Targeted Therapy for T-cell Lymphomas

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Physiological and Pathologic Roles of CXCR5: A Therapeutic Target for Angioimmunoblastic T cell Lymphoma (AITL)

- AITL is a rare T cell lymphoma, 3000 cases per year
- **Median survival** 50% at 2 years, 30% at 5 yr
- All AITL cells secrete CXCL13 and express CXCR5 receptor
- Microenvironment has increased secretion of CXCL13
- Cutaneous T cell lymphoma (CTCL) patients may also express CXCR5 on the malignant cells and expression is associated with a worse outcome

Moser, Front. Immunol., 2015
Proof-of-Principal for CXCR5 Small Molecule Antagonism at Nanomolar Concentrations

Inhibition of Gαq-mediated Ca²⁺ flux at an EC₈₀ of CXCL13

<table>
<thead>
<tr>
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<th>Compound A+EC80</th>
<th>Compound B+EC80</th>
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<tbody>
<tr>
<td>Log IC₅₀</td>
<td>-6.779</td>
<td>-6.969</td>
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<tr>
<td>HillSlope</td>
<td>-1.356</td>
<td>-1.492</td>
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<tr>
<td>IC₅₀</td>
<td>1.664e-007</td>
<td>1.075e-007</td>
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**In Vivo** Proof-of- Principle in a Human AITL PDX Mouse Model

- NSG (NOD/SCID, IL-2R knockout) mice
- Patient-derived AITL tissue with CXCR5 at 50% of other patients
- Oral gavage 2x/day with vehicle or 40 mg/kg Compound A

**% Human CD45 in Bone Marrow**

<table>
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<tr>
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<th>% hCD45 in BM</th>
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<tr>
<td>Vehicle</td>
<td>20.0±1.4</td>
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<tr>
<td>Compound A</td>
<td>15.8±1.2</td>
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\[**p=0.0017\]

**% Human CD45 in Peripheral Blood**

<table>
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\[**p=0.0013\]

**Unpaired t test**

- P value
  - 0.0017
- P value summary
  - **
- Significantly different (P < 0.05)?
  - Yes
- One- or two-tailed P value?
  - Two-tailed
- t, df
  - t=3.882 df=14

- P value
  - 0.0013
- P value summary
  - **
- Significantly different (P < 0.05)?
  - Yes
- One- or two-tailed P value?
  - Two-tailed
- t, df
  - t=4.016 df=14
Phage Display Screen for Biotherapeutics and CAR T

- Phage display library of 168,000 CXCL13 variants used to screen for five rounds to identify potent variant CXCL13 antagonists.

- NGS and bioinformatics to determine 102 sequences likely to represent most potent sequences.

Target prevalence and enrichment factor of 24 (of 102) redacted sequences

<table>
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<tr>
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<th>Target prevalence</th>
<th>Enrichment factor</th>
<th>Translation</th>
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Business landscape

• Market
  – Rare disease, orphan status for AITL

• Competition
  – Several approved agents for T cell lymphoma, all with low response rates and short progression free survival, remains unmet medical need

• Unique aspects of this product
  – Targeting chemokine/chemokine receptor pathways for treatment of AITL using a library of CXCR13 ligands for:
    • A biotherapeutic
    • Chimeric Antigen Receptor targeting
Next Steps for Mutant CXCL13 Variants

• Express, purify, characterize 102 CXCL13 variants
  – Assay for Ca$^{2+}$ flux to test CXCL13 variants and confirm antagonism
  – Characterize IC$_{50}$ and $k_{off}$ rate
• Molecular biology of the most potent CXCL13 antagonist-IgG1.
  – Expression, purify, and characterize therapeutic properties (IC$_{50}$, PK, ADCC)
• Molecular biology for CAR T
  – In vitro testing for efficacy
• Test biotherapeutic and CAR T in AITL-PDX model?