-1 therapy

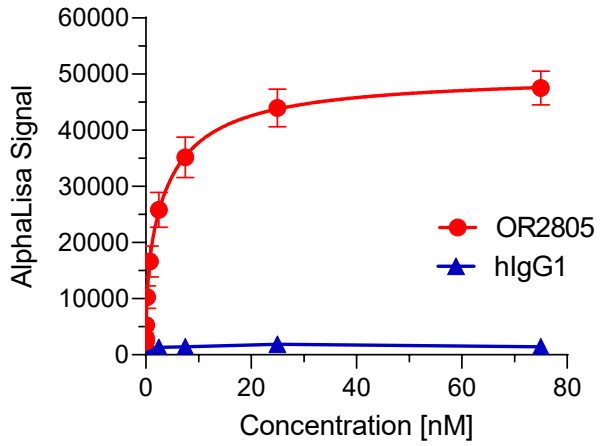




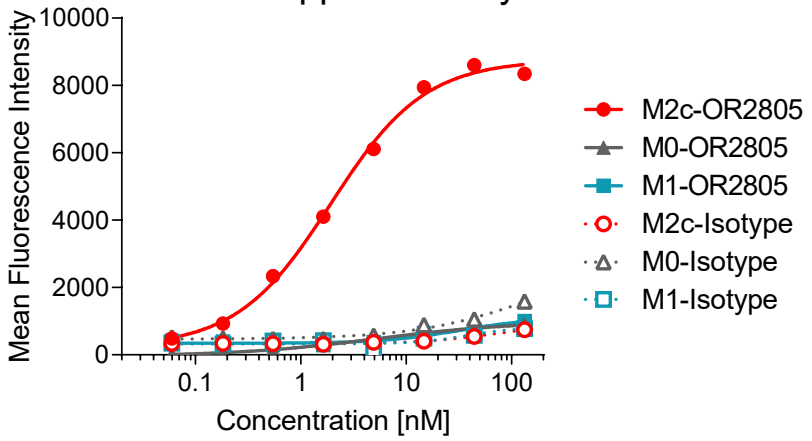
Cell. 2016;165:35–44.
J Exp Med. 2019;216:2394-2411.

OR2805 demonstrates specific binding to immunosuppressive myeloid cells

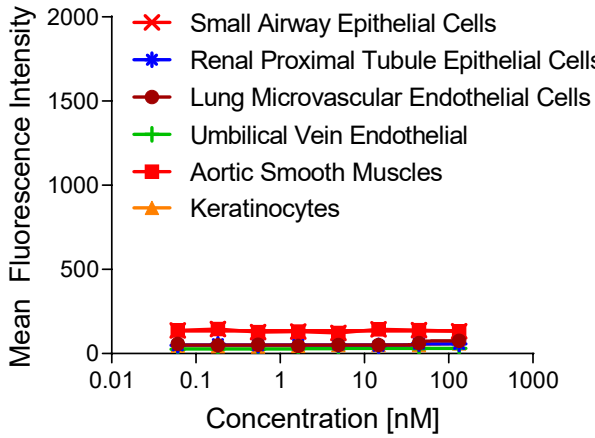
OR2805 binds to human CD163



Specific binding to human immunosuppressive myeloid cells



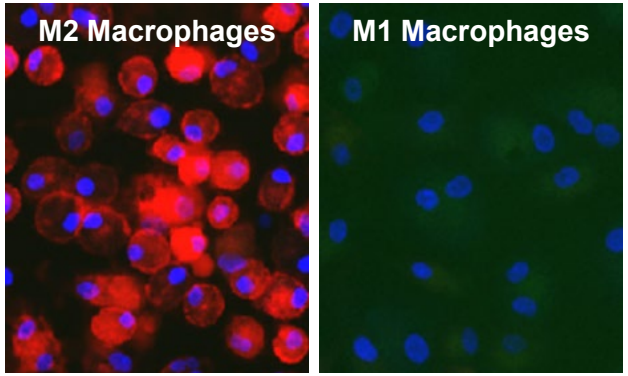
No binding to a panel of human primary immune and non-immune cells

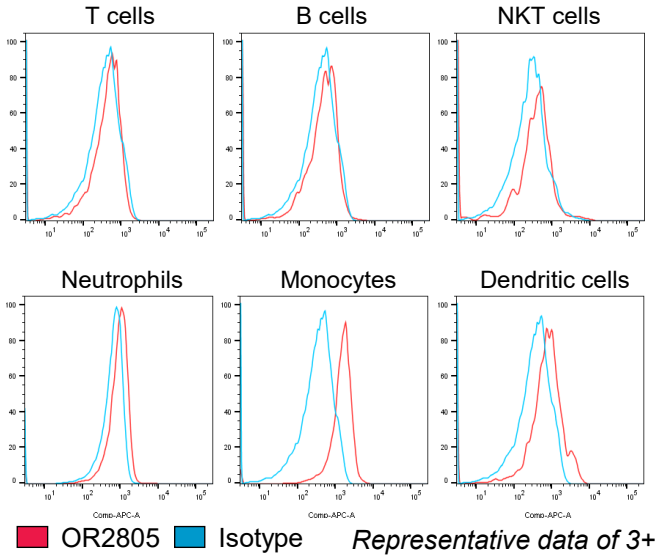


OR2805 binds to TAMs in dissociated NSCLC tumors

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



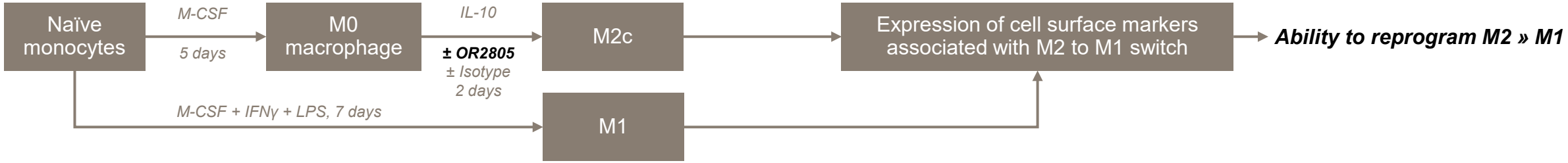


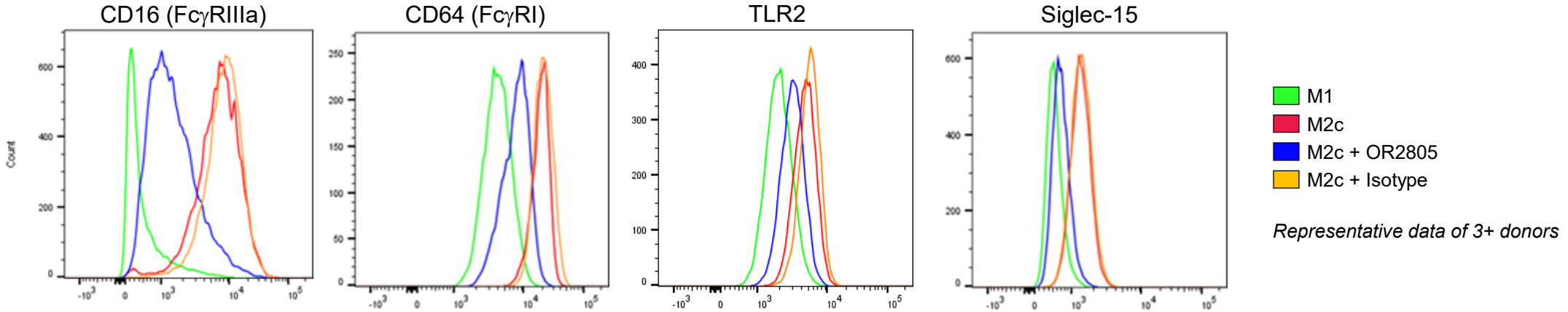
Representative data of 3+ donor

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





Representative data of 3+ donors

Low affinity IgG receptor. Highly expressed on M2cs.

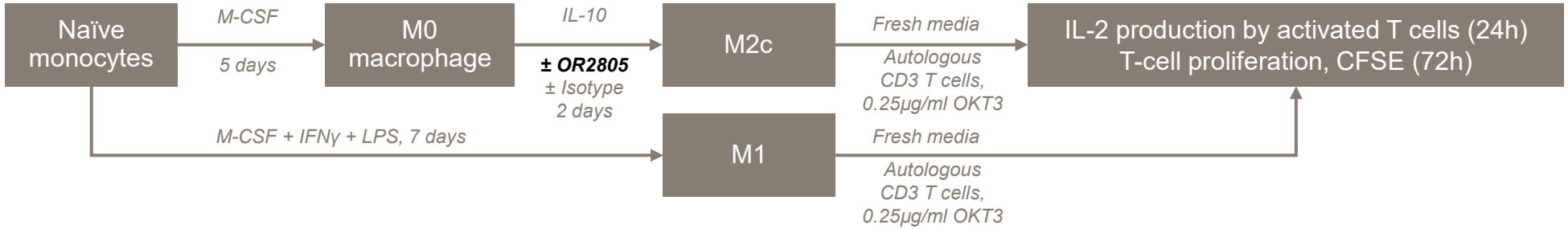
High affinity IgG receptor. Highly expressed on M2cs.

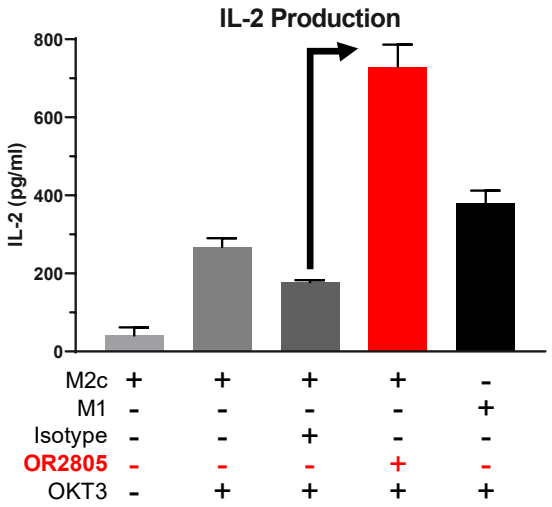
Innate immune receptor involved in immune modulation. Highly expressed on M2cs.

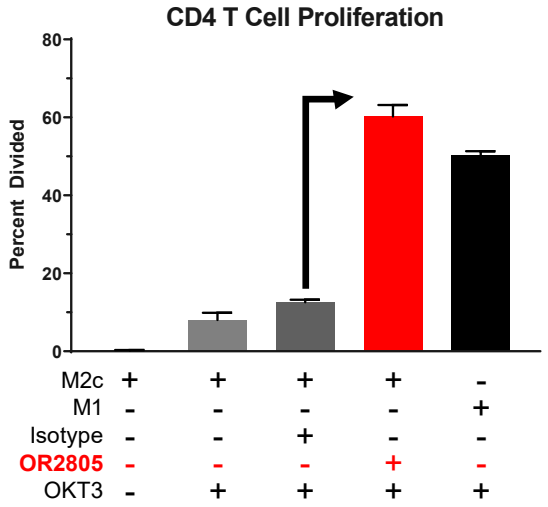
Transmembrane protein involved in immune suppression. Specific expression on M2c.

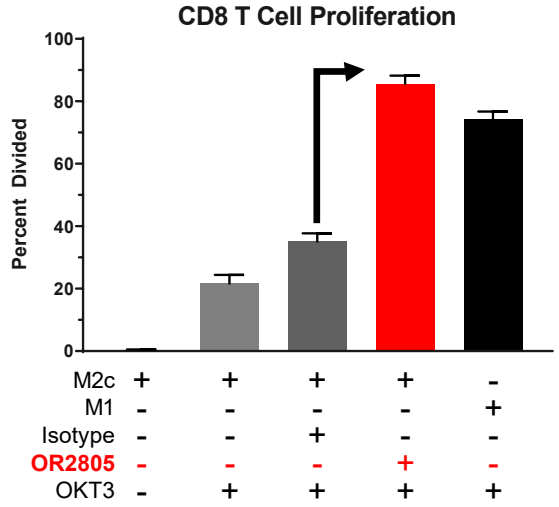
OR2805-treatment reduces expression of cell-surface markers associated with tumor-promoting M2c macrophages

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





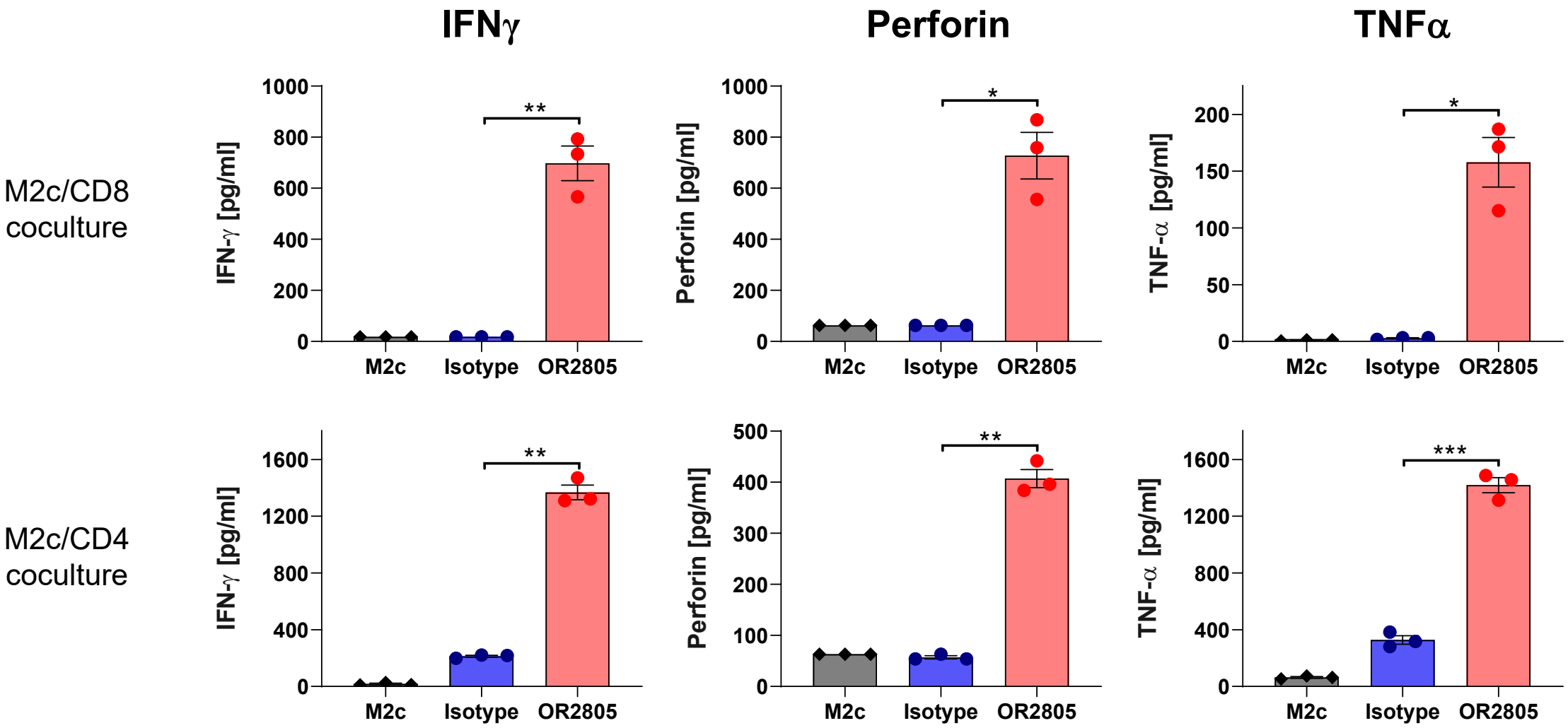




Representative data of 12+ donors

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

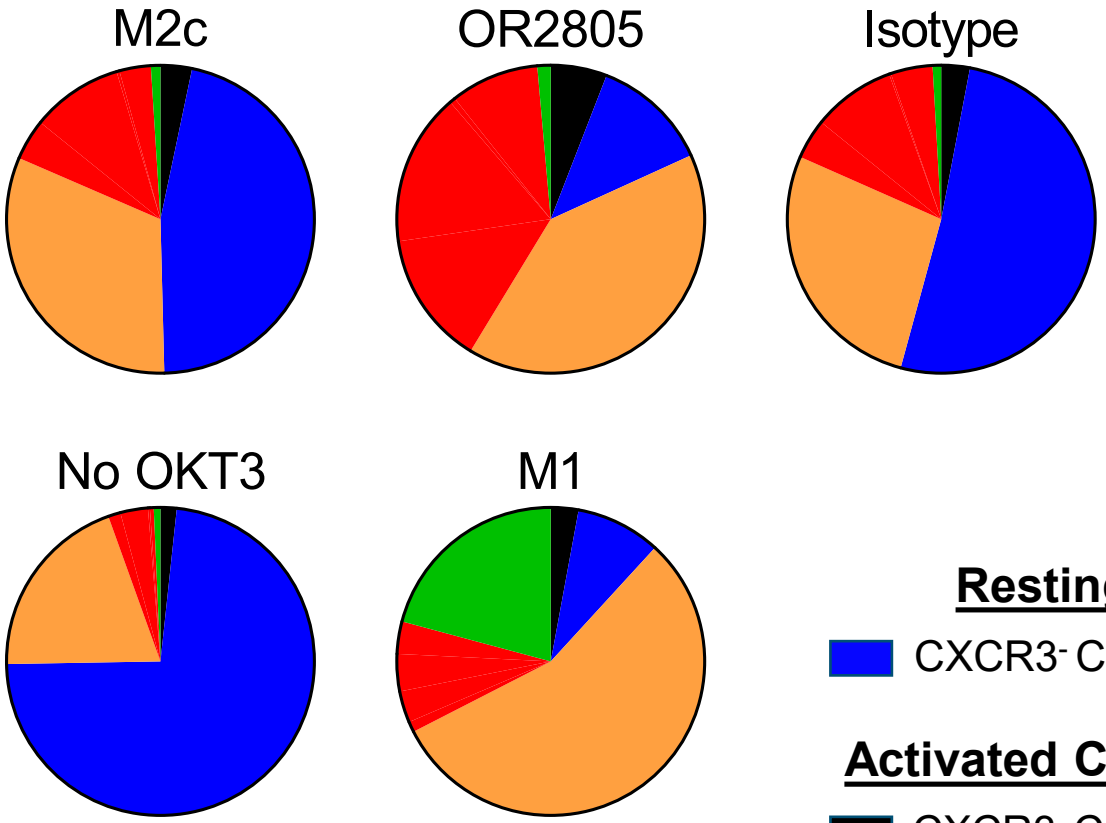
OR2805-treated M2c macrophages promote T-cell activation



Representative data from n=3 donors

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

Distribution of CD4⁺ T cells phenotypes



- CXCR3 is preferentially expressed on Th1 cells
- IFNγ production within the TME enhances the 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

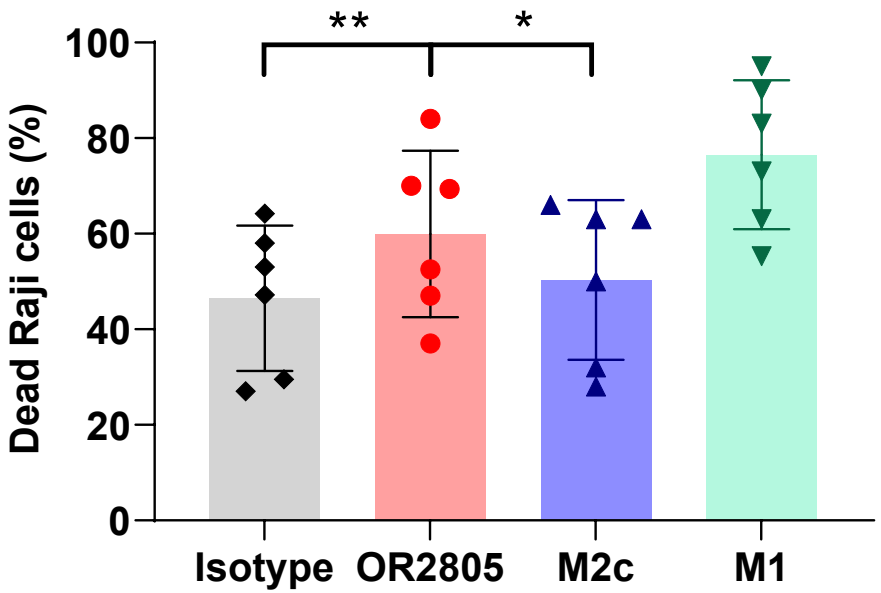
CXCR3⁺ CD69⁺ CD25⁻

CXCR3⁺ CD69⁺ CD25⁺

CXCR3⁺ CD69⁻ CD25⁺

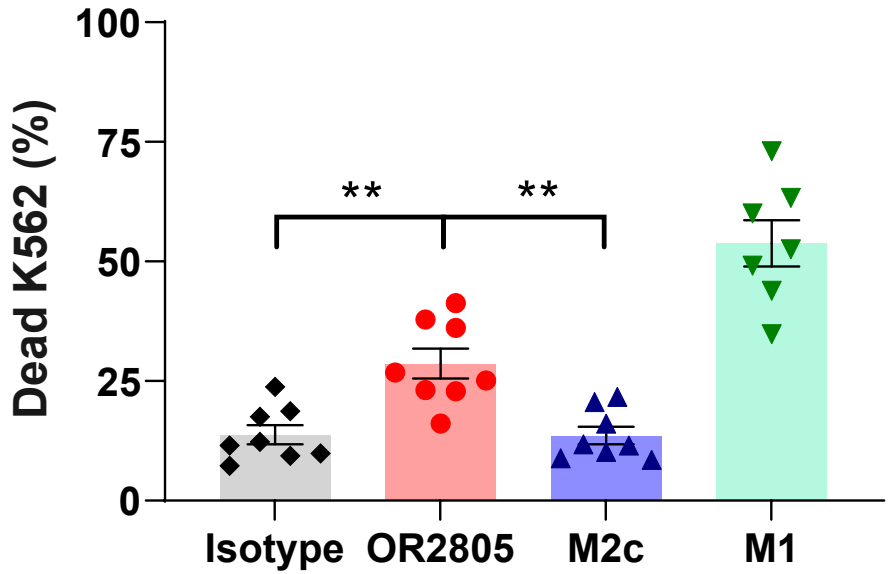
Proliferated CD8+ T cells show enhanced ability to kill cancer cells

Raji B cell killing activity of CD8+ T cells in the presence of CD19-CD3 BiTE



Composite data from n=6 donors

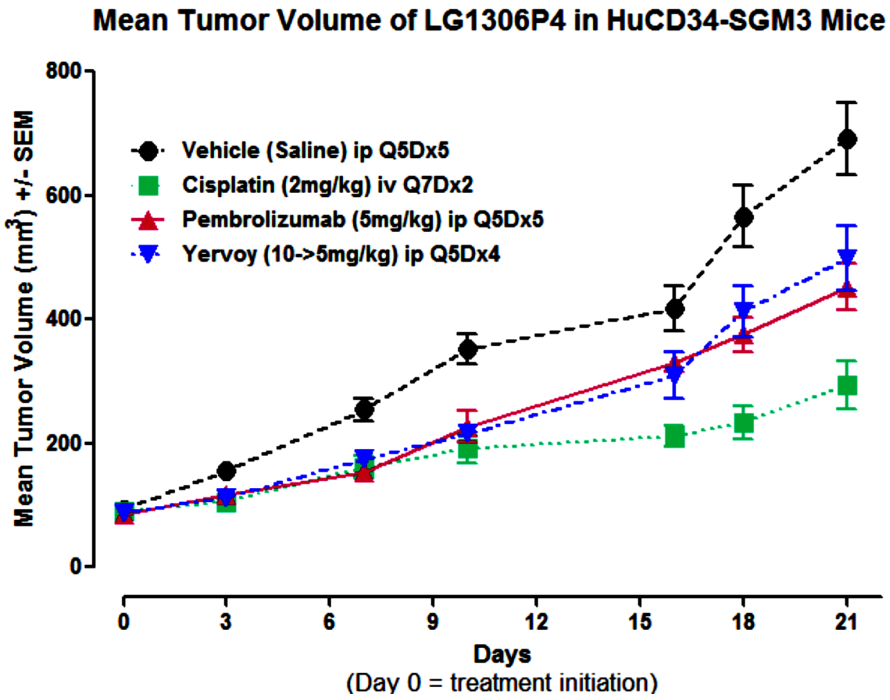
K562 cell killing activity of non-HLA restricted CD8+ T cells



Composite data from n=8 donors

OR2805-treatment induces robust anti-tumor activity in lung cancer xenograft models in humanized NSG-SGM3 mice

NSCLC PDX



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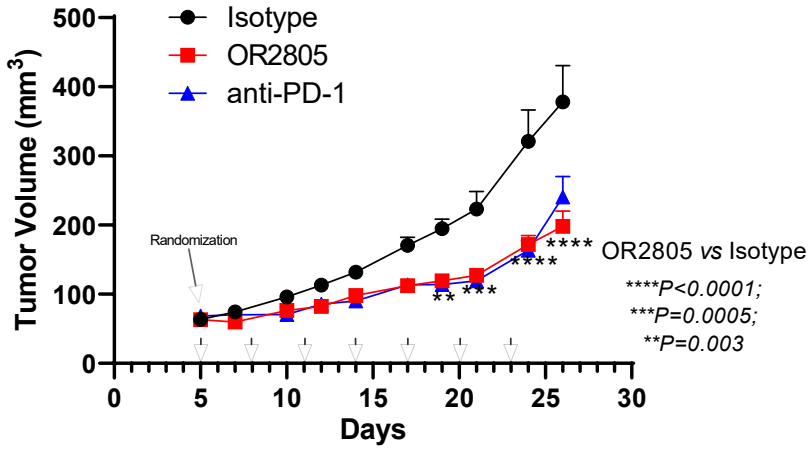
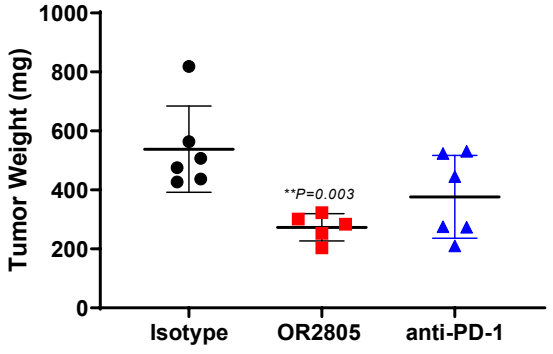
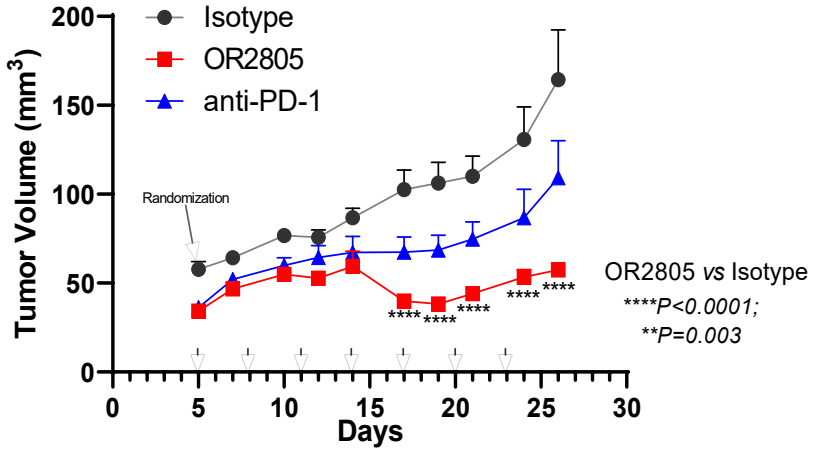
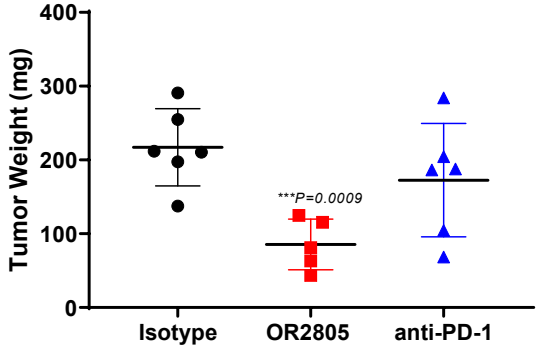
A549 (p53 WT)



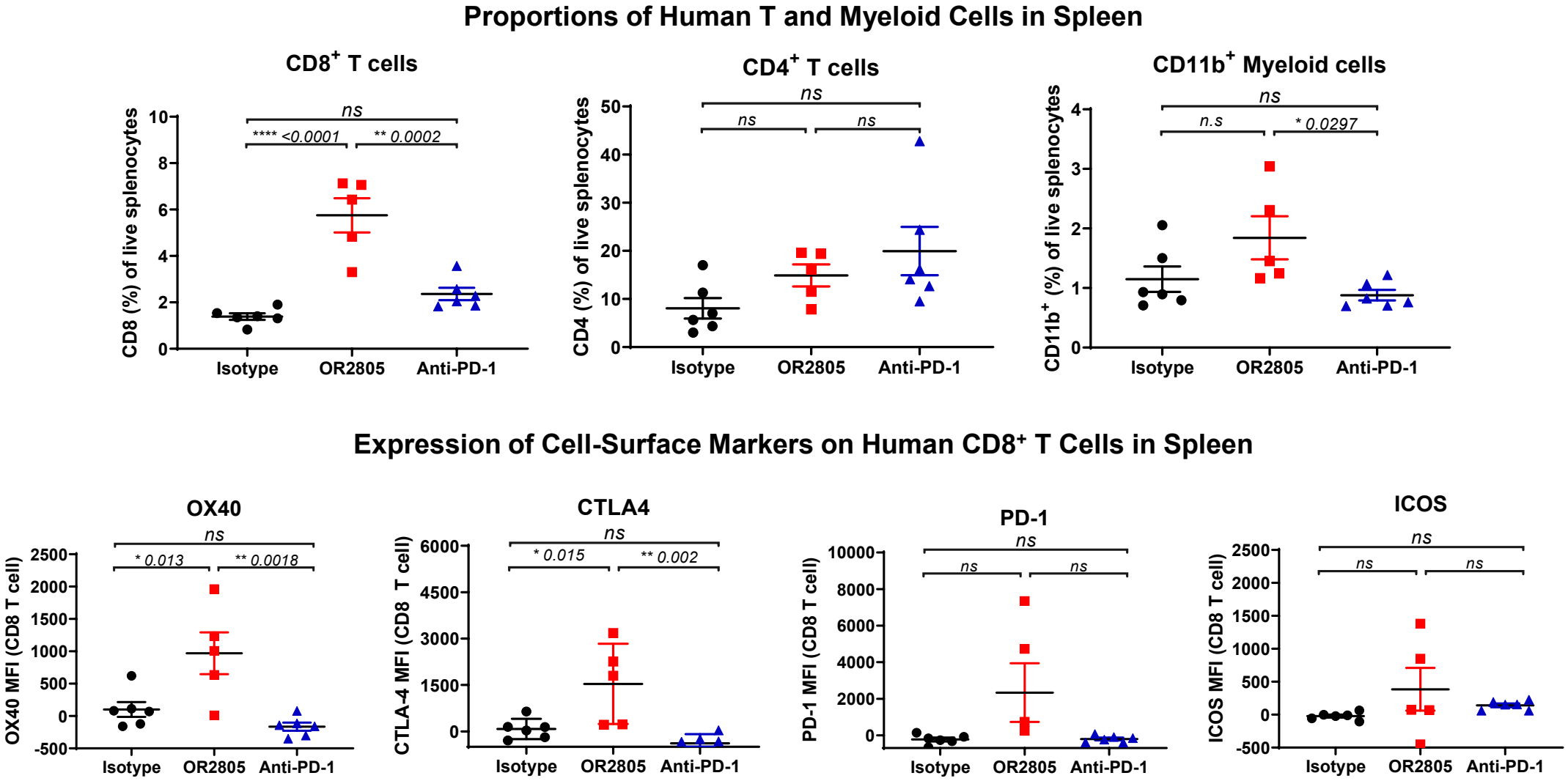


H1975 (p53 mutated, p.R273H)

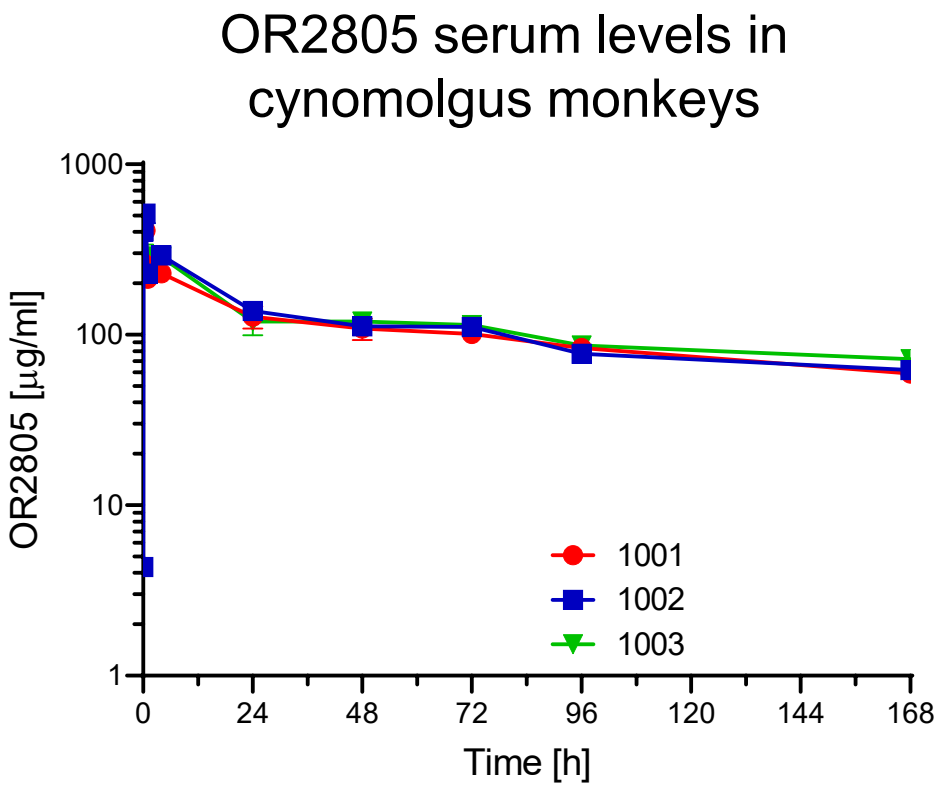




OR2805-treatment increases proportions of CD8 and myeloid cells in xenograft models in humanized NSG-SGM3 mice



OR2805 non-GLP exploratory toxicokinetics study in cynomolgus monkeys



Parameter	OR2805
Dose	10 mg/kg
$t_{1/2}$	141.6 h (5.9 days)
T_{max}	0.5 h
Cmax	435.6 µg/ml
AUC 0-t	18212 µg/ml x h
Auc 0-Inf	31494 µg/ml x h

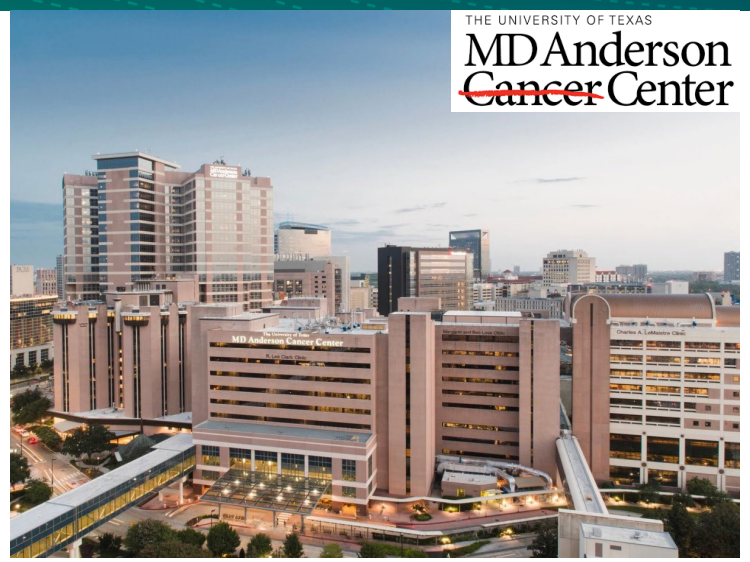
- **Observed OR2805 half-life in cynomolgus monkeys is about 5.9 days**
- **No acute toxicity observed**

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

- Binds with high-specificity to M2 macrophages and TAMs in human primary NSCLC tumors
- Reduces expression of cell-surface markers associated with tumor-promoting M2c macrophages
- Reduces M2 suppressive effect on T-cell activation and proliferation and skews T cells towards anti-tumor Th1 phenotype
- Cocultured T cells show enhanced expression of activation markers and cancer-killing ability
- Shows robust anti-tumor activity in lung cancer xenograft models in humanized NSG-SGM3 mice
- Demonstrates predictable kinetics in cynomolgus monkey without evidence of acute toxicity at doses tested
- IND on track to be filed in mid-2021

OR2805 reduces TAM-mediated immunosuppression and enhances anti-tumor immune responses, and has the potential as a single agent or in combination with CPI to increase the number of patients who may benefit from immunotherapy

Acknowledgements



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