Discovery of Highly Selective Small Molecule Oral Inhibitors of Integrin $\alpha_4\beta_7$ for the Treatment of Inflammatory Bowel Diseases

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Disclosures

• Jamie Wong is a paid employee and shareholder of Morphic Therapeutic.
Inhibition of $\alpha_4\beta_7$ is a clinically validated mechanism for IBD

Data from VARSITY Trial (Sands et al. NEJM 2019)

- Vedolizumab inhibits immune cells that adhere to MAdCAM-1 positive endothelial surfaces in GI tract
- Vedolizumab is an effective and safe agent (150,000+ patients since approval in 2014; no PML)
- “Oral vedolizumab”, if approved, could become a preferred backbone for chronic therapy in IBD
MORF-057 demonstrates high selectivity for $\alpha_4\beta_7$

- MORF-057 has more than 41,600-fold selectivity for $\alpha_4\beta_7$ over $\alpha_4\beta_1$ in cell adhesion assays in 50% human serum

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>$\alpha_4\beta_7$ IC$_{50}$ *</th>
<th>$\alpha_4\beta_1$ IC$_{50}$ *</th>
<th>Fold selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MORF-057</td>
<td>1.2 nM</td>
<td>&gt;50 µM</td>
<td>&gt;41,600</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>0.15 nM</td>
<td>1.8 nM</td>
<td>12</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>0.059 nM</td>
<td>&gt;180 nM</td>
<td>&gt;3,060</td>
</tr>
<tr>
<td>BIO 5192</td>
<td>&gt;50 µM</td>
<td>0.65 nM</td>
<td>&lt;1.3x10$^{-5}$</td>
</tr>
</tbody>
</table>

- MORF-057 has high selectivity against other integrins in fluorescence polarization assays with purified proteins.

*RPMI8866 and Jurkat cell lines used for $\alpha_4\beta_7$ and $\alpha_4\beta_1$, respectively*
MORF-057 inhibits gut homing leukocytes in mice

- Treatment with MORF-057 blocks gut homing of $\alpha_4\beta_7^+$ cells in mice
- MORF-057 achieves inhibition of gut trafficking equivalent to antibody treatment
Orally dosed MORF-057 blocks memory T cell trafficking in Cynomologus Monkeys

- Oral treatment with MORF-057 causes sustained increases in $\alpha_4\beta_7^{hi}$ memory cells in blood reflecting blockage of gut homing in monkeys

15mpk, 5 days; N=5
Conclusions

- Vedolizumab is a safe and effective therapy for Ulcerative Colitis but an oral therapy would be advantageous
- MORF-057 is a potent, selective, and orally bioavailable small molecule inhibitor of $\alpha_4\beta_7$
- MORF-057 inhibits gut homing in mouse and increases systemic $\alpha_4\beta_7^{hi}$ cells in monkeys
- Potential IND mid-2020

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