Interrogating Elite Responder humoral responses to identify novel targets and therapeutic antibodies for the treatment of cancer

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Abstract #39

Background: The development of checkpoint inhibitors (CPIs) has transformed the treatment landscape for certain cancers. However, the response rates are modest for most cancers and some cancers are not amenable to CPIs and represent a significant unmet medical need. CPIs promote anti-tumor adaptive responses by lifting the brakes off immune activation, which is known to break tolerance to self-antigens and induce autoantibody formation. A subset of these autoantibodies may mediate anti-tumor responses and enhance CPI efficacy. B cells and tertiary lymphoid structures have been shown to contribute to CPI efficacy. We have evaluated serum autoantibody profiles of cancer patients who responded well to CPI therapy and interrogated their memory B cell repertoires to identify novel targets, epitopes, biomarkers, and immunomodulatory anti-cancer antibodies.

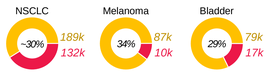
Methods: Solid tumor patients who remain on CPI therapy for at least 6 months with stable disease, or at least 3 months with a partial or complete response were designated as Elite Responders for this study. Serum samples from healthy donors and matched serum and peripheral blood mononuclear cells from Elite Responders were collected. For novel targets, epitopes, and biomarker discovery, serum samples were tested on proteome microarrays containing >21,000 unique full length human proteins. Serum samples were also probed for binding, by flow cytometry, to a panel of myeloid cells. Elite Responders with seroreactivity specific to suppressive myeloid cells were selected for B cell activations and antibody discovery using the OncoResponse platform. Myeloid-targeting antibodies were subsequently cloned, expressed and evaluated for anti-tumor activity in functional assays.

Results: Autoantibody profiling using the microarrays corroborated some targets known to have immunomodulatory activities in the TME across several cancer types, e.g., LILRB2, VSIG1, CD47, Siglec, and identified additional immune-oncology targets of interest. Some autoantigens exhibited broad serological responses across several solid tumor types, while others were specific to a cancer type. The functional importance of the Elite Responder's humoral response was demonstrated by the discovery of a myeloid-targeting antibody, OR2805, which specifically binds immunosuppressive M2 macrophages and converts them into an immunostimulatory phenotype. In M2 macrophage/T cell coculture assays, OR2805 rescues T cell activation and proliferation and amplifies anti-PD-1 activity. A phase 1-2 dose escalation-expansion study of OR2805 alone or in combination in subjects with advanced solid tumors is ongoing (NCT05094804).

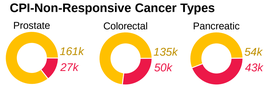
Conclusions: Interrogation of humoral responses in cancer Elite Responders is an attractive strategy for discovery of novel targets and therapeutic antibodies for the treatment of cancer.

The Immuno-Oncology opportunity

CPI-Responsive Cancer Types



CPI-Non-Responsive Cancer Types

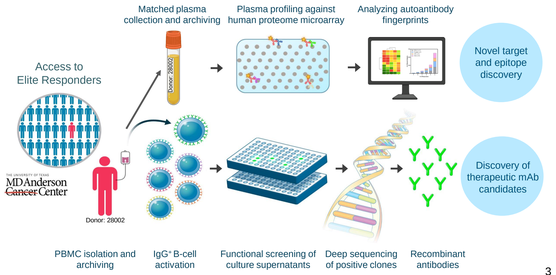


- Response to checkpoint inhibitors (CPI) continue to be low in part due to the suppressive Tumor Microenvironment (TME)
- Large unmet need to overcome immune suppression in the TME to increase response and survival
- B cell enrichment in the tumors correlates with response to CPI in melanoma, sarcoma, lung, head and neck, and kidney cancer[1-6]
- CPI can directly affect B cell responses and induce autoantibodies, including to clinically relevant immunomodulatory targets[7-10]

Cancer patients who have successfully responded to CPI (Elite Responders) may harbor antibodies that contribute to clinical response

[1]Helmink, *et al. Nature. 2020*; [2]Petitprez, *et al. Nature. 2020*; [3]Cabrita, *et al. Nature. 2020*; [4]Kim, *et al. Clin. Cancer Res. 2020*; [5]Ruffin, *et al. Nat Commun. 2021*; [6]Patil, *et al. Cancer Cell. 2022*; [7]Jinushi, *et al. PNAS. 2006*; [8]Schoenfeld, *et al. Cancer Res. 2010*; [9]Kwek, *et al. J Immunol. 2012*; [10]Kruo, *et al. Cancer Immunol Res. 2015*

OncoResponse interrogates the B cell and antibody repertoire of Elite Responders for clues to attack cancer



Advantages of our approach

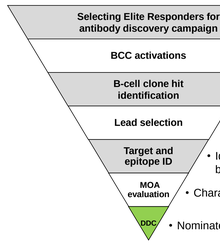
Discovery of Abs that target immune cells and relieve suppression in the TME
- Primary screen for binding to immune cells in the TME or known immunomodulatory targets
- Functional screen for immune modulation

Discovery of antibodies that directly target tumor cells
- Fc-mediated effector function (ADCC)
- Internalization for ADC development
- Direct inhibition of cancer cell growth/proliferation
- Precursor to further engineering (CAR-T, bi-specific, etc.)

Discovery of Abs for "immune excluded" and "immune desert" cancer phenotypes
- Primary screen for binding to stromal elements in cancer
- Functional screen for modulation of tumor-stromal-immune cell crosstalk

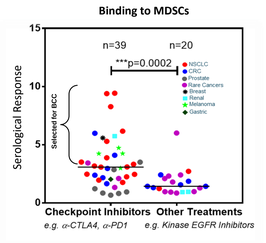
Discovery of novel targets, epitopes, and potential biomarkers
- Profiling longitudinal autoantibody responses in CPI-treated individuals
- Agnostic serology screen against human proteome
- Target and epitope ID of novel antibodies discovered from Elite Responders

TME program workflow



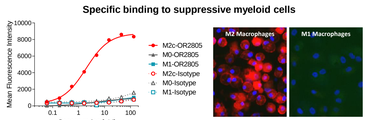
- Selected Elite Responders with serum antibodies to MDSCs for B cell culture (BCC)
- *In vitro* activation and culturing of IgG+ memory B cells
- Screening supernatants against a panel of myeloid cells; rescue antibody sequences; hit confirmation with purified mAbs
- Selected OR2805 as lead mAb based on its functional activity
- Identified CD163 as the target receptor for OR2805 and elucidated the binding epitope
- Characterized the mechanism of action of OR2805
- Nominated OR2805 for IND

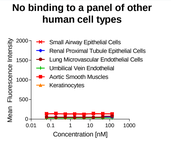
Serology screen to identify Elite Responders with antibody responses to MDSCs



- CPI-treated Elite Responders show increased serological response to MDSCs
- All patients in study had ≥ 6 months durable clinical response (CR, PR, or SD)
- MDSC seropositive patients were selected for Ab discovery
  - Target ID using protein microarrays
  - Antibody discovery using BCC

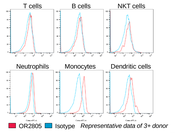
OR2805 demonstrates specific binding to immunosuppressive myeloid cells





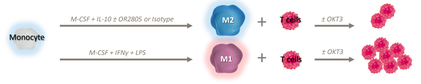
Binding to TAMs in dissociated NSCLC tumors

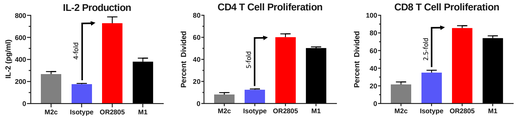
Cell surface markers	Patient 1 cells (%)	Patient 2 cells (%)
Total CD14$^+$ (monocytes)	26	30
CD163$^+$ of CD14$^+$ (M2c)	69	88
OR2805$^+$ of M2c	82	77
CD163$^-$ CD80$^+$ of CD14$^+$	20	11
OR2805$^+$ of CD163$^-$ TAMs	11	9



Representative data of 3+ donor

OR2805 treated M2c macrophages promote T-cell activation & proliferation

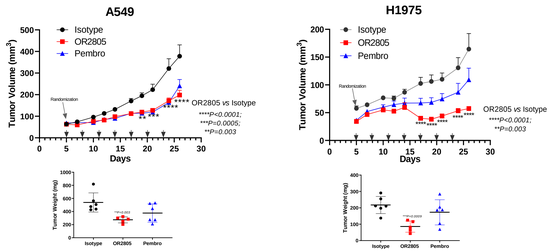




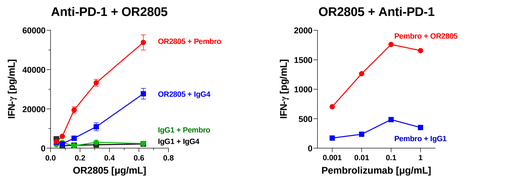
Representative data of 12+ donors

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 induces anti-tumor activity in humanized NSG-SGM3 mice



OR2805 amplifies anti-PD-1 activity in M2c/Exhausted T cell coculture assays

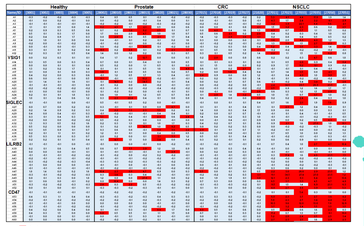


OR2805 has the potential as a single agent or in combination with CPI to increase the number of patients who may benefit from immunotherapy

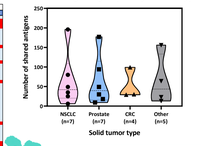
A phase 1/2 dose escalation-expansion study of OR2805 alone or in combination in subjects with advanced solid tumors is ongoing (NCT05094804)

Autoantibody profiling of Elite Responders identifies potential new targets for cancer treatment

Serum antibodies in Elite Responders (representative of >22K antigens)



Shared antigens grouped by cancer type



IgG from Elite Responders recognized known immunomodulatory targets

Some autoantigens exhibited broad serological responses across several solid tumor types

OncoResponse is building a "Seromics" database for discovery of novel targets and potential biomarkers

Summary and conclusions

- OR2805 was derived from a cancer patient who achieved complete response with CPI treatment
- OR2805 binds with high specificity to suppressive macrophages
- Relieves the suppressive effect of M2 macrophages leading to increased T cell activation and proliferation
- Demonstrates robust anti-tumor activity in lung cancer xenograft models
- Combination with OR2805 amplifies anti-PD-1 activity in coculture assays
- A phase 1/2 study of OR2805 alone or in combination in subjects with advanced solid tumors is ongoing (NCT05094804)
- Autoantibody profiling of Elite Responders identified additional immuno-oncology targets of interest

Interrogation of humoral responses in Elite Responders is an attractive strategy for discovery of novel targets and therapeutic antibodies for the treatment of cancer

Acknowledgements
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