**Abstract**

The recognition of tumors by the immune system has long been appreciated and the presence of tumor associated lymphocytes that have evaded immune clearance is now well described. However, despite evidence of immune reactivity, tumors are still able to grow suggesting a sub-optimal response. Fragmented evidence of immune cell activity in tumors consistent with an immune checkpoint receptor expressed by T cells has been noted. Tumor associated lymphocytes express immune checkpoint receptors such as Tim-3, Lag-3, PD-1 and PD-L1 which interact in a complex network of receptor-ligand interactions. The functional antagonist of these receptor-ligand interactions, TSR-042, is a potent anti-PD-1 antibody with pre-clinical activity of TSR-042 to augment immune responses of primary human CD4+ T cells. TSR-042 was found to enhance the effect of both anti-TIM-3 and anti-LAG-3 agents (Figure 6). In this system, TSR-042 was well tolerated and displayed a profile that supported assessment of the compound in Phase 1 clinical trials.

**Introduction**

PD-1 is one of several checkpoint receptors that have been implicated in T cell exhaustion and limiting the activity of T cells in tumors. Blocking the PD-1 pathway has yielded promising results with the introduction of several agents. TSR-042 is an anti-PD-1 immunoglobulin G4 (IgG4) humanized monoclonal antibody (mAb) generated under TRUMP (Tesarobio) technology that binds with high affinity to PD-1 and is currently in clinical testing.

**Material and Methods**

Table 1: Binding of TSR-042 to human PD1 receptor

<table>
<thead>
<tr>
<th>Species</th>
<th>Kassoc (Ms)</th>
<th>Kdissoc (s-1)</th>
<th>KD (nM)</th>
<th>EC50 (nM)</th>
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<tbody>
<tr>
<td>Human</td>
<td>1.4 x 10^-6</td>
<td>0.06</td>
<td>0.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Cynomolgus</td>
<td>1.9 x 10^-6</td>
<td>0.9</td>
<td>1.3</td>
<td>0.75</td>
</tr>
</tbody>
</table>

**Figures**

**Figure 1. Blocking the PD-1 pathway**

**Figure 2. TSR-042 binds to native PD-1 on PBMCs**

**Figure 3. Receptor-ligand competition**

**Figure 4. Mixed Lymphocyte Reaction**

**Figure 5. huNOG-EXL Mouse Model**

**Figure 6. Combination Mixed Lymphocyte Reaction**

**Figure 7. TSR-042 exhibits anti-tumor activity in a humanized tumor xenograft model**

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