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

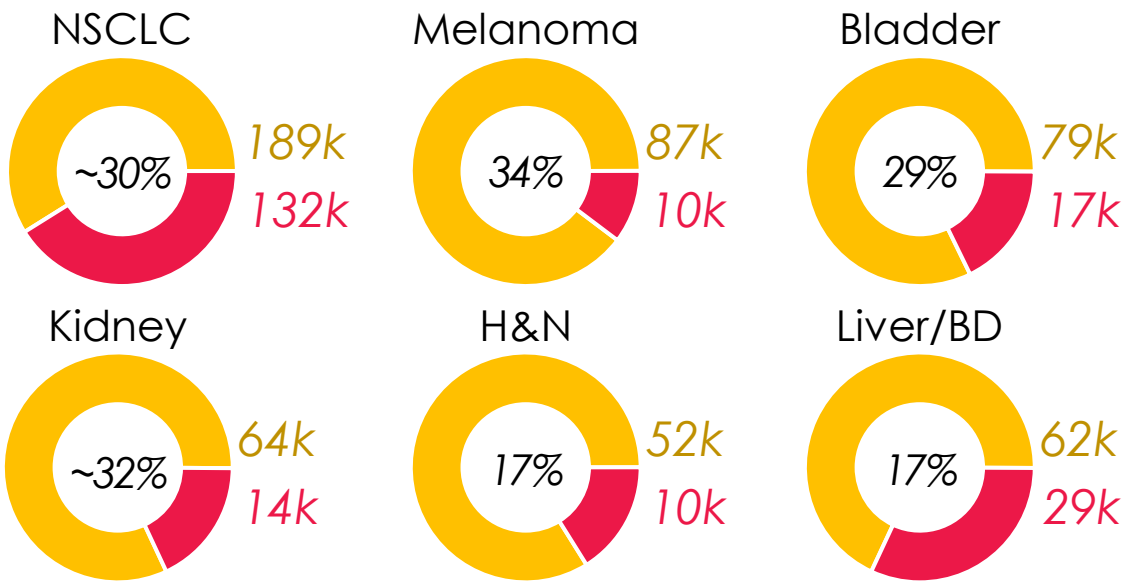
Kamal D. Puri

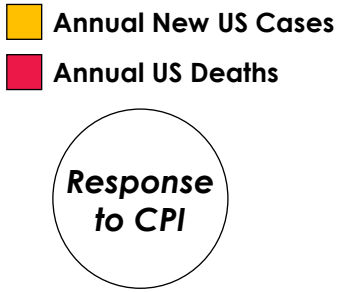
Macrophage-directed Therapies Summit

September 28-30, 2021

The Immuno-Oncology (IO) opportunity

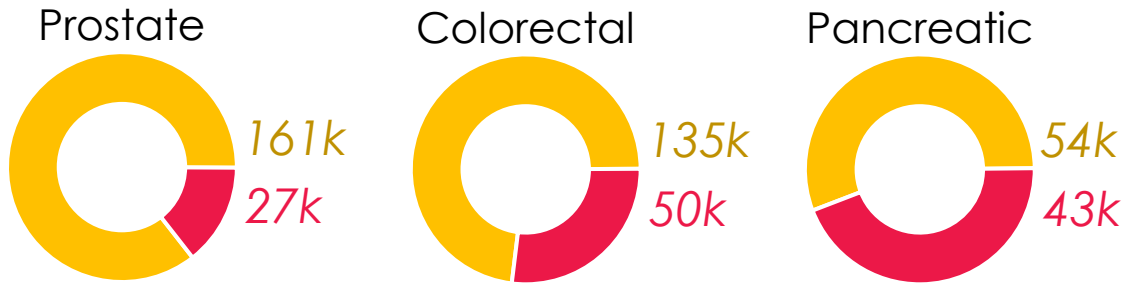
CPI-Responsive Cancer Types





- 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

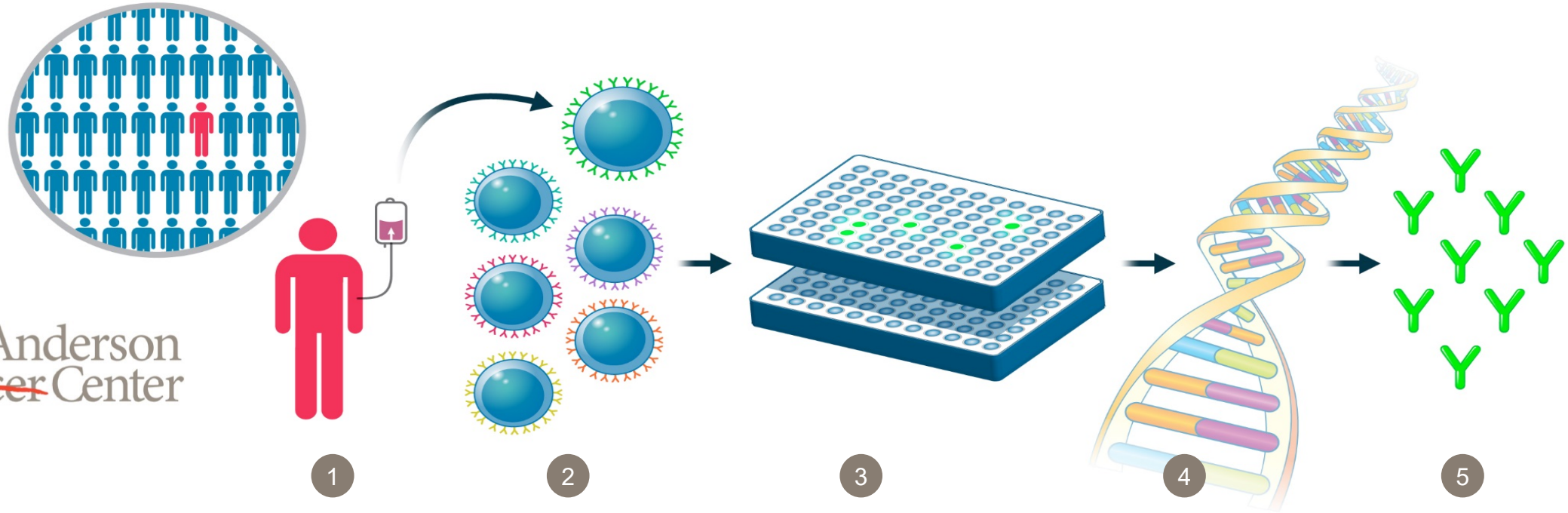
Attack cancer based on clues offered by the immune systems of Elite Cancer Responders

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

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,

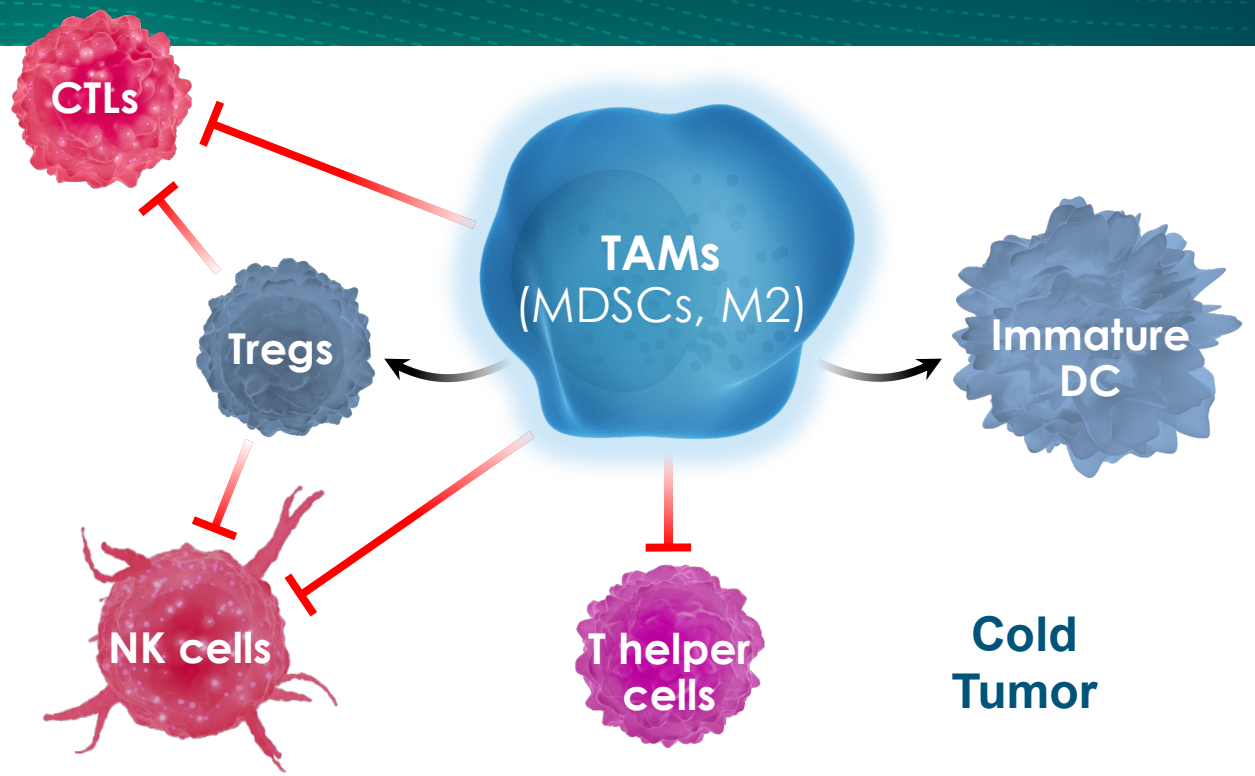
OR2805 targets TAMs in the TME to broaden and deepen responses

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

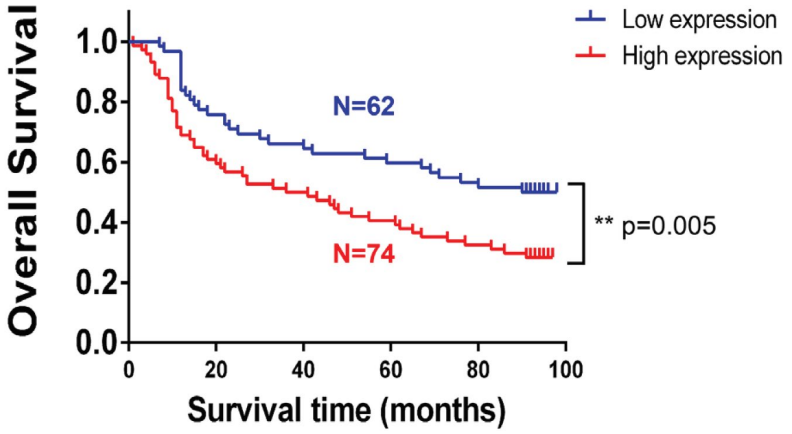
- Expression predominantly limited to and upregulated on immunosuppressive macrophages[1]
- Binding by its ligands induces secretion of immunosuppressive cytokines[2,3]
- Inhibits T-cell proliferation[4,5]
- Overexpression in human macrophages results in an M2 phenotype[6]
- Knockout mice develop normally 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.

CD163 expression correlates with poor clinical outcome in cancer

Gastric Cancer

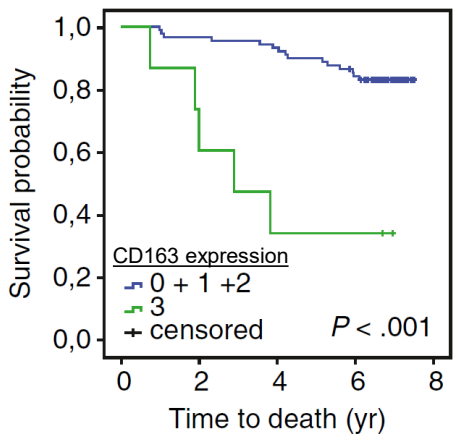
Overall survival



DOI: 10.18632/oncotarget.20244

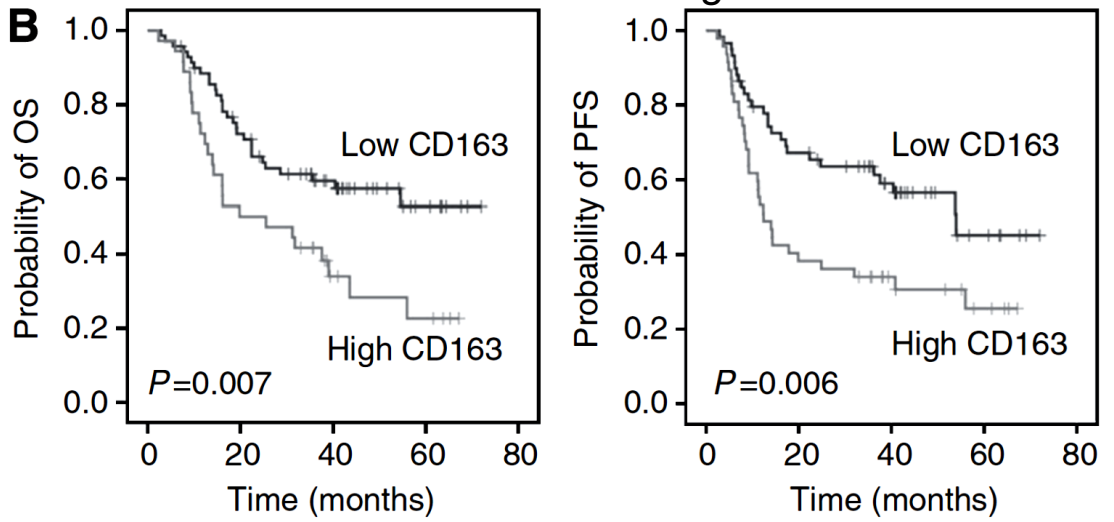
Breast Cancer

Survival probability



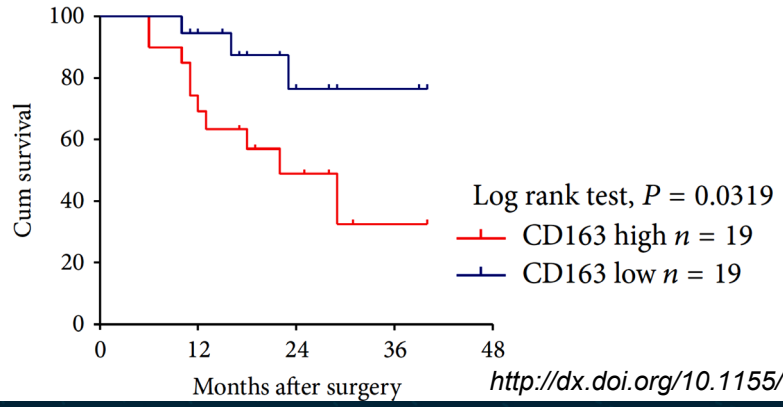
DOI: 10.1186/1471-2407-12-306

Head and Neck Cancer



DOI:10.1038/bjc.2014.446

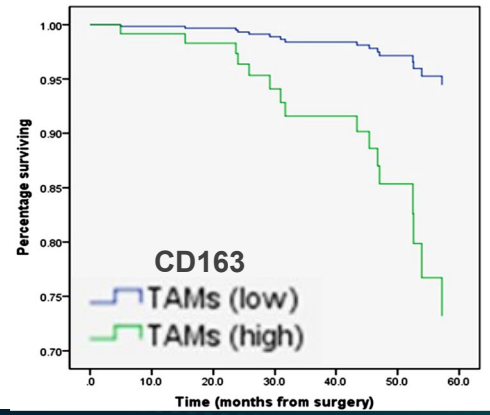
Oral Squamous Cell Carcinoma

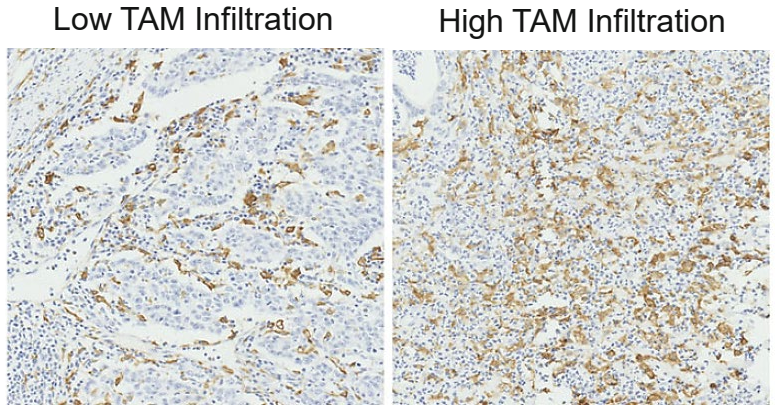


http://dx.doi.org/10.1155/2014/838632

Colorectal Cancer

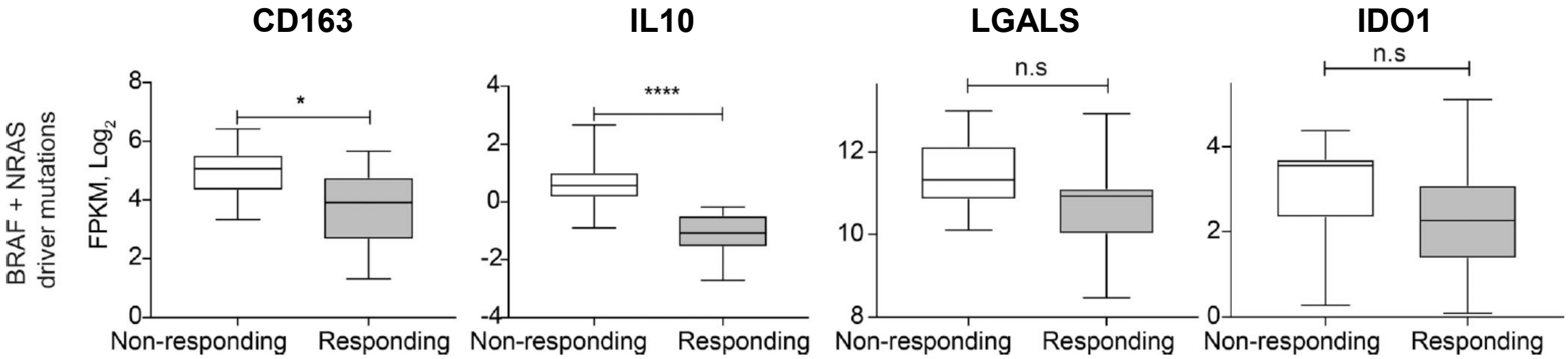
Overall Survival



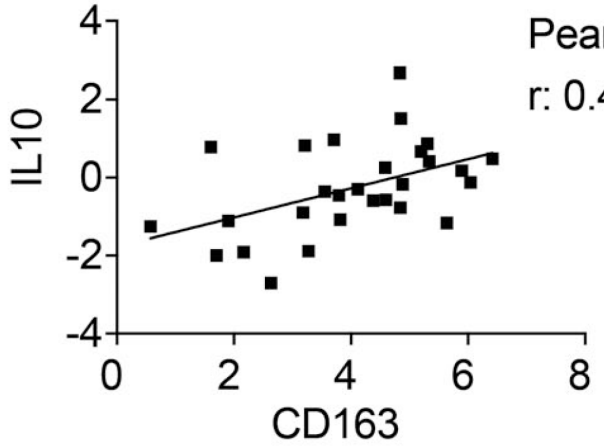


doi: 10.1186/s12957-021-02299-y

CD163 expression is increased in anti-PD-1 resistant patients with BRAF-driven melanoma



(n = 23 [nonresponders, n = 10; responders, n = 13])

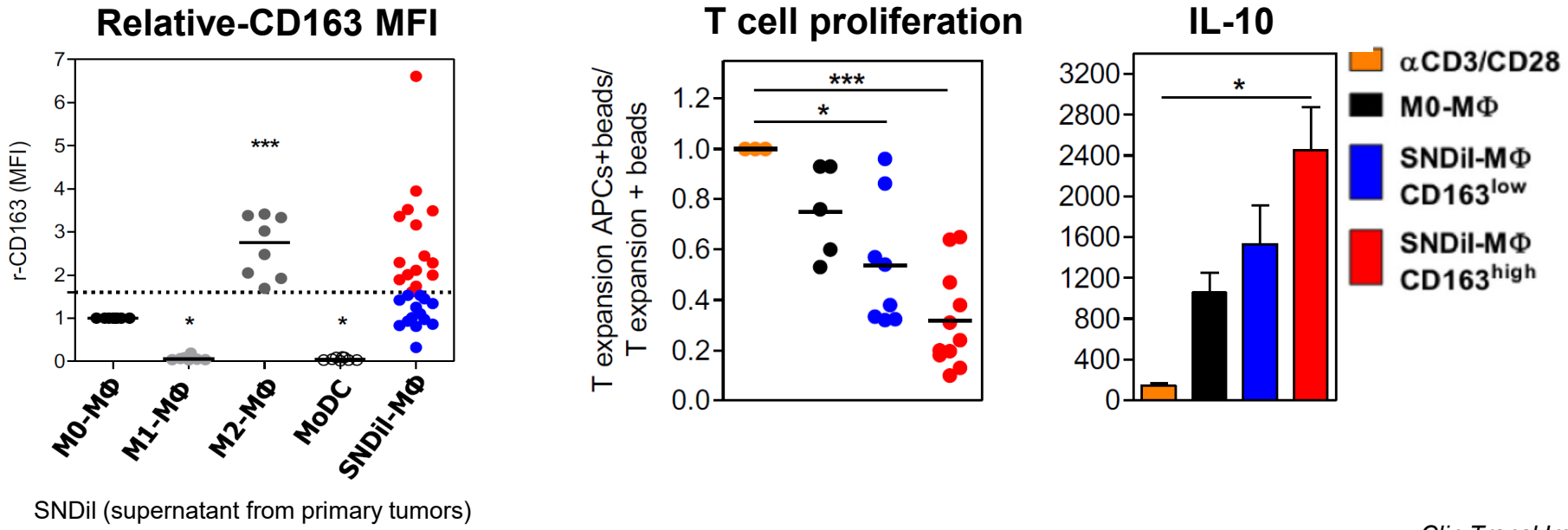


CD163 expression correlates with IL10 expression in pretreatment tumor biopsy specimens from metastatic melanoma patients

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

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

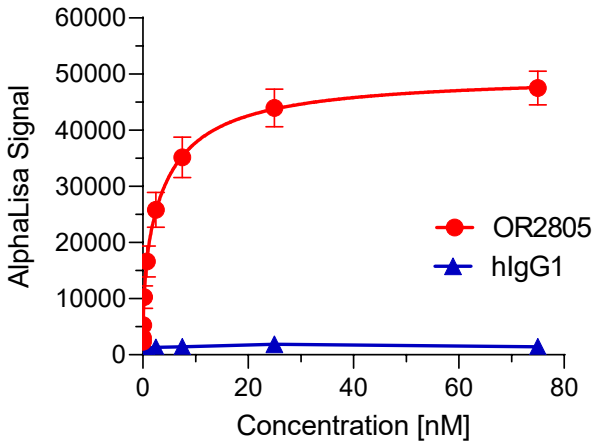


SNDil (supernatant from primary tumors)

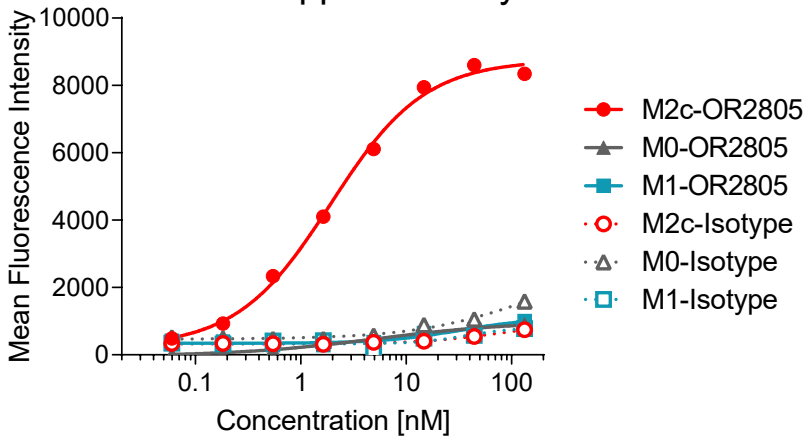
Clin Transl Immunology. 2020;9:e1108

OR2805 demonstrates specific binding to immunosuppressive myeloid cells

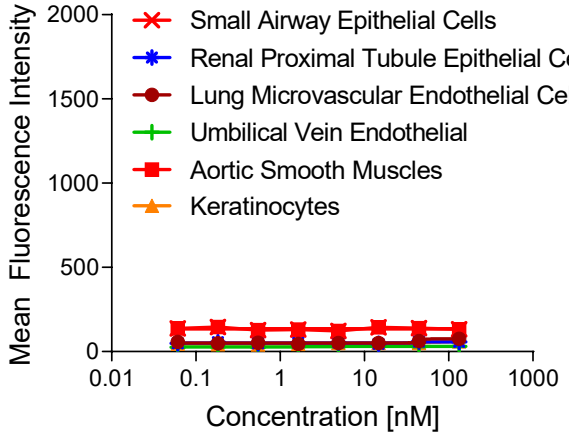
OR2805 binds to human CD163



Specific binding to human immunosuppressive myeloid cells



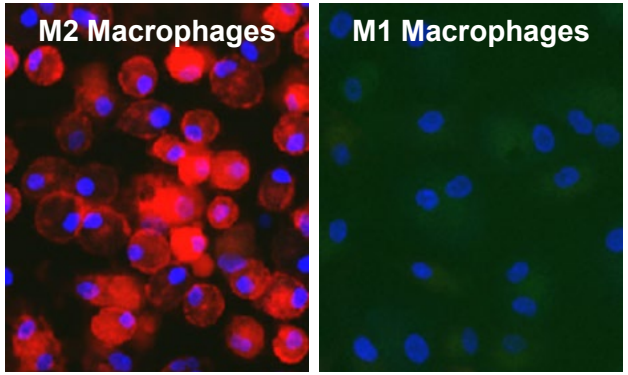
No binding to a panel of human primary immune and non-immune cells

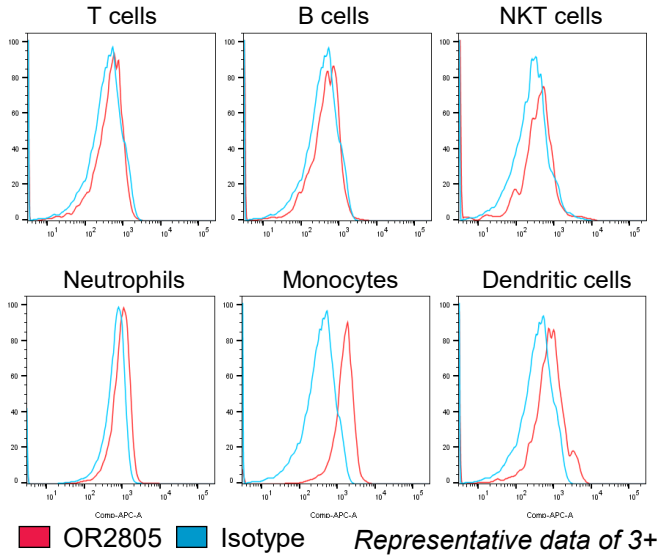


OR2805 binds to TAMs in dissociated NSCLC tumors

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

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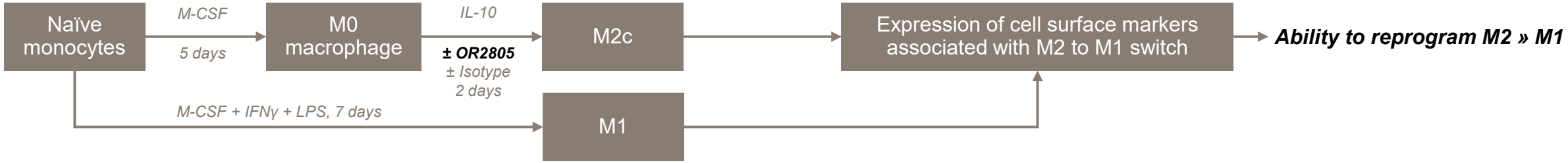
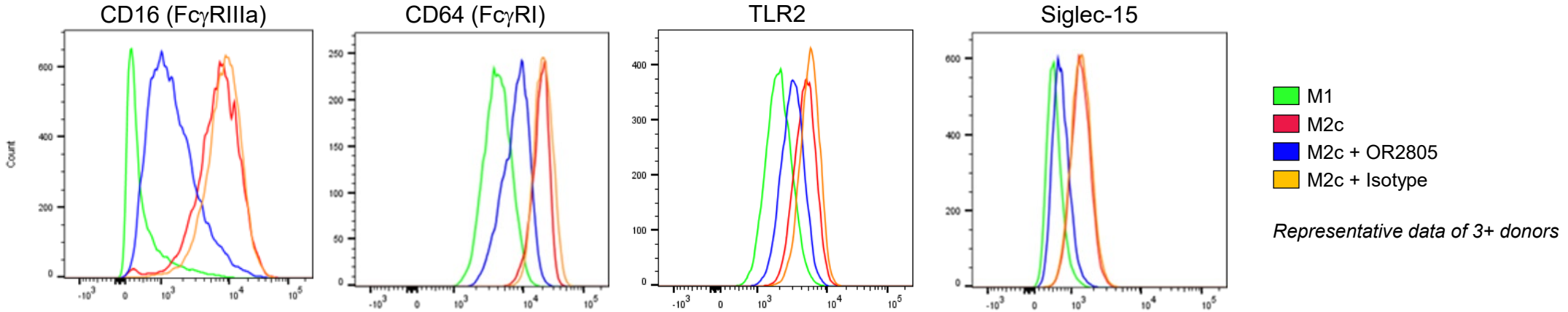
OR2805 reduces expression of M2c macrophage surface markers





Low affinity IgG receptor. Highly expressed on M2cs.

High affinity IgG receptor. Highly expressed on M2cs.

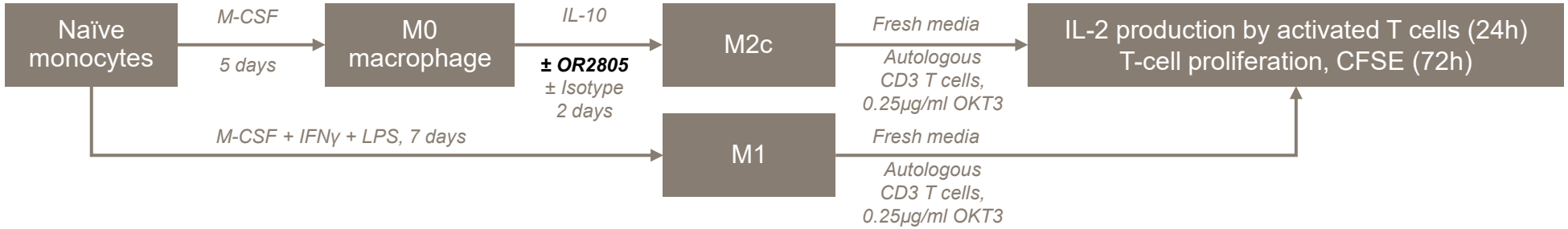
Innate immune receptor involved in immune modulation. Highly expressed on M2cs.

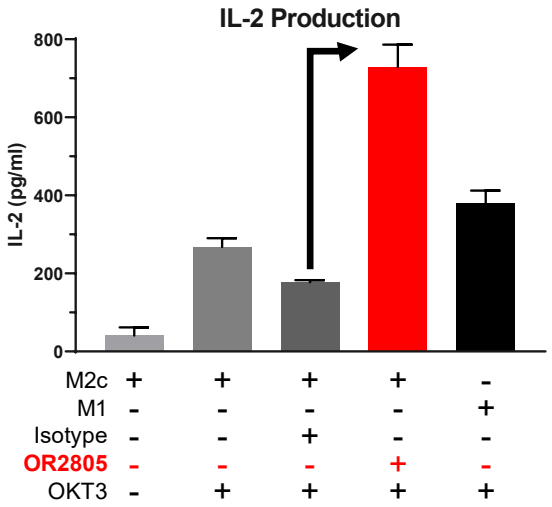
Transmembrane protein involved in immune suppression. Specific expression on M2c.

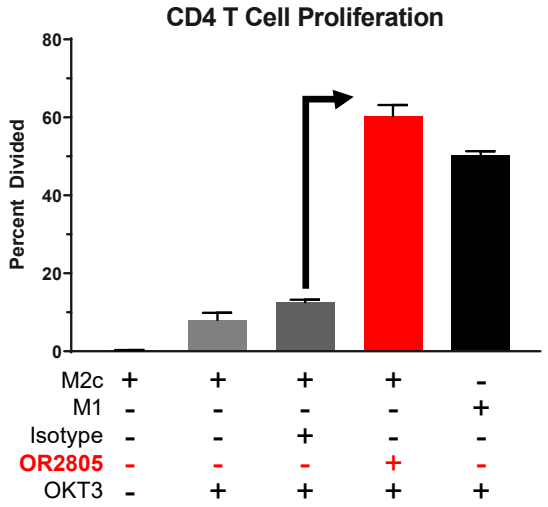
Representative data of 3+ donors

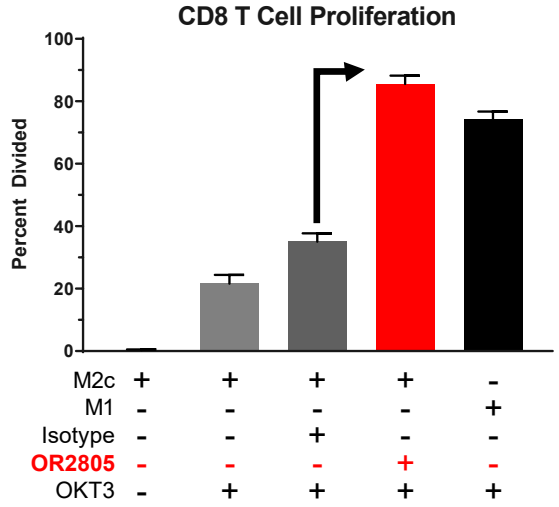
OR2805 treatment reduces expression of cell-surface markers associated with tumor-promoting M2c macrophages

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









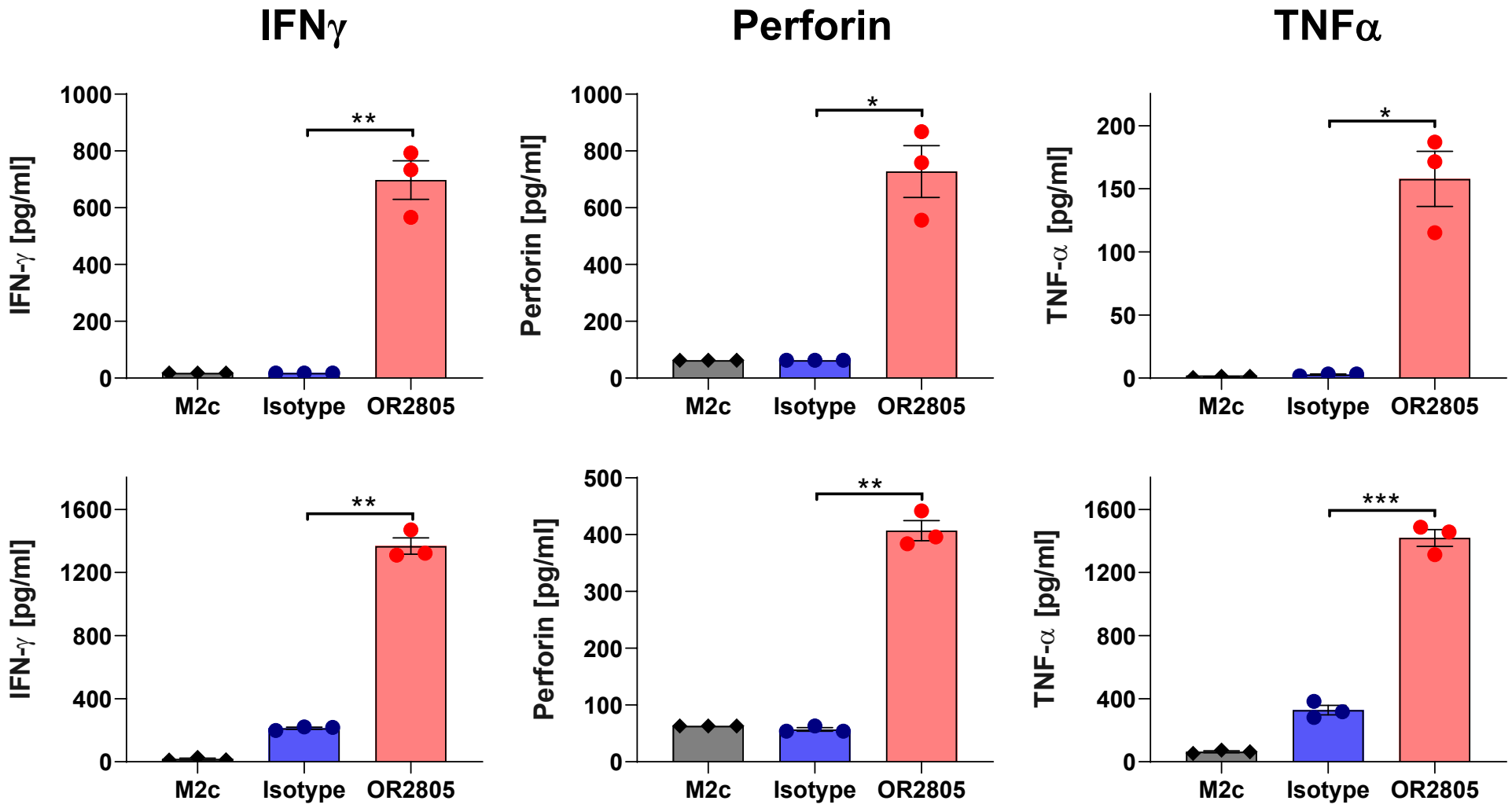
Representative data of 12+ donors

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 T-cell proliferation

OR2805-treated M2c macrophages promote T-cell activation

M2c/CD8 coculture

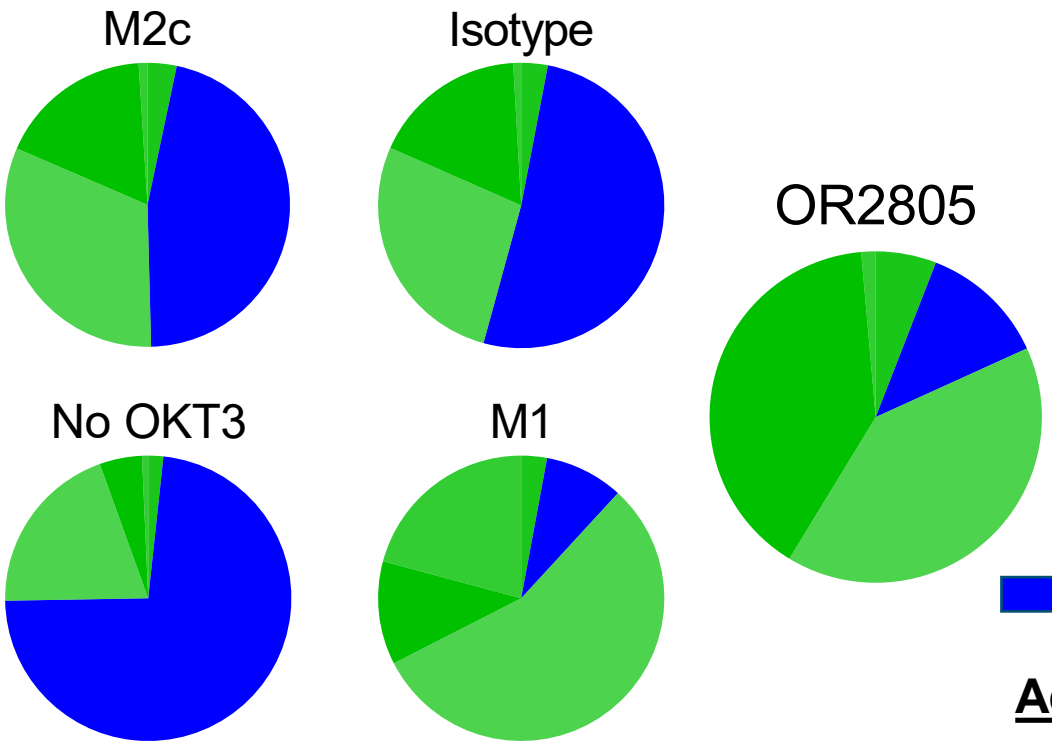
M2c/CD4 coculture



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 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

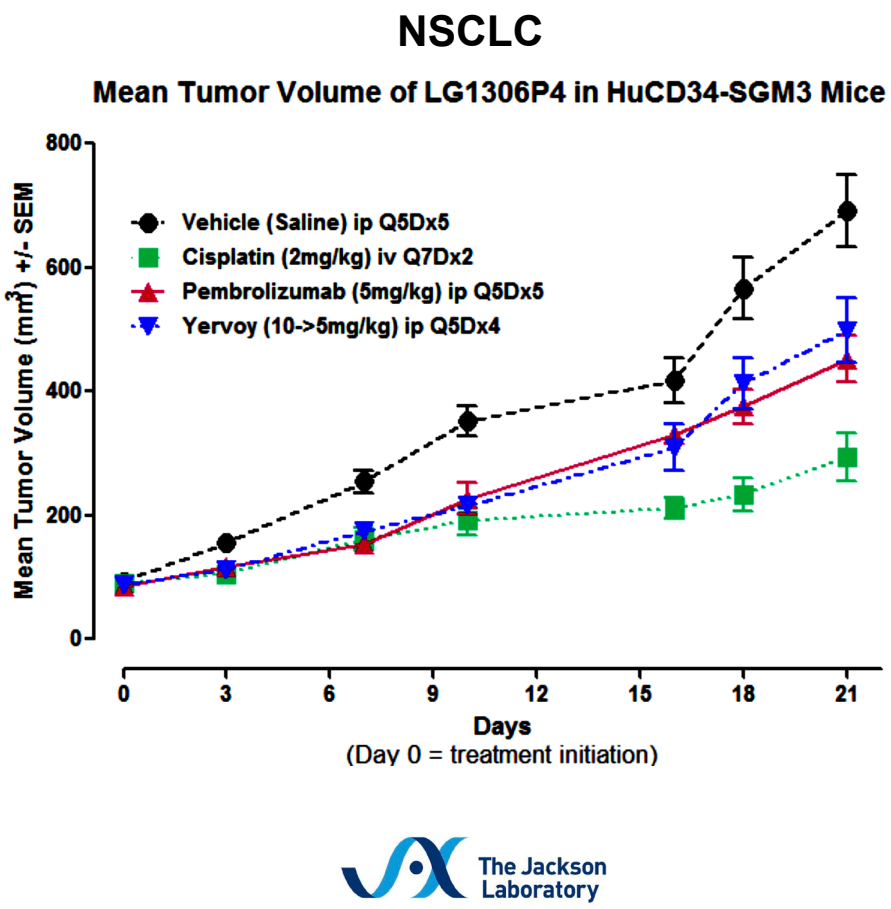
CXCR3⁺ CD69⁺ CD25⁻

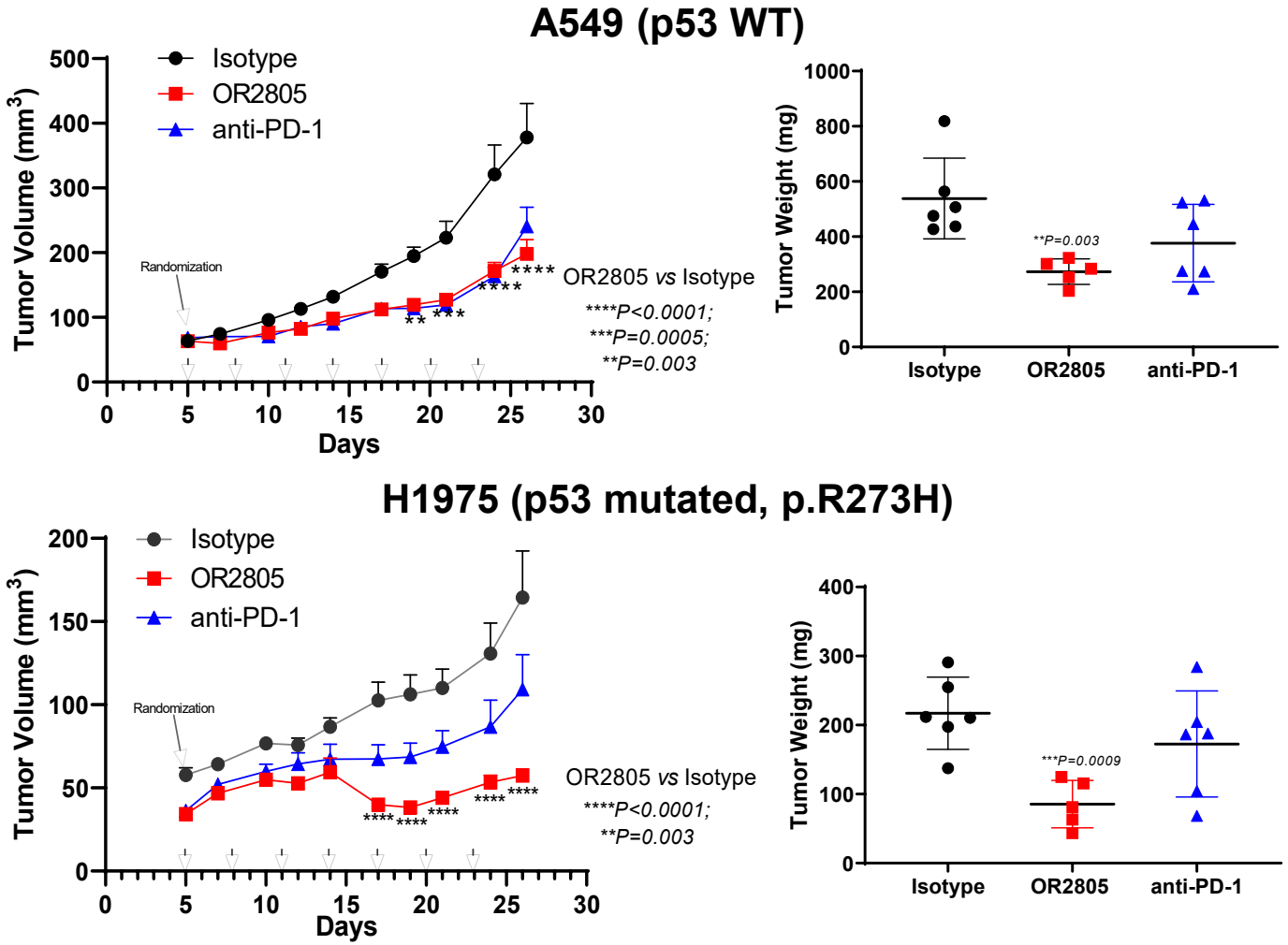
CXCR3⁺ CD69⁺ CD25⁺

CXCR3⁺ CD69⁻ CD25⁺

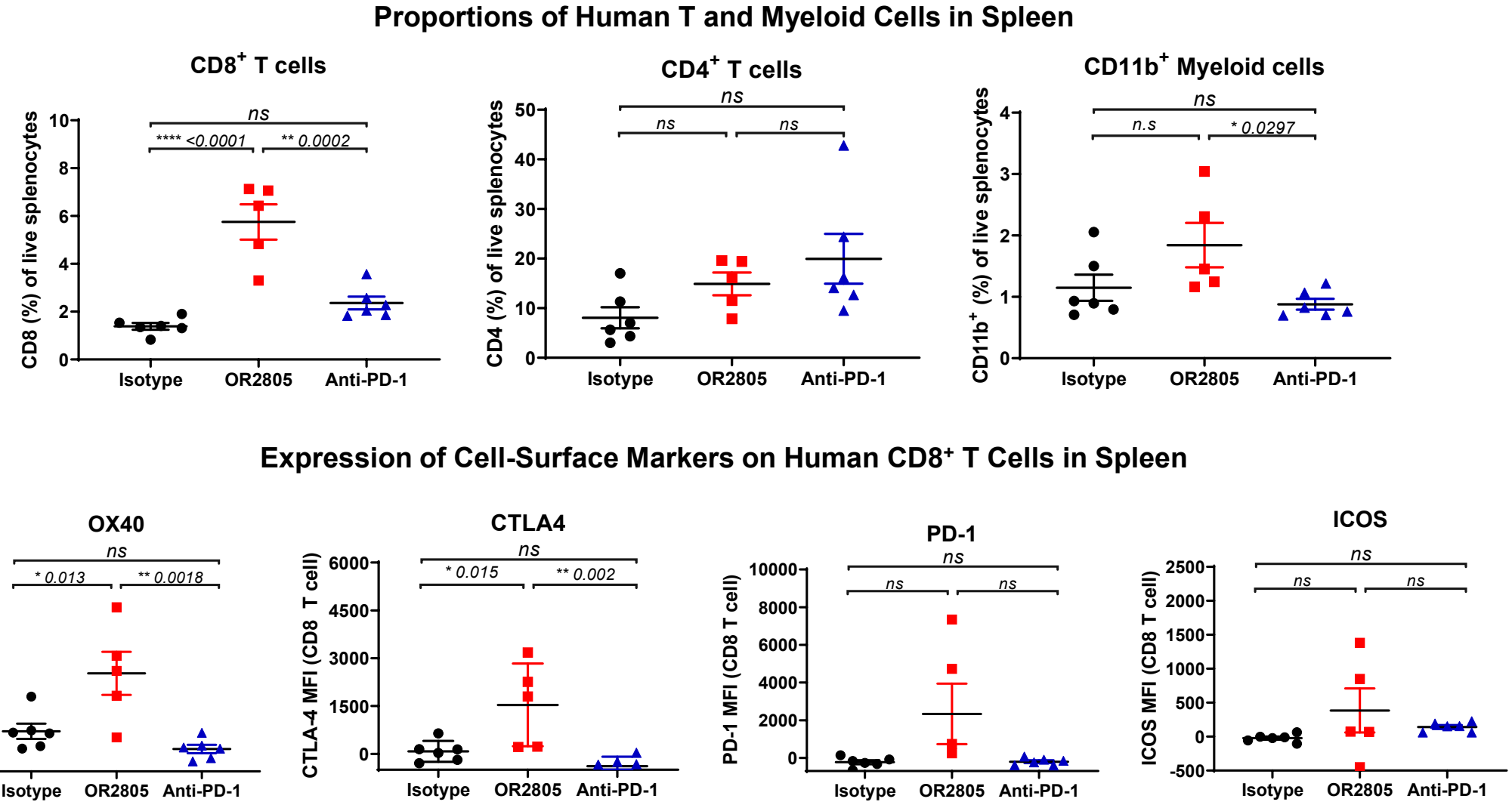
OR2805-treated macrophages promote T-cell activation leading to greater expression of T-cell activation markers (CD69, ICOS, OX40)

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



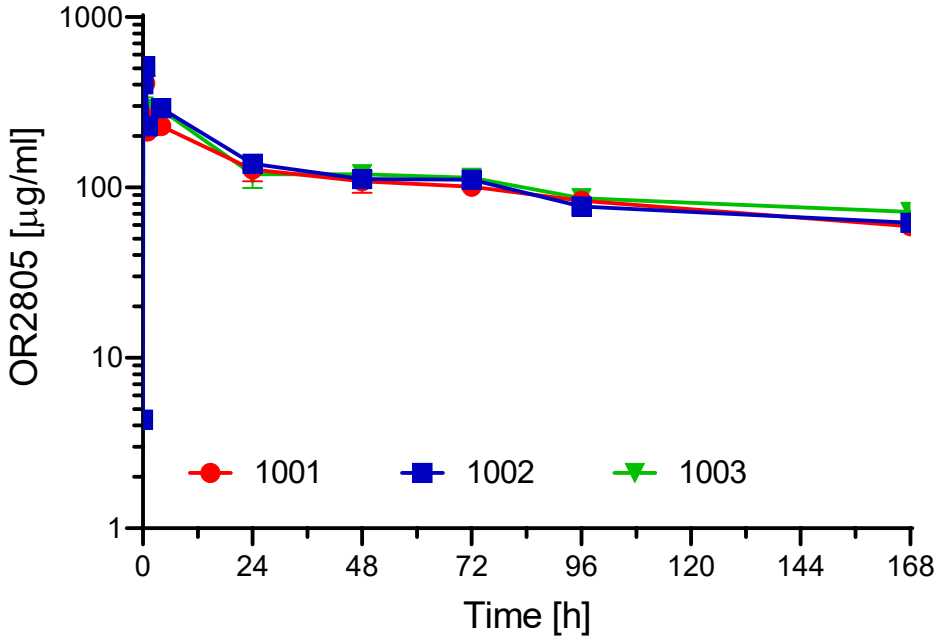


OR2805 treatment increases proportions of CD8 and myeloid cells in NSG-SGM3 model



OR2805 toxicology predicts tolerable safety profile

OR2805 serum levels in cynomolgus monkeys



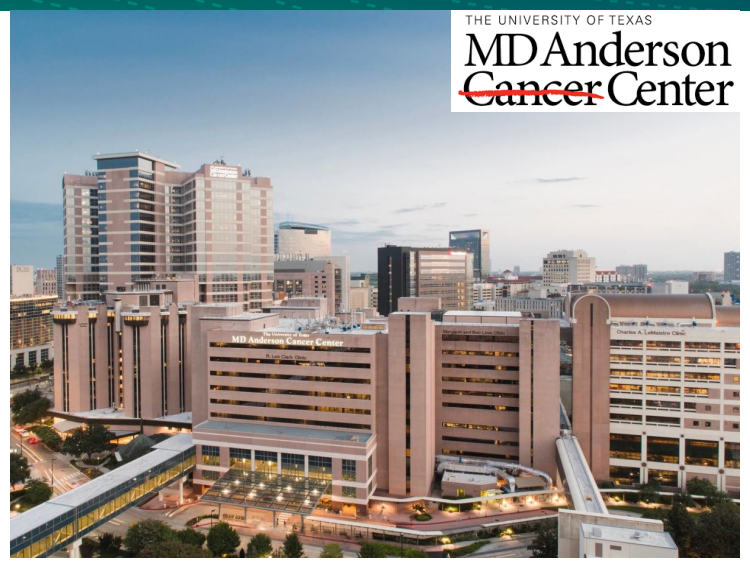
- Completed pilot, dose-range finding and GLP tox studies up to 100 mg/kg
- Observed OR2805 half-life in cynomolgus monkeys is about 5.8 days
- No in-life toxicity observed
- No abnormalities on pathological exam
- Normal serum chemistries and hematology
- No changes in immune cell subsets
- Slight elevation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

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
- 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 in humanized NSG-SGM3 mice
- Reduces TAM mediated immunosuppression and enhances anti-tumor immune responses
- OR2805 toxicology predicts tolerable safety profile
- IND cleared by FDA

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

Acknowledgements



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