Bispecific MIF - D-DT Targeting to Enhance Immunotherapy Responses

Thuy Tran, MD, PhD
Assistant Professor in Internal Medicine (Medical Oncology)
Yale Smilow Cancer Center

Richard Bucala, MD, PhD
Waldemar Von Zedtwitz Professor of Medicine
Chief, Yale Rheumatology, Allergy & Immunology

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The Yale MIF Team and Its Mission

Dr. Thuy Tran, MD, PhD
- Assistant Professor, Yale Cancer Center
- Member of the melanoma disease aligned research team
- Principal investigator in multiple commercial melanoma clinical trials and IITs
- Research lead in developing MIF/D-DT preclinical studies in melanoma
- Funded by the Yale SPORE in Skin Cancer
- Mentored by Drs. Richard Bucala, Mario Sznol, and Harriet Kluger

Dr. Richard Bucala, MD, PhD
- The first to clone and characterize MIF
- Developed the clinical anti-MIF (Imalumab)
- Waldemar Von Zedtwitz Professor of Medicine
- Professor of Medicine, Pathology, and Epidemiology & Public Health
- Chief, Section of Rheumatology, Allergy & Immunology

Dr. David Lewin, PhD
- Director of Business Development
Targeting both MIF and D-DT (MIF-2) Is Critical for Pathway Inhibition

- Prior anti-MIF trials have shown partial responses but demonstrated tolerability and safety
- CD74 is not an ideal target (T cell immunity and correlates with improved outcomes)
- No prior clinical attempt at D-DT targeting
- **Rationale for a bispecific**
  - Avoid protein aggregation issues seen with imalumab
  - More efficient than developing two monospecific drugs
  - Increases depletion of both targets with high affinity and enrichment within the tumor
High Levels of MIF Result in Worse Cancer Outcomes

- MIF and D-DT signaling causes immune suppression and tumor evasion
- Higher MIF levels are associated with poorer survival, worse disease responses and resistance to immune therapy in melanoma

MIF and D-DT in Oncology

Serum Protein

R = 0.91
p = 0.0001

Tumor mRNA

R = 0.52
p = 1.8e-10

Yale Melanoma Patients Treated with Immune Therapy

CD74:MIF

- Proportion of Relapse
- Proportion of Survival

CD74:D-DT

- Proportion of Relapse
- Proportion of Survival

High
Low

p = 0.029
p = 0.17

p = 0.016
p = 0.016
MIF and D-DT Targeting Enhances Immune Response

- Dual MIF - D-DT inhibition led to superior anti-cancer responses
  - Inhibition resulted in increased tumor infiltration of cDC1 and CD8 T cells along with Th1 cytokines and macrophage activation

- Novel, complementary checkpoint targeting

- Tumor agnostic immune response

- Numerous *in vitro* and *in vivo* assets developed for preclinical testing

- Intellectual property: specific and selective anti-MIF and anti-D-DT monoclonal antibodies
Melanoma Immune Therapy Remains Limited

- Large potential market – total revenue $60 billion in 2021
- Many agents are **redundant**
- **Limited responses to existing immune therapies**; best response ~58%
- No standard options after failure of ipilimumab/nivolumab
- Current need to overcome immune resistance

**Bispecific MIF – D-DT targeting could be a leap forward**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>FDA-Approval</th>
<th>Mechanism</th>
<th>Objective response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>2011</td>
<td>anti-CTLA-4</td>
<td>19%</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2014</td>
<td>anti-PD-1</td>
<td>34.2-40.1%</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>2014</td>
<td>anti-PD-1</td>
<td>32-45%</td>
</tr>
<tr>
<td>Ipilimumab/nivolumab</td>
<td>2015</td>
<td>anti-CTLA-4 anti-PD-1</td>
<td>57.6%</td>
</tr>
<tr>
<td>Nivolumab/relatlimab</td>
<td>2022</td>
<td>anti-PD-1 Anti-LAG-3</td>
<td>43.1%</td>
</tr>
</tbody>
</table>
Use of Funding to Engineer a Clinical Candidate

*In vivo* validated, high affinity CDRs in hand reactive to human and mouse MIF and D-DT

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
<th>Pre-clinical Validation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cloning &amp; Validation</td>
<td>In Silico Ab Design</td>
<td>Generation of mAb Variants</td>
<td>Stable Cell Line Development</td>
<td>in vitro and in vivo testing, PK, PD, and safety assessment</td>
</tr>
</tbody>
</table>

Collaboration with antibody engineering experts

Bucala Lab & CRO

External Funding

External Funding

$8,000 $10,000 $12,000

Total Cost: $30,000