Antibody derived from an elite responder to checkpoint inhibitor therapy relieves immunosuppression by tumor associated macrophages

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Abstract

Backgraound: Tumor-associated macrophages (TAM)s in the tumor microenvironment (TME) contribute to tumor immune evasion by suppressing anti-tumor immune responses and by promoting a tumorigenic milieu. High infiltration of immunosuppressive myeloid cells generally predicts unfavorable prognosis. Reduction or repolarization of suppressive myeloid cells is an attractive strategy to enhance clinical responses to immune checkpoint inhibitor (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.

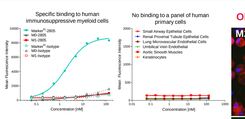
Methods: B cells derived from elite responders were cloned and screened for IgG antibodies binding to myeloid derived suppressor cells. Hits were prioritized based on myeloid binding profiles and their variable-regions sequenced, cloned, and expressed as recombinant IgG1. Cloned antibodies underwent further characterization to evaluate their ability to reverse the immunosuppressive effects of myeloid cells in assays modelling the TME. Primary human monocytes and T cells were used to interrogate antibody-dependent immunomodulatory responses in vitro. A humanized mouse model was used to evaluate the anti-tumor activity of the lead antibody, OR2805.

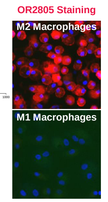
Results: The target of OR2805 is highly expressed on TAMs and M2-like macrophages. OR2805 does not bind to other hematopoietic cells nor a panel of human primary non-immune cells. The antibody stains positively on M2-like TAMs from primary human lung tumor samples. OR2805 treatment reduces expression of cell-surface markers associated with tumor-promoting M2c-like macrophages. In co-culture assays, OR2805 relieves the suppressive effect of M2 macrophages and resulted 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 50% reduction in A549 tumor growth and a 60% reduction in H1975 tumor growth. In this model, OR2805 treatment significantly increased the proportions of human CD8$^+$ T cells and human CD11b$^+$ myeloid cells in the spleen as well as significantly enhanced expression of activation markers (ICOS, OX-40) by human CD8$^+$ T cells.

Conclusions: OR2805 reduces TAM-mediated immunosuppression and enhances anti-tumor immune responses. OR2805 treatment induces robust anti-tumor activity in lung cancer xenograft models in humanized mice. This data justifies further development of OR2805 as anti-cancer therapy in combination with other CPI treatments. OR2805 has the potential to increase the number of patients who may benefit from current CPI therapy.

OR2805 Demonstrates Specific Binding to Immunosuppressive Myeloid Cells

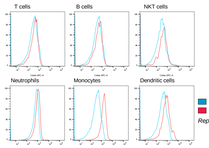
CELL TYPE	OR2805 BINDING
M2c macrophages	Dose-dependent binding
M1 macrophages	No detectable binding
Monocytes	Sub-population binding
Dendritic cells	Sub-population binding
T cells	No detectable binding
B cells	No detectable binding
NK cells	No detectable binding
Granulocytes	No detectable binding





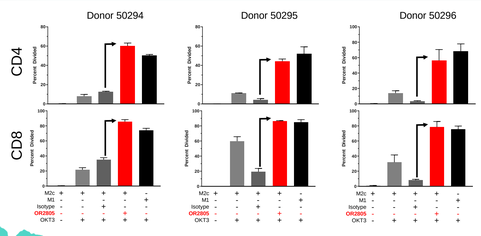
OR2805 binds to TAMs in dissociated NSCLC tumors

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



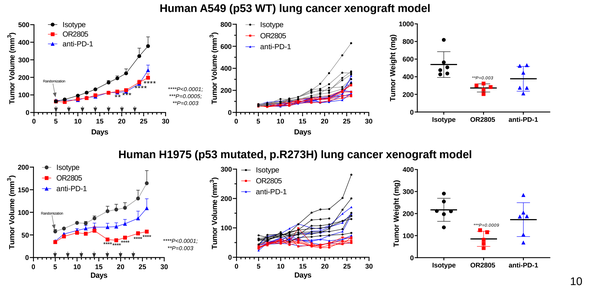
OR2805 has a potential to target immunosuppressive myeloid cells in the TME without impacting other cells

OR2805 Reduces Ability of M2c Macrophages to Suppress T Cell Proliferation

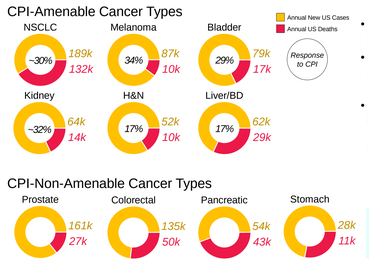


OR2805 reduced ability of M2c cells to suppress both CD4$^+$ and CD8$^+$ T cell proliferation

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



The Immuno-Oncology (IO) Opportunity

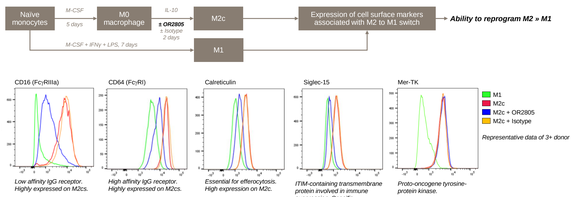


- IO is now aimed at almost every major solid tumor cancer type
- However, response rates from CPI continue to be low due to suppressive TME
- There is great need to overcome immunosuppression of the TME to dramatically increase response rates and overall survival

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

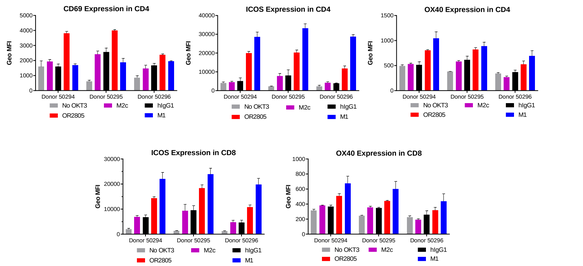
OncoResponse leverages the power of the Elite Responder's immune system to discover immunomodulatory antibodies

OR2805 Reduces Expression of M2c Macrophage Surface Markers

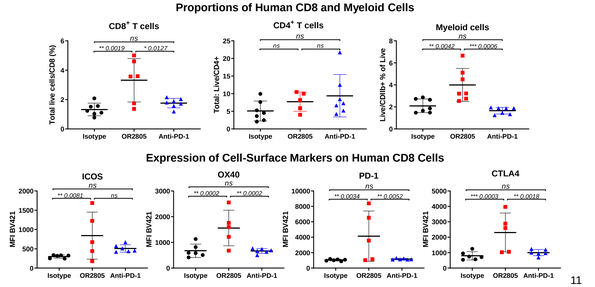


OR2805 treatment reduces expression of cell-surface markers associated with tumor-promoting M2c macrophages

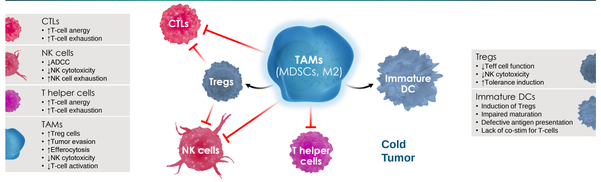
Proliferated T Cells Show Enhanced Expression of Activation Markers



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

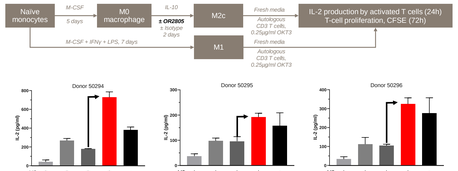


OncoResponse Targets the TME to Broaden and Deepen Responses



- Tumor-associated macrophages in the TME contribute to tumor immune evasion by suppressing anti-tumor immune responses and by promoting a tumorigenic milieu. Reduction or 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 anti-tumor Th1 phenotype, and enhanced T cell mediated killing of cancer cells. This reprogramming of TAMs may therefore enhance clinical responses to immunotherapy

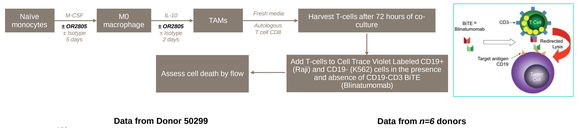
OR2805 Reduces Ability of M2c Macrophages to Suppress T Cell Activation

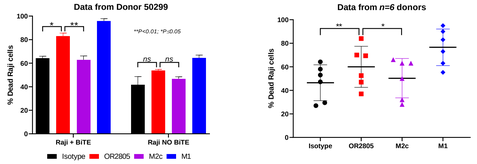


OR2805 blocks the ability of M2c cells to suppress T-cell activation leading to greater T-cell stimulation and IL-2 production

OR2805 treatment also enhanced production of IL-1β, CCL4, and perforin in M2c:T-cell cocultures.

Proliferated T Cells Show Enhanced Ability to Kill Cancer Cells





Summary and Conclusions

- OR2805 was isolated from a cancer patient who achieved CR with CPI treatment
- OR2805 target is highly specific to M2 macrophages and not expressed on other hematopoietic cells nor a panel of human primary non-immune cells
- Stains positively on TAMs from human primary lung tumors
- Reduces expression of cell-surface markers associated with tumor-promoting M2c macrophages
- Relieves the suppressive effect of M2 macrophages leading to increased T cell activation and proliferation, T cell skewing towards anti-tumor Th1 phenotype
- Proliferated T cells show elevated expression of activation markers and enhanced ability to kill cancer cells
- OR2805 treatment induces robust anti-tumor activity in lung cancer xenograft models in humanized NSG-SGM3 mice

OR2805 reduces TAM-mediated immunosuppression and enhances anti-tumor immune responses and has the potential to increase the number of patients who may benefit from current CPI therapy

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