OncoResponse

Interrogating for Cures™

Targeting Tumor-Associated Macrophages to Reverse Immunosuppression in the Tumor Microenvironment

Peter Probst

Immuno-Oncology Summit

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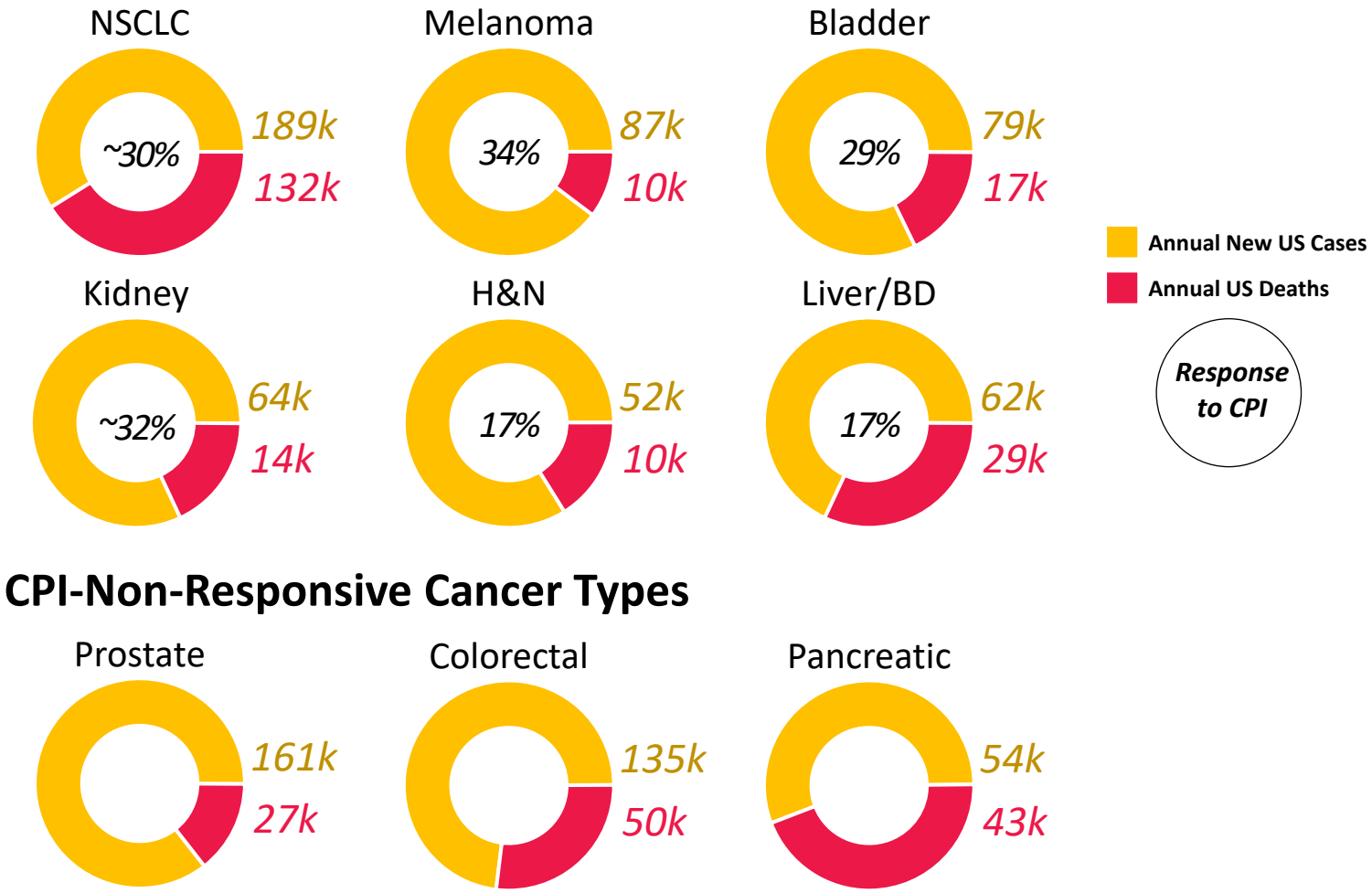
Overcoming resistance to CPI therapy

CPI-Responsive Cancer Types



CPI-Non-Responsive Cancer Types

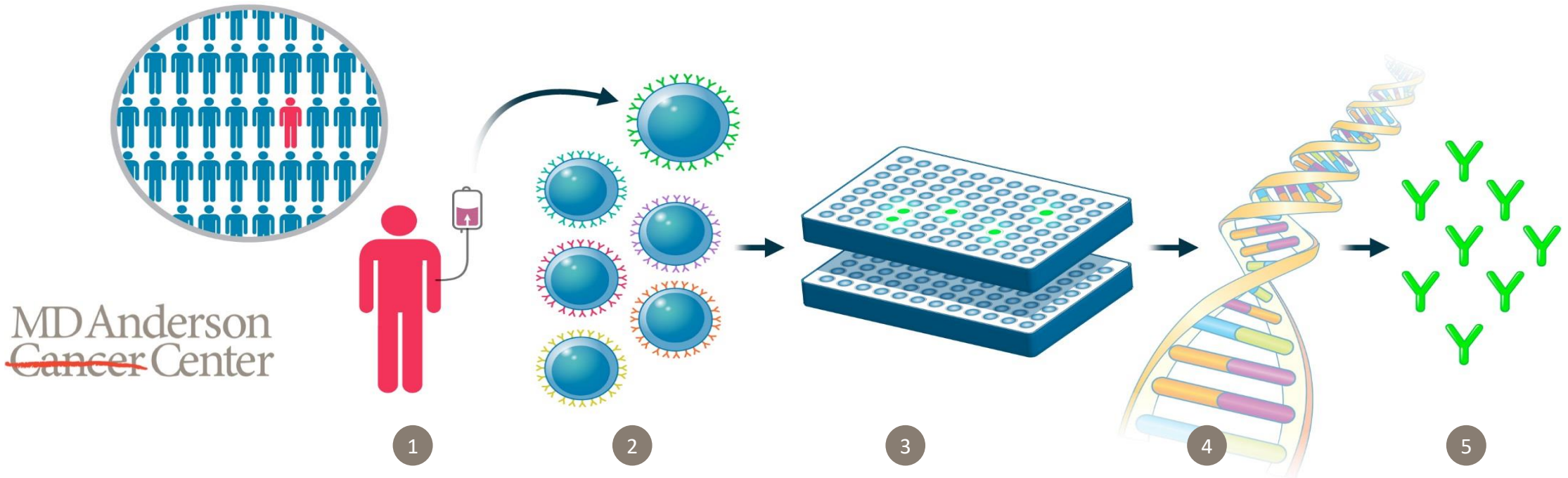
Abbreviations: CPI, checkpoint inhibitor; IO, immuno-oncology; TME, tumor microenvironment

- 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 platform interrogates the entire B-cell repertoire to discover antibodies modulating the TME

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

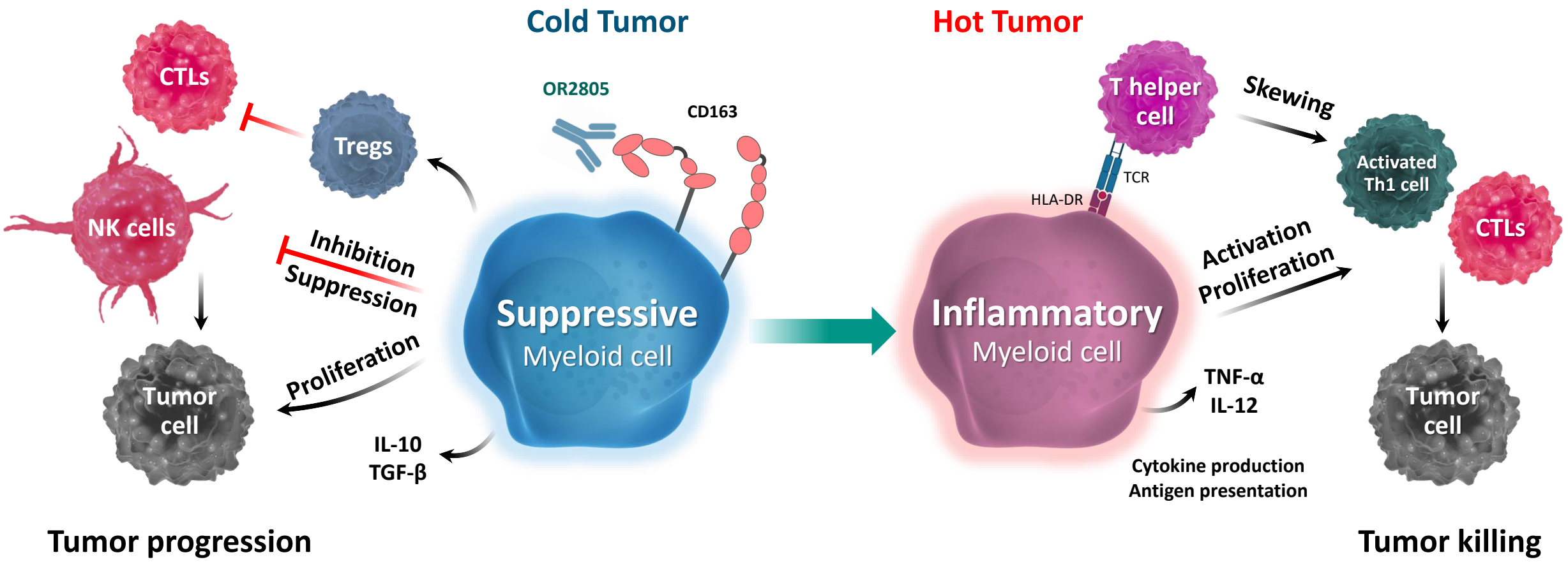


MD Anderson Cancer Center

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 myeloid cell mediated immune suppression in the TME



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

CD163 - Normal physiology and role in cancer

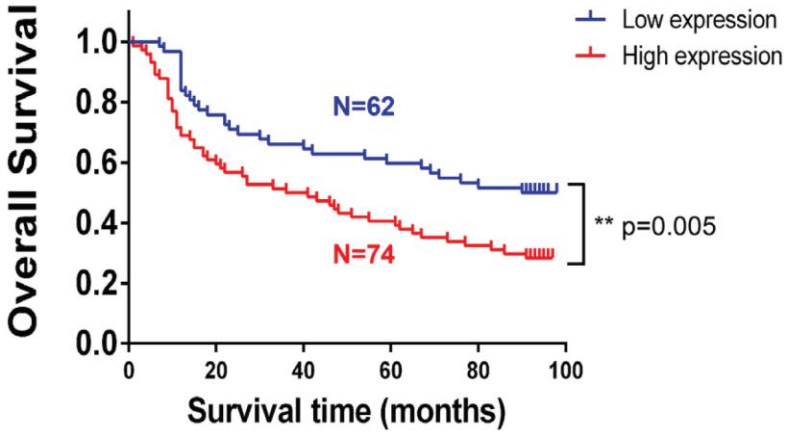
- Expression predominantly limited to and upregulated on immunosuppressive macrophages[1]
- Binding by its ligands induces secretion of immunosuppressive cytokines [2,3]
- Overexpression in human macrophages results in an immune suppressive phenotype[4]
- Knockout mice develop normally but have impaired tumor implantation[5]
- Expression in tumors correlates with poor survival [6-9]

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

CD163 expression on TAMs is a negative prognostic marker in cancer

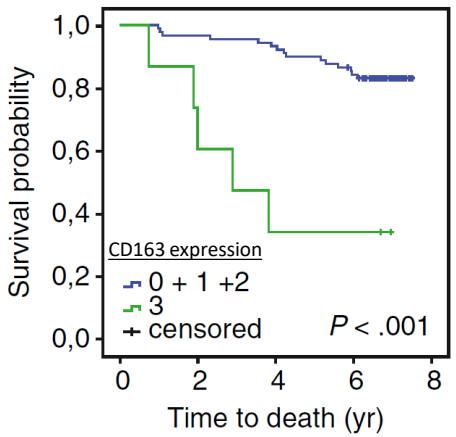
Gastric Cancer[10]

Overall survival



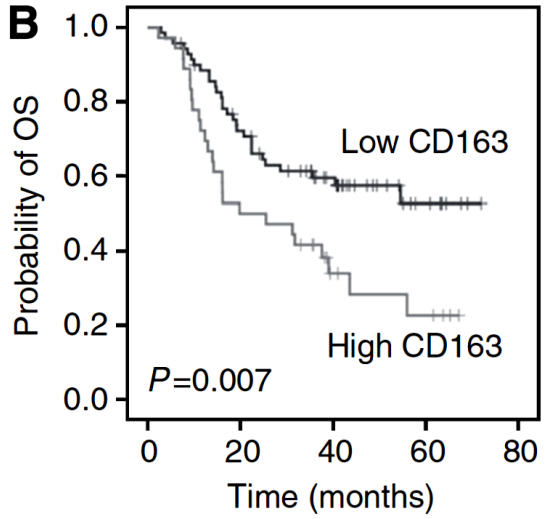
Breast Cancer[11]

Survival probability

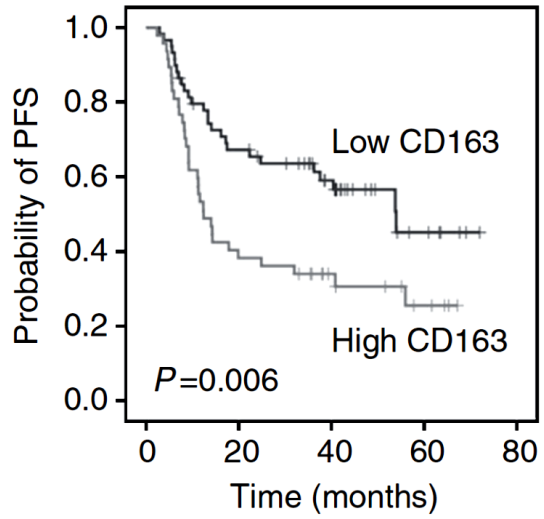


Head and Neck Cancer[12]

Overall survival

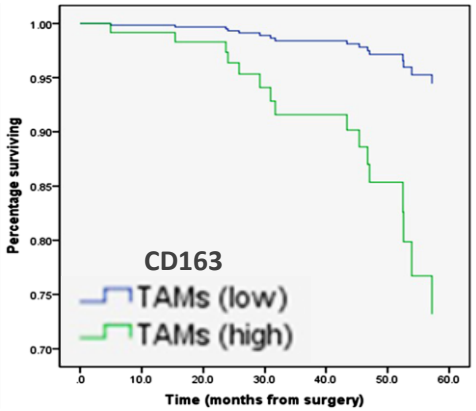


Progression-free survival

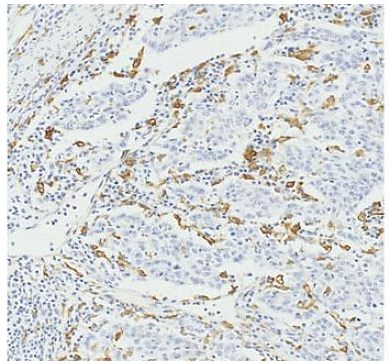


Colorectal Cancer[14]

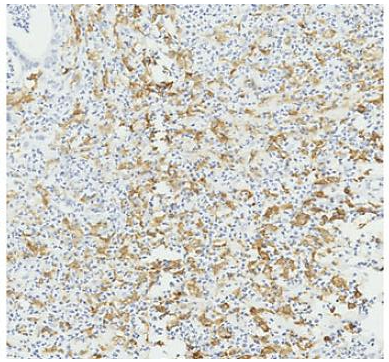
Overall Survival



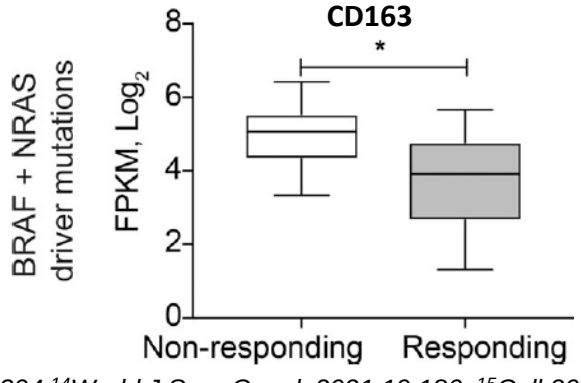
Low TAM Infiltration

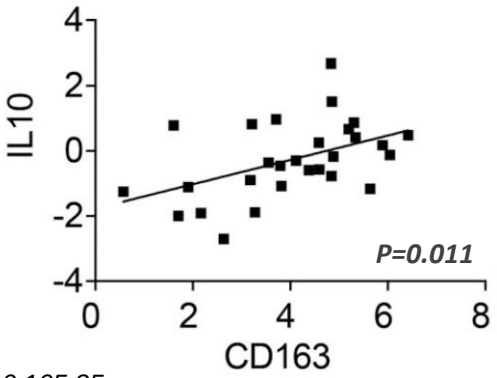


High TAM Infiltration



Melanoma patients on anti-PD-1 therapy[13,15]

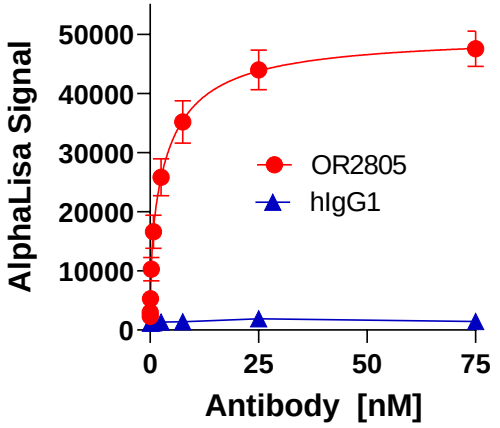




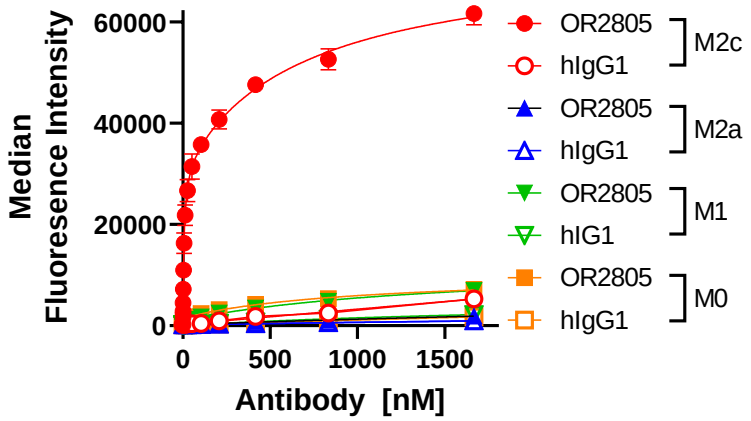
[10]Oncotarget 2017;8:87244, [11]BMC Cancer 2012;12:306, [12]Br J Cancer 2014;111:1509,[13]J Exp Med. 2019;216:2394,[14]World J Surg Oncol. 2021;19:186, [15]Cell 2016;165:35.

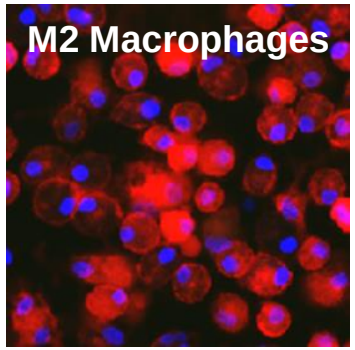
OR2805 demonstrates specific binding to immunosuppressive myeloid cells

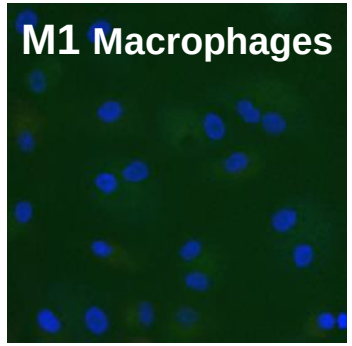
OR2805 binds to CD163



OR2805 preferentially binds to M2c macrophages







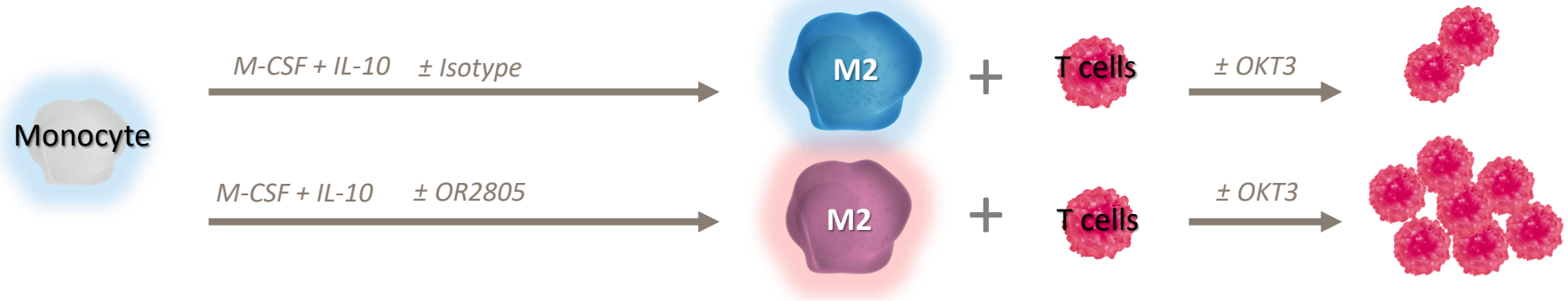
OR2805 Staining

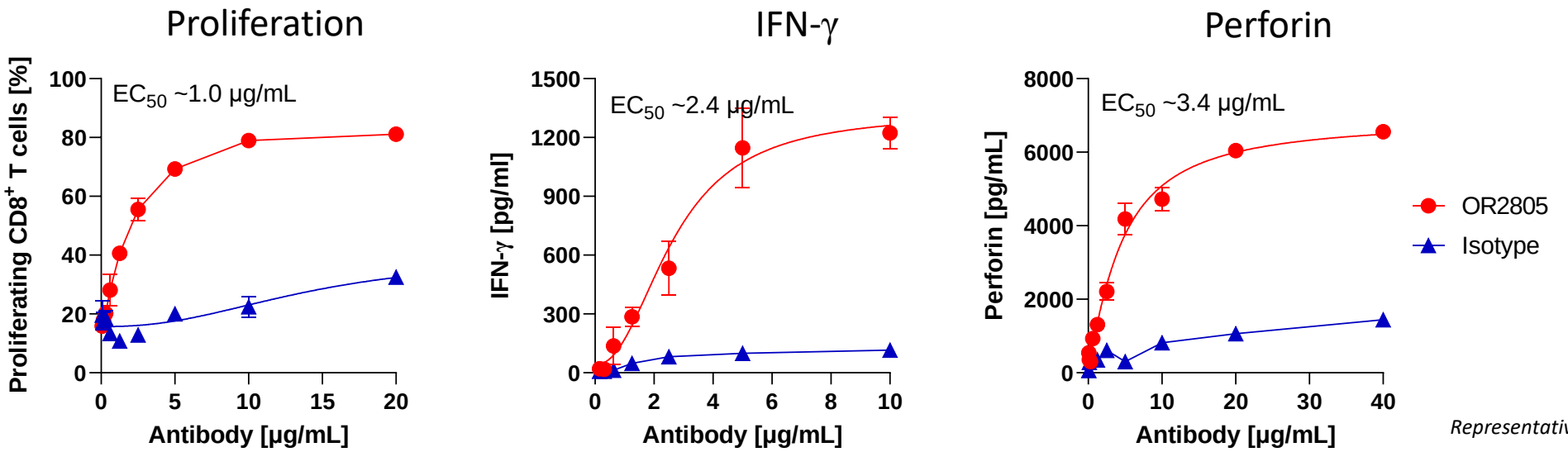
Binding to TAMs in dissociated NSCLC tumors

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

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



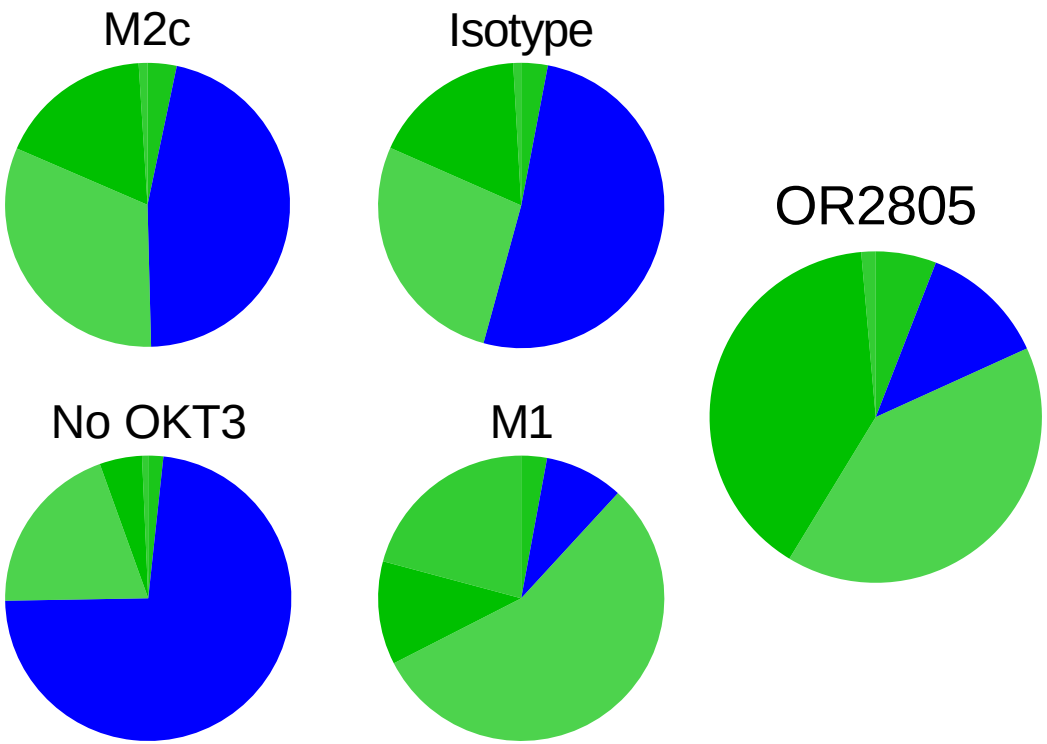


Representative data of 10 subjects

OR2805-treatment reduces the ability of M2c to suppress T-cell stimulation leading to enhanced T-cell proliferation and activation (IL-2, IFN-γ, TNF-α, & perforin production)

OR2805-treated M2c macrophages skew T cells towards a CXCR3$^+$ Th1 phenotype

Distribution of CD4$^+$ T cells phenotypes



- CXCR3 expression promotes T cell infiltration
- IFN-γ 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$^+$

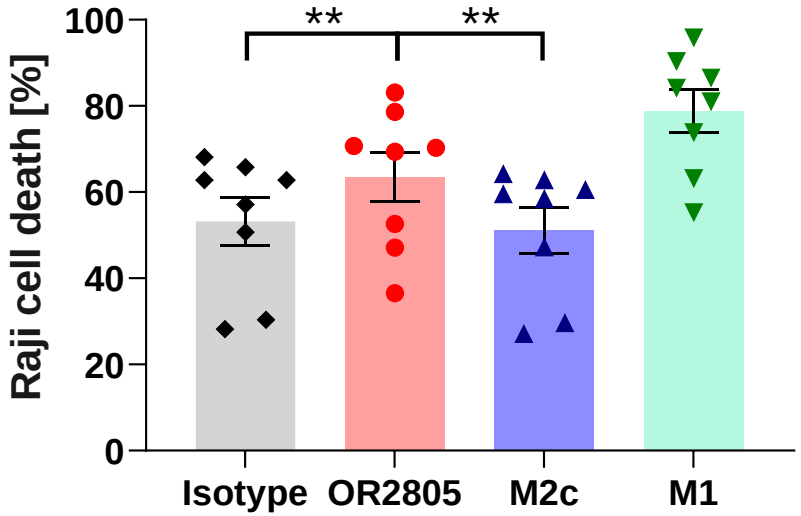
CXCR3$^+$ CD69$^+$ CD25$^-$

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

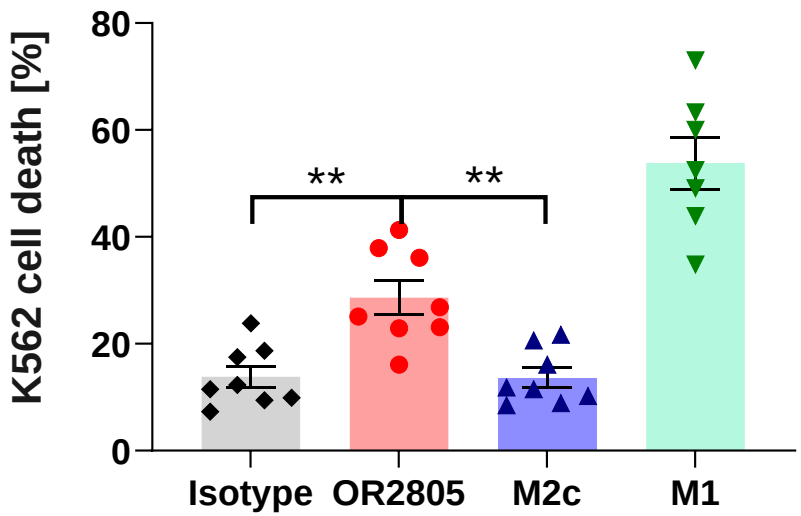
OR2805-treated macrophages promote T-cell activation leading to greater expression of T-cell activation markers (CD69, ICOS, OX40)

OR2805-treated M2c macrophages enhance the cytotoxic anti-tumor activity of CD8⁺ T cells

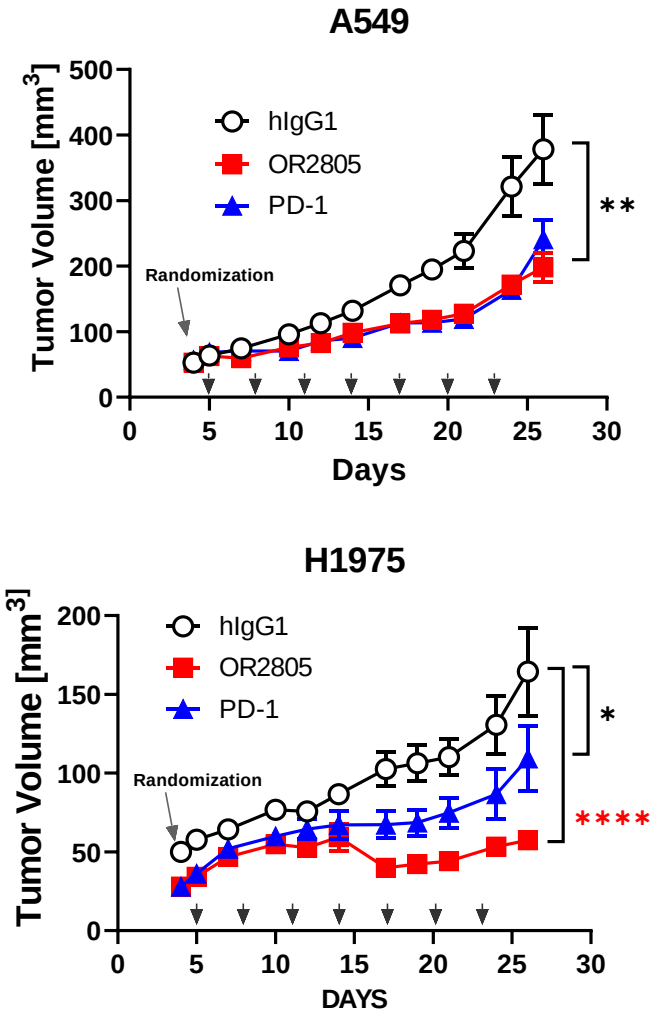
CD19-CD3 BiTE®-mediate killing of B-cell lymphoma by CD8⁺ T cells

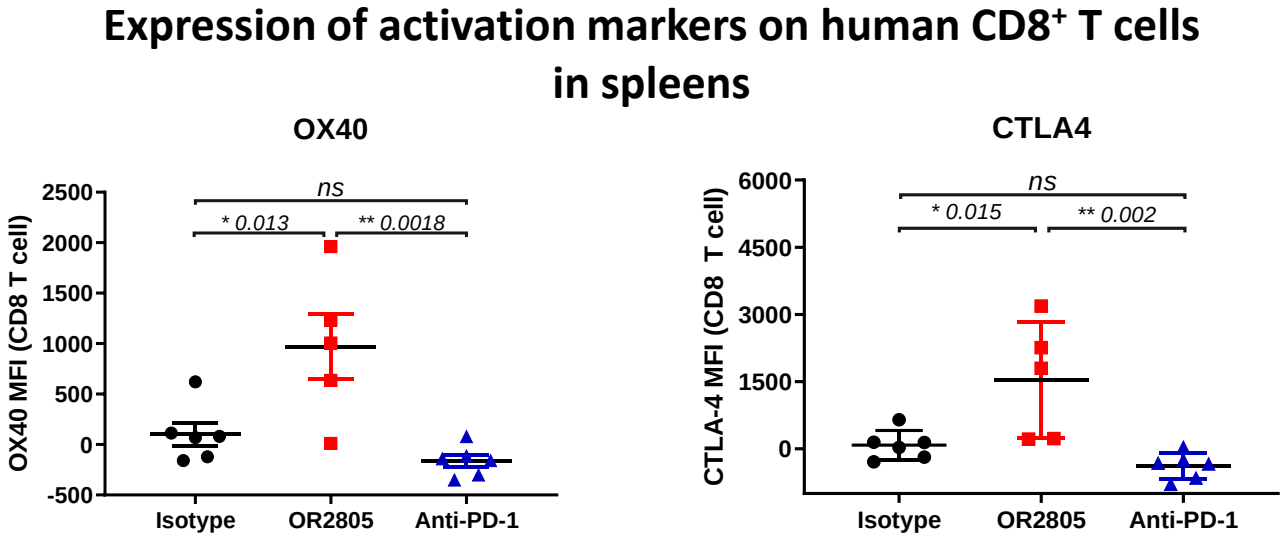


Killing of K562 leukemia cells by non-HLA restricted CD8⁺ T cells

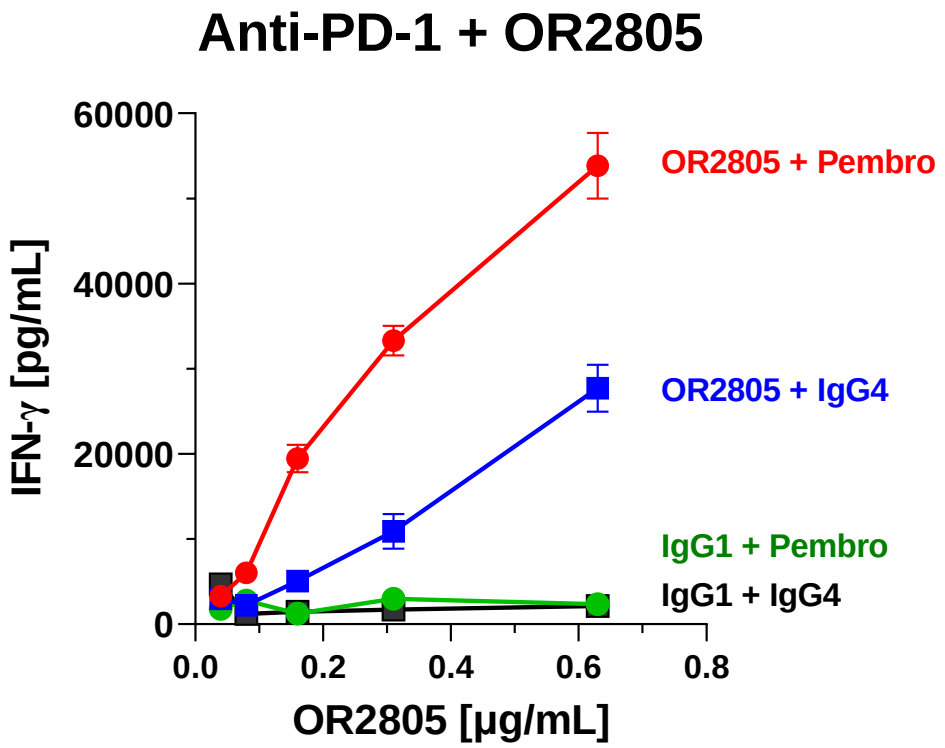


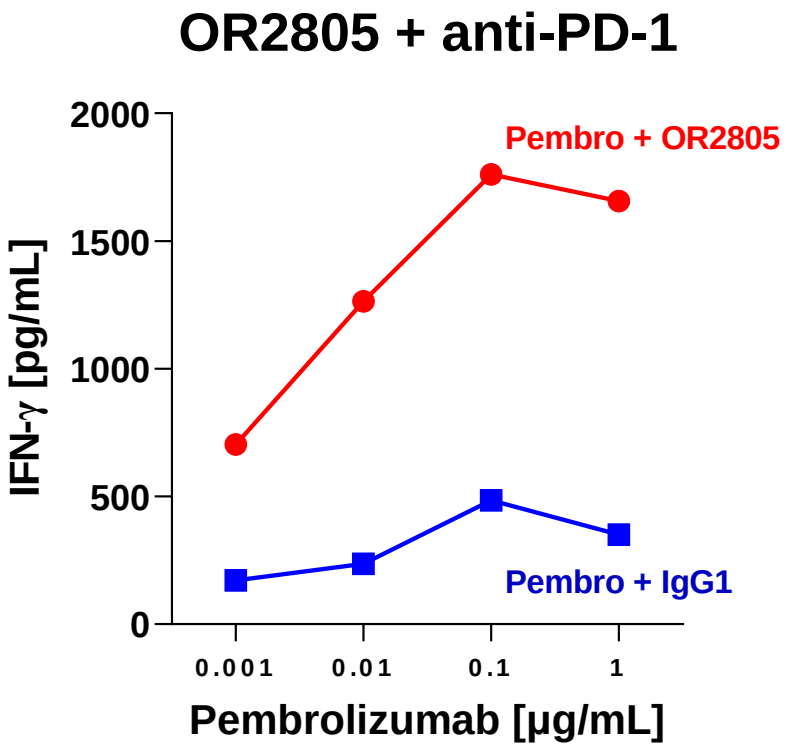
OR2805 treatment induces robust anti-tumor activity in humanized lung cancer xenograft models





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 immunosuppressive TAMs
- Minimizes suppressive effect of macrophages on T-cell activation and proliferation and skews T cells towards an anti-tumor Th1 phenotype
- Enhances the cytolytic anti-cancer activity of cocultured T cells
- Demonstrates robust anti-tumor activity in lung cancer xenograft models
- Combination with OR2805 amplifies anti-PD-1 activity on exhausted T cells 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

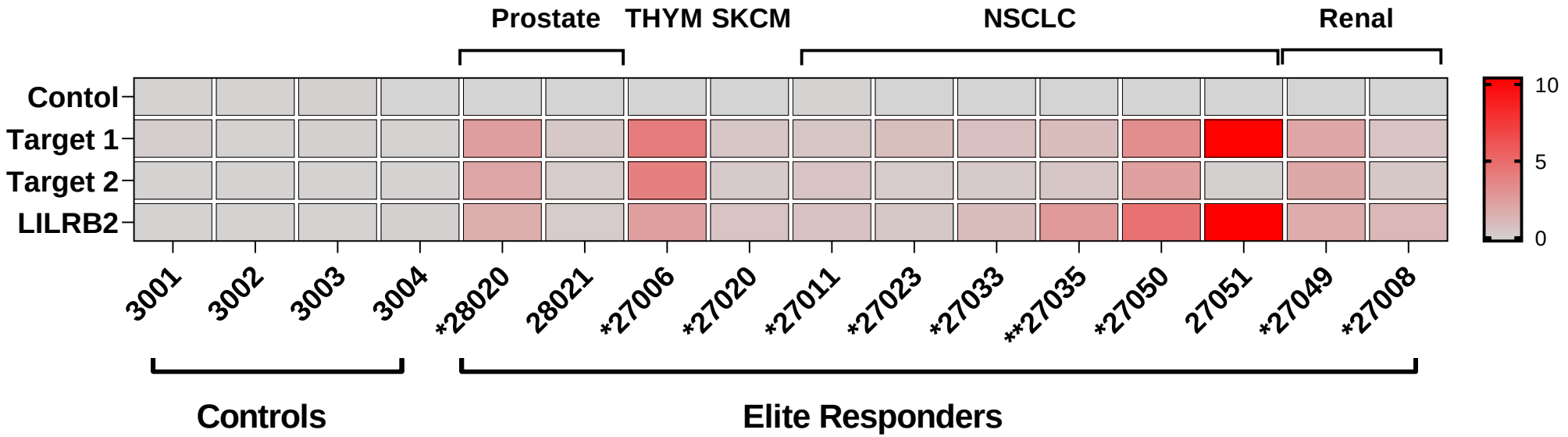
OncoResponse

Leukocyte Immunoglobulin-Like Receptor B2 (LILRB2/ILT4)

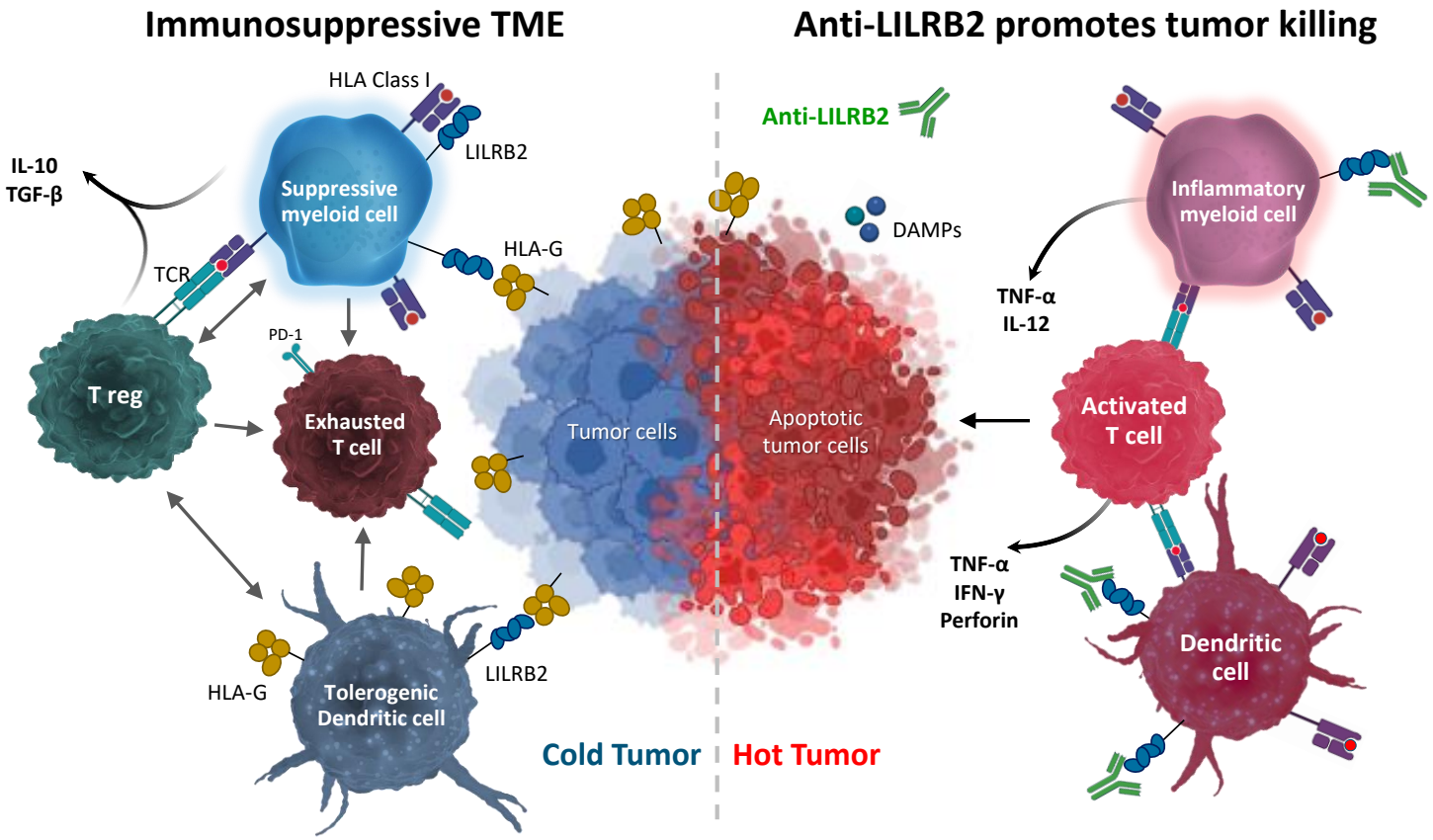
Targeting LILRB2–HLA class I binding to reverse immunosuppression in cancer

Elite Responders of immunotherapy mount a strong antibody response to leukocyte immunoglobulin-like receptor B2 (LILRB2/ILT4)]

Presence of anti-LILRB2 antibodies in Elite Responder sera



LILRB2 promotes immunosuppression and blockade drives anti-tumor activity



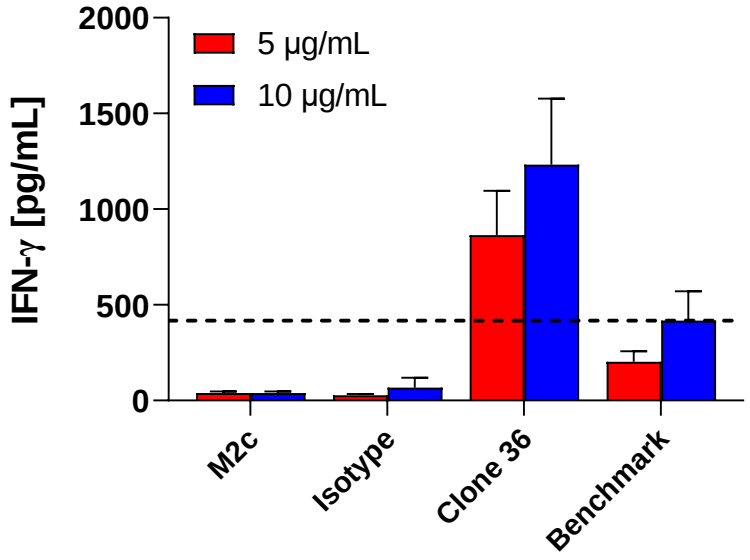
- ITIM-containing inhibitory receptor expressed on myeloid cells
- Expression correlates with poor survival in multiple cancers including NSCLC, breast, CRC, and renal
- Expression contributes to anti-PD1 resistance
- Receptor with multiple immune inhibitory activities mediated by SHP-1 recruitment
- 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, 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

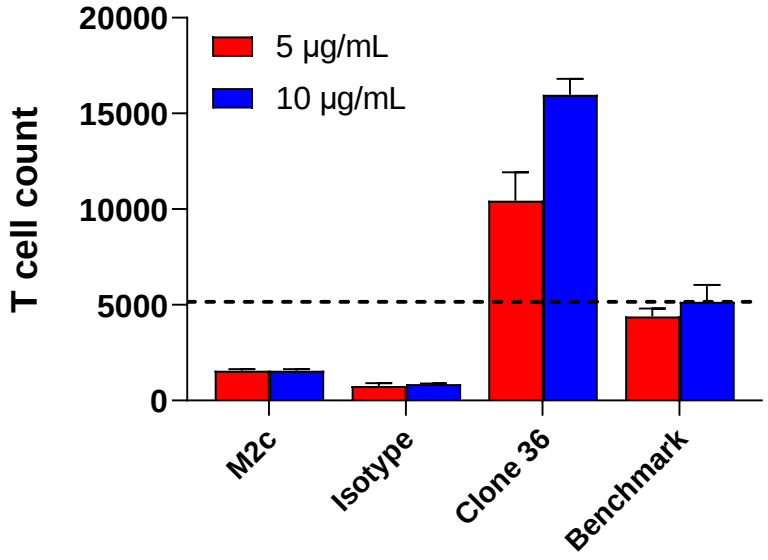
OncoResponse antibody enhances CD8⁺ T cell proliferation and IFN-γ production in M2c/T cell coculture assay

M2c/CD8⁺ T cell coculture

IFN-γ production

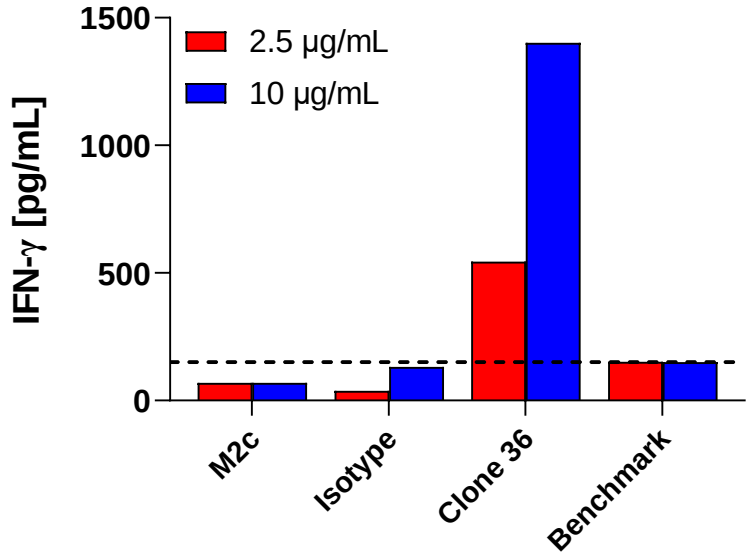


CD8⁺ T cell proliferation



M2c/exhausted T cell coculture

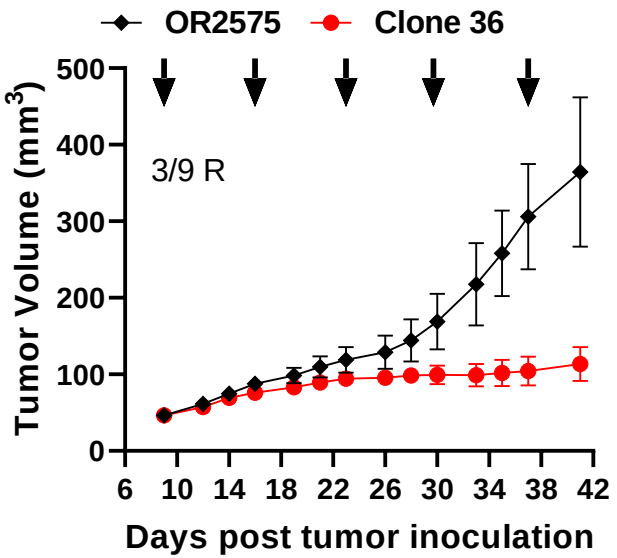
IFN-γ production



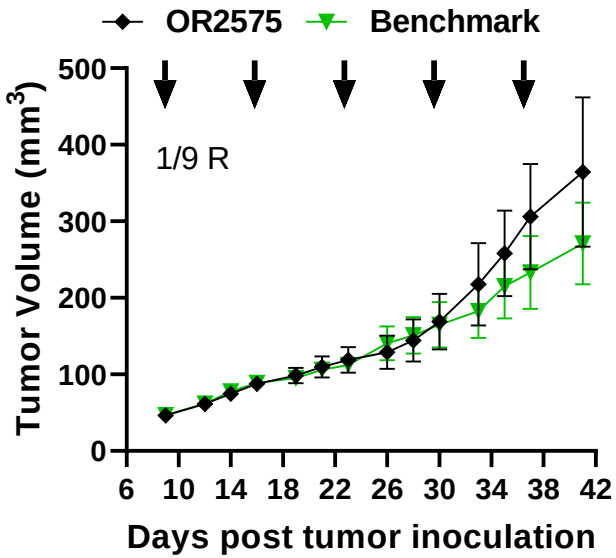
OncoResponse antibody outperforms benchmark in M2/T cell coculture assay

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

Clone 36 (OncoResponse)



Benchmark)



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

All groups N=9

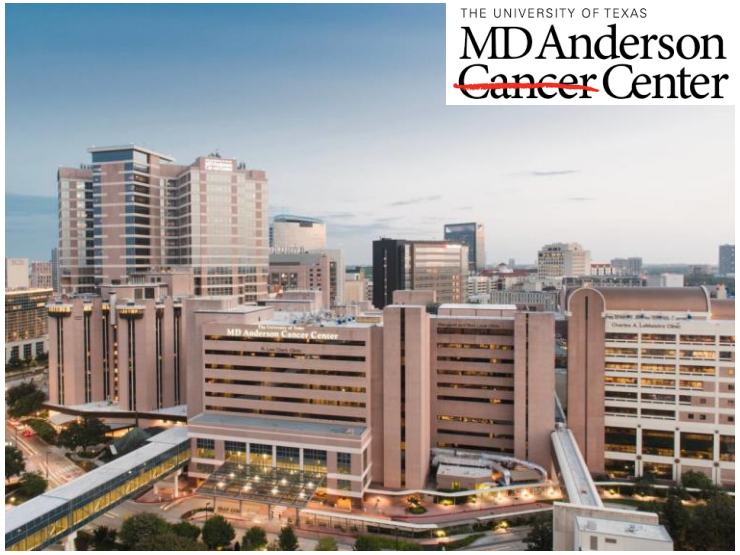
	Tumor Growth Inhibition (%)						Regression (%)
Group	***d28***	***d30***	***d33***	***d35***	***d37***	***d41***	***d41***
Clone 36 (OncoResponse)	47	57	69	74	78	79	33
Benchmark	-5	3	16	17	24	26	11

Summary

- Identified LILRB2 lead antibodies that block the interaction of LILRB2 with HLA-G and other HLA-class I molecules
- LILRB2 blockade modulates the immunosuppressive function of TAMs and enhances adaptive anti-tumor responses
- LILRB2 blockade boosts the innate immune response and enhances cytokine secretion to make a cold tumor hot
- A representative anti-LILRB2 clone inhibits human SK-MEL-5 melanoma tumor growth by 79% in humanized NSG-SGM3 mice
- Superior profile compared to benchmark

Preclinical data support further development of anti-LILRB2 lead antibodies

Acknowledgements



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Patients who provided precious tissue samples for this study

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