Interrogating the human memory B cell repertoire to discover novel targets, epitopes, and therapeutic antibodies

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Tumor Myeloid-Directed Therapies Summit
June 14-16, 2022
• Considering the desirable characteristics of myeloid cell targets, and contrasting the benefits and challenges of targeting different cellular mechanisms such as cross-presentation, polarization, and pathway modulation

• Defining the cause of immune suppression by myeloid cells, identifying master regulators, and discussing which processes in a signaling pathway can be effectively targeted

• Selecting targets on myeloid subsets which are tumor-specific

• Discussing the challenges of demonstrating single agent effect on target validation, and tips to overcome these

• Sharing in vivo target validation workflows, and exploring translational and preclinical data to support target validation alongside clinical proof of myeloid targeting

• Decoding RNA signals, discussing the contributions of RNA sequencing to the field, and highlighting remaining limitations
Workshop discussion questions

• What target discovery platform(s) are you using? What has worked and what are some of the challenges?
• How are you bridging the gap between mice and patients?
• What information are you using to select patients?
• How to utilize patient data in target discovery? What datasets are critically missing for target discovery?
• The problems and opportunities of combinatorial approaches in IO
• How to convince the world to invest into clinical development of the new targets?
• Advantages and pitfalls of narrow and broad applicability
The Immuno-Oncology opportunity

**CPI-Responsive Cancer Types**

- NSCLC: ~30%
  - 189k new cases
  - 132k deaths
- Melanoma: 34%
  - 87k new cases
  - 10k deaths
- Bladder: 29%
  - 79k new cases
  - 17k deaths
- Kidney: ~32%
  - 64k new cases
  - 14k deaths
- H&N: 17%
  - 52k new cases
  - 10k deaths
- Liver/BD: 17%
  - 62k new cases
  - 29k deaths

**CPI-Non-Responsive Cancer Types**

- Prostate: 161k new cases
  - 27k deaths
- Colorectal: 135k new cases
  - 50k deaths
- Pancreatic: 54k new cases
  - 43k deaths

- 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
Our Mission

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

The humoral immune response toward autologous antigens in cancer patients

- **De novo autoantibodies in cancer patients**
  - Defects in tolerance and inflammation
    - Downregulation of regulatory T cells
    - Clonal selection defects
  - Changes in protein expression levels
    - Overexpression of the corresponding antigen
    - Aberrant expression site of the corresponding antigen
  - Altered protein structure
    - Neoepitope exposure
    - Mutations
    - Post-translational modifications
  - Cellular death
    - Presentation of self-antigen peptides on cell surface
    - Tumor-associated antigens spillage into circulation

- **Preexisting antibodies due to autoimmune disorders**

Leveraging Elite Responders to checkpoint inhibitors

Opportunity to discover novel targets, novel epitopes, and potential biomarkers

• Interrogation of humoral responses in Elite Responders to checkpoint inhibitors
  • Generalized immunorestorative activities of CPI
  • CPI directly affect B cell responses and induce autoantibody production
  • Develop enhanced antibody response to more antigens than non-responders
  • Show presence of antibodies to clinically relevant targets

The OncoResponse platform interrogates the entire B-cell repertoire

- Access to Elite Responders
- Identify functional Abs inaccessible to other Ab discovery platforms
- Develop therapeutic mAb candidates

1. Blood/PBMC Collection “Archive of immunological history”
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
### Hallmarks of OncoResponse human antibody discovery platform

<table>
<thead>
<tr>
<th>Core Technology</th>
<th>Unparalleled Flexibility</th>
<th>Broad Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prolonged B cell viability</td>
<td>• Multiple screening paradigms for rapid discovery of functional antibodies</td>
<td>• Oncology, immuno-oncology, infectious diseases, autoimmunity, fibrotic disorders</td>
</tr>
<tr>
<td>• Robust proliferation and differentiation into plasmablasts</td>
<td>• Target-dependent and target-agnostic functional phenotypic screens</td>
<td>• Immune-excluded and immune-desert phenotypes that generally don’t respond to CPI</td>
</tr>
<tr>
<td>• Shedding of antibodies in culture supernatants</td>
<td>• Both dominant and rare antibodies to known or novel epitopes</td>
<td>• Superior to other platforms which focus on dominant clonal families and lack function-based screening</td>
</tr>
</tbody>
</table>

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OncoResponse human antibody discovery platform

A unique opportunity to discover novel targets, epitopes, and potential biomarkers

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

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

• **Discovery of Abs to target “immune excluded” and “immune desert” cancer phenotypes**
  • Primary screen of binding to stromal cells or cancer-associated fibroblast (CAF) subtypes
  • Functional screen for modulation of tumor-CAF-immune cell crosstalk
Example Case Study #1

Discovery of OR2805 to relieve immunosuppression caused by TAMs
(Target agnostic cell-based functional phenotypic screen)
Rationale for targeting tumor associated macrophages (TAMs)

- M2 TAMs create a highly **immunosuppressive** environment promoting tumor growth
- TAMs are central to treatment resistance
  - Presence of M2 macrophages correlates with **poor patient prognosis**
  - 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
- Emerging clinical data support targeting TAMs for anti-cancer therapy

**Tumor tissue MDSCs correlate with outcomes**

**Survival benefit with anti-CTLA-4**

Elite Responders show autoantibody responses to immunosuppressive TAMs

- CPI-treated Elite Responders show increased serology response to mMDSCs
- All patients in study had ≥ 6 months durable clinical response (CR, PR, or SD)
- mMDSC seropositive patients were selected for Ab discovery
  - Target ID using protein microarrays
  - Antibody discovery using BCC
TAM-targeting antibody discovery program workflow

- Selected Elite Responders with serum antibodies to mMDSCs for B-cell activations (BCC)
- Tested BCC supernatants and selected B-cell wells for cloning based on myeloid panel binding profiles
- Identified & assembled VH and VL chains for mAb expression and hit confirmation using purified mAbs
- Selected OR2805 as lead mAb based on activity in various functional assays
- Identified the target, elucidated the binding epitope and characterized the mechanism of action
- Nominated OR2805 for IND

Serology to identify Elite Responders with antibodies to mMDSCs

BCC activations

B-cell clone hit identification
Screen supernatants in myeloid cell panel binding and counter-screen

Lead selection
Rescue and scale-up antibodies Evaluate in functional assays

Target and epitope ID and confirmation

MOA evaluation, In vivo evaluation

DDC
OR2805 relieves immunosuppression caused by myeloid cells in the TME

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\(^8-11\)

CD163 is a negative prognostic marker in cancer

**Gastric Cancer**
Overall survival

**Breast Cancer**
Survival probability

**Head and Neck Cancer**
Overall survival

**Colorectal Cancer**
Overall survival

**Melanoma patients on anti-PD-1 therapy**

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1. Oncotarget 2017;8:87244
3. Br J Cancer 2014;111:1509
OR2805 demonstrates specific binding to immunosuppressive myeloid cells

Specific binding to human immunosuppressive myeloid cells

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

Specific binding to human immunosuppressive myeloid cells

No binding to a panel of human cell types

Binding to TAMs in dissociated NSCLC tumors

<table>
<thead>
<tr>
<th>Cell surface markers</th>
<th>Patient 1 cells (%)</th>
<th>Patient 2 cells (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CD14+ (monocytes)</td>
<td>26</td>
<td>30</td>
</tr>
<tr>
<td>CD163+ of CD14+ (M2c)</td>
<td>69</td>
<td>88</td>
</tr>
<tr>
<td><strong>OR2805+ of M2c</strong></td>
<td><strong>82</strong></td>
<td><strong>77</strong></td>
</tr>
<tr>
<td>CD163-CD80+ of CD14+</td>
<td>20</td>
<td>11</td>
</tr>
<tr>
<td>OR2805+ of CD163- TAMs</td>
<td>11</td>
<td>9</td>
</tr>
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</table>
OR2805 treated M2c macrophages promote T-cell activation & proliferation

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

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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

Representative data of 12+ donors
OR2805-treated M2c macrophages skew T cells to activated Th1 phenotype

- CXCR3 expression promotes CD8$^+$ infiltration
- IFNγ enhances CXCR3-mediated T-cell recruitment
- CXCR3-expressing CD8$^+$ T cells show enhanced anti-tumor cytotoxicity

OR2805-treated macrophages promote T-cell activation leading to greater expression of T-cell activation markers (CD69, ICOS, OX40)
OR2805 induces anti-tumor activity in humanized NSG-SGM3 mice

**A549**

- **Isotype**
- **OR2805**
- **Pembro**

Randomization

**H1975**

- **Isotype**
- **OR2805**
- **Pembro**

Randomization

**Pembro** vs **OR2805**

**P<0.0001;**

**P=0.003**

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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 M2 TAMs
- 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
- Combination with OR2805 amplifies anti-PD-1 activity 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
Example Case Study #2

Targeting Leukocyte Immunoglobulin-Like Receptor B2 (LILRB2/ILT4)–HLA-G binding to reverse immunosuppression in cancer
Serum analysis identified potential targets for cancer treatment

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

<table>
<thead>
<tr>
<th>Name/ID</th>
<th>Healthy</th>
<th>NSCLC</th>
<th>Prostate</th>
<th>CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>JHU04098.P043G05</td>
<td>0.8</td>
<td>0.6</td>
<td>0.9</td>
<td>0.6</td>
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<tr>
<td>JHU04198.P043G05</td>
<td>0.6</td>
<td>0.4</td>
<td>0.9</td>
<td>0.6</td>
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<tr>
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<td>0.4</td>
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<td>JHU04498.P043G05</td>
<td>0.8</td>
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</tr>
<tr>
<td>JHU04598.P043G05</td>
<td>0.6</td>
<td>0.4</td>
<td>0.9</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Shared antigens grouped by cancer type

<table>
<thead>
<tr>
<th>Solid tumor type</th>
<th>NSCLC (n=7)</th>
<th>Prostate (n=7)</th>
<th>CRC (n=4)</th>
<th>Other (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD47</td>
<td>0.1</td>
<td>0.2</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Siglec</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>LIR82</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

- IgG from Elite Responders recognized targets involved in immunosuppression
- OncoResponse is building a “SeroCim” database for discovery of novel targets, epitopes, and potential biomarkers
LILRB2 antagonism reprograms TAMs and promotes anti-tumor immunity
OncoResponse antibody enhances CD8⁺ T cell proliferation and IFNγ production in M2c/T cell coculture assay

**M2c/CD8⁺ T cell coculture**

<table>
<thead>
<tr>
<th></th>
<th>IFNγ [pg/mL]</th>
<th>T cell count</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR3289</td>
<td>5 μg/mL</td>
<td>10 μg/mL</td>
</tr>
<tr>
<td>MK-4830</td>
<td>5 μg/mL</td>
<td>10 μg/mL</td>
</tr>
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</table>

**M2c/Exhausted T cell coculture**

<table>
<thead>
<tr>
<th></th>
<th>IFNγ [pg/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2c</td>
<td>2.5 μg/mL</td>
</tr>
<tr>
<td>Isotype</td>
<td></td>
</tr>
<tr>
<td>OR3289</td>
<td>5 μg/mL</td>
</tr>
<tr>
<td>MK-4830</td>
<td>10 μg/mL</td>
</tr>
</tbody>
</table>

OncoResponse antibody OR3289 outperforms MK-4830 in M2/T cell coculture assay
OncoResponse antibody induces anti-tumor response in SK-MEL-5 tumor model in humanized NSG-SGM3 mice

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

### Tumor Growth Inhibition (%) and Regression (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>d28</th>
<th>d30</th>
<th>d33</th>
<th>d35</th>
<th>d37</th>
<th>d41</th>
<th>d41</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR3289 (OncoResponse)</td>
<td>47</td>
<td>57</td>
<td>69</td>
<td>74</td>
<td>78</td>
<td>79</td>
<td>33</td>
</tr>
<tr>
<td>MK-4830 (Merck)</td>
<td>-5</td>
<td>3</td>
<td>16</td>
<td>17</td>
<td>24</td>
<td>26</td>
<td>11</td>
</tr>
</tbody>
</table>
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