OR2805, an anti-CD163 antibody derived from an elite responder to checkpoint inhibitor therapy relieves immunosuppression caused by tumor associated macrophages

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Abstract # 1719

Background: OR2805 is a fully human IgG1 antibody that binds to CD163, an immune-suppressive receptor highly expressed on tumor associated macrophages (TAMs). High numbers of CD163-expressing TAMs generally predict an unfavorable prognosis in solid tumors. CD163-expressing TAMs contribute to an immune-suppressive tumor microenvironment (TME) and inhibit an anti-tumor T-cell response by engaging immune checkpoints, producing immune-suppressive cytokines, and promoting T-cell skewing towards a pro-cancer Th2 phenotype. Relieving the immune suppression of CD163-expressing TAMs in the TME to improve T-cell-mediated responses is a rational adjunct to immune checkpoint inhibitor (CPI) therapy.

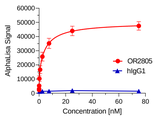
Methods: OR2805 was discovered using OncoResponse's discovery platform by cell-based functional and phenotypic assays. B cells derived from CPI elite responders were cultured at clonal density, and IgG antibodies in supernatants were evaluated for binding to myeloid-derived suppressor cells. Variable-regions from positive hits were sequenced, cloned, and expressed as recombinant IgG1. OR2805 was identified as one of the top hits that relieved myeloid cell-mediated immune suppression. Cocultures of immunosuppressive primary human M2 macrophages and autologous T cells were used to interrogate OR2805-dependent immunomodulatory responses in vitro. The anti-tumor activity of OR2805 in vivo was evaluated in a humanized mouse model.

Results: OR2805 binds to CD163 expressed on TAMs and M2-like macrophages. OR2805 does not bind to other hematopoietic cells nor to a panel of human primary non-immune cells. OR2805-treatment reduces expression of cell-surface markers associated with tumor-promoting M2c-like macrophages. In co-culture assays, OR2805 relieves the suppressive effect of M2 macrophages and results in increased T-cell activation and proliferation, upregulation of T-cell activation markers, and enhanced T-cell-mediated tumor cell killing. Administration of OR2805 in humanized NSG-SGM3 mouse tumor models resulted in approximately 55% and 75% reduction in A549 tumor growth and NCI-H1975 tumor growth, respectively. In this model, OR2805-treatment significantly increased the proportions of human CD8⁺ T cells and human CD11b⁺ myeloid cells, as well as significantly enhanced expression of activation markers by human CD8⁺ T cells.

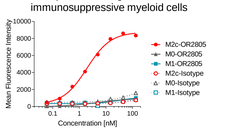
Conclusions: OR2805 reduces M2 macrophage-mediated immunosuppression and enhances anti-tumor immune responses. OR2805-treatment induces anti-tumor activity in lung cancer xenograft models in humanized mice. These data support further development of OR2805 as an anti-cancer therapy, both as a monotherapy and an addition to current CPI therapy.

OR2805 Demonstrates Specific Binding to Immunosuppressive Myeloid Cells

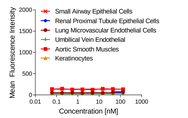
OR2805 binds to human CD163



Specific binding to human immunosuppressive myeloid cells



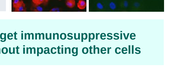
No binding to a panel of human primary immune and non-immune cells

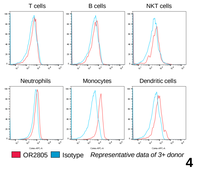


OR2805 binds to TAMs in dissociated NSCLC tumors

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

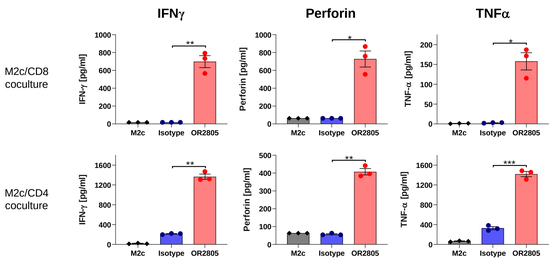




Representative data of 3+ donor

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

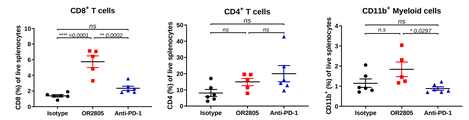
OR2805-Treated M2c Macrophages Promote T-Cell Activation



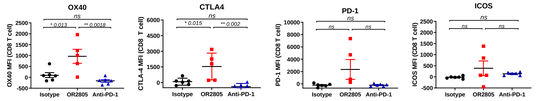
Representative data from n=3 donors

OR2805-Treatment Increases Proportions of CD8 and Myeloid Cells in Xenograft Models in Humanized NSG-SGM3 Mice

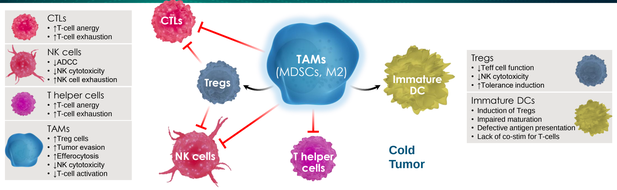
Proportions of Human T and Myeloid Cells in Spleen



Expression of Cell-Surface Markers on Human CD8⁺ T Cells in Spleen

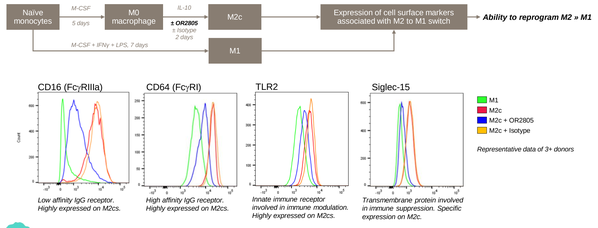


OncoResponse Targets the TME to Broaden and Deepen Responses



- M2 TAMs contribute to tumor immune evasion by suppressing anti-tumor immune responses and by promoting a tumorigenic milieu. Repolarization of suppressive myeloid cells is an attractive strategy to enhance clinical responses to CPI therapy.
- Cancer patients who achieved durable response to CPI therapy (elite responders) may harbor antibodies that contribute to clinical response by promoting an anti-tumor TME. OncoResponse is leveraging the power of the Elite Responder's immune system to discover & develop immunomodulatory antibodies that reverse and relieve immunosuppression in the TME to enhance responses of CPI therapy to greater cures.
- OncoResponse lead antibody, OR2805 targets immunosuppressive M2-like TAMs and relieves their suppressive effect leading to increased T cell activation and proliferation, T cell skewing towards Th1 phenotype, and enhanced T cell mediated killing of cancer cells. This reprogramming of TAMs may therefore enhance clinical responses to immunotherapy.

OR2805 Reduces Expression of M2c Macrophage Surface Markers

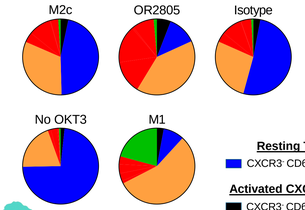


Representative data of 3+ donors

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

OR2805-Treated M2c Macrophages Skew T Cells Towards Activated Th1-Like Phenotype

Distribution of CD4⁺ T cells phenotypes

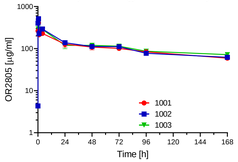


- CXCR3 is preferentially expressed on Th1 cells
- IFNγ production within the TME enhances the CXCR3-mediated T-cell recruitment to the tumor site
- CXCR3 signaling promotes CD8⁺ T cell infiltration
- CXCR3 expressing CD8⁺ T cell populations display enhanced cytotoxicity against tumor cells

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

OR2805 non-GLP Exploratory Toxicokinetics Study in Cynomolgus Monkeys

OR2805 serum levels 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

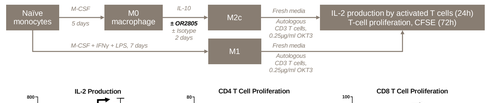
- **Observed OR2805 half-life in cynomolgus monkeys is about 5.9 days**
- **No acute toxicity observed**

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 chemotherapy
  - 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.

OR2805-Treated M2c Macrophages Promote T-Cell Activation and Proliferation

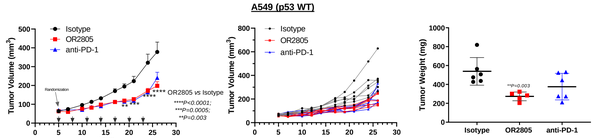


Representative data of 12+ donors

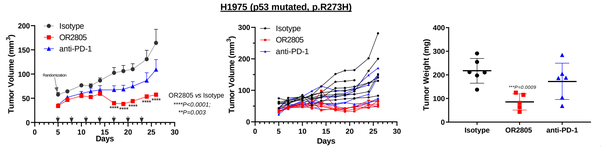
OR2805-treatment reduces the ability of M2c to suppress T-cell activation leading to greater T-cell stimulation (IL-2, IL-1β, IFNγ, TNFα, CCL4 & perforin production), and both CD4⁺ and CD8⁺ T cell proliferation

OR2805-Treatment Induces Robust Anti-Tumor Activity in Lung Cancer Xenograft Models in Humanized NSG-SGM3 Mice

A549 (p53 WT)



H1975 (p53 mutated, p.R273H)



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

MD Anderson Cancer Center

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