Treatment of Ulcerative Colitis With AMT-101, A Novel Oral Interleukin-10 Immunomodulatory Fusion Biologic That Traffics Across Intestinal Epithelium

Randall Mrsny, CSO
Applied Molecular Transport
South San Francisco, CA USA
Interleukin-10 is a well-established modulator of intestinal immune homeostasis

- Deficiencies in IL-10 signaling correlate to early onset of colitis in humans\(^1\)
- Numerous pre-clinical models support the potential of systemic IL-10 to resolve intestinal inflammation\(^1\)
- Clinical studies with systemically-administered rhIL-10 exhibited clinical improvement but were dose-limited by anemia and thrombocytopenia\(^2\)

Oral GI-selective IL-10 may improve efficacy and limit systemic exposure-related side effects

AMT-101: an oral human IL-10 fusion protein

- Genetic fusion of cytokine IL-10 with epithelial trafficking sequences of Cholix (Chx)
- Chx derived from *Vibrio cholerae* secreted protein
- Chx enables active transport of IL-10 to the lamina propria
In vivo uptake of Chx fusion proteins to the lamina propria occurs rapidly

Fusion Protein Interacts at Epithelial Surface

Rapidly Translocates Across GI Epithelium

Localizes in Submucosa

T=0

T=10 min

T=20+ min

Red: Chx-RFP fusion protein
Blue: cell nuclei
AMT-101 transports across intestinal epithelium and induces STAT3 activation

IL-10 Concentration (nM)

- PBS
- IL-10
- AMT-101

<table>
<thead>
<tr>
<th>Region</th>
<th>PBS</th>
<th>IL-10</th>
<th>AMT-101</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal Colon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle Colon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal Colon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Murine CD4⁺ CD45RB<sup>high</sup> transfer model

Murine IL-10 knockout model
AMT-101 prevents oxazolone-induced colitis in mice

Oxazolone chronic mouse model of ulcerative colitis. Treated via oral gavage.
AMT-101 limits oxazolone-induced systemic cytokines

Efficacy: Oral AMT-101 treatment improves colonic histopathology in vivo – similar to...
Colonic exposure of AMT-101 in NHP induces proximal and systemic pharmacodynamic effects

IL-1 Receptor Antagonist (IL-1Ra)

Inhibition of IL-1β signaling

↓ proinflammatory genes & co-stimulatory molecules

↑ anti-inflammatory genes

IL-1Ra

NFκB

Colonic STAT3 activation

Systemic IL-1Ra

Figure adapted from Schulke, S. (2018). Front Immunol 9: 455
Oral AMT-101 generates robust systemic PD response (IL-1Ra) with minimal systemic PK in NHPs.
AMT-101: a once daily oral human IL-10 fusion protein

Demonstrates efficacy in pre-clinical models of colitis and has advanced to the clinic

AMT-101

• GI selectivity should lead to improved safety
• Has the potential for standalone as well as combination therapy
• Systemic response creates potential to address extra-intestinal inflammation
• Has completed Phase 1a study in healthy subjects

Next Steps:
• Complete Phase 1b study in UC patients (1H 2020)
• Initiate Phase 2 clinical studies in 2020

©ECCO'20 Vienna Congress - Speaker: Randy Mrsny