Melanocortin-1 (MC1) Receptor Agonists for Irritable Bowel Disease (IBD)

- MC1 receptor agonism is an endogenous mechanism that downregulates inflammatory/immune responses.
- MC1 receptors are upregulated in IBD and expressed on the cell surface of intestinal epithelia.
- Alpha-melanocortin stimulating hormone (α-MSH) is an endogenous agonist of 4 of the 5 melanocortin receptors (MC1, MC3, MC4, and MC5), and was shown in numerous animal models to prevent and reverse intestinal inflammation.
- The MC1 receptor has the highest affinity for α-MSH.
- However, it is difficult to determine which specific melanocortin receptor is responsible for the effects of α-MSH on intestinal inflammation.
- Experimental studies were conducted to determine whether PL-8177, a highly selective MC1 receptor agonist, demonstrates actions and efficacy similar to those of α-MSH in preventing and reversing intestinal inflammation.

Table 1. In Vitro Selectivity of PL-8177 Compared With Endogenous MC1 Receptor Agonists

<table>
<thead>
<tr>
<th>Compound</th>
<th>Functional-CEREP (EC50, nM)</th>
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<tbody>
<tr>
<td>α-MSH</td>
<td>4.47 &gt;10,000 9.8 10.8 560</td>
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<tr>
<td>ACTH</td>
<td>980 4.8 390 350 4100</td>
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<tr>
<td>PL-8177</td>
<td>0.57 &gt;10,000 &gt;10,000 510 &gt;10,000</td>
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ACTH: adrenocorticotropic hormone; α-MSH: alpha-melanocortin stimulating hormone; MC1: melanocortin-1.

PL-8177: Preclinical Proof of Principle Overview

- A series of studies with PL-8177 were conducted to assess/establish:
  - In vitro activity and safety profile
  - Preclinical proof of principle/method of mechanism data
  - Formulation assessments to allow oral dosing

In Vitro Activity and Safety Data

- PL-8177 demonstrated similar inhibition of lipopolysaccharide-induced tumor necrosis factor alpha inhibition compared with the endogenous MC1 receptor agonists α-MSH and adrenocorticotropic hormone (Figure 1).
- In a Eurofins lead profile (© Eurofins Scientific 2018), no activity in any of 72 in vitro assays at 10 µM was detected; highlights included no activities in:
  - Cytosyme P450 enzymes 1A2, 2C19, 2C9, 2D6, and 3A4
  - Potassium channel hERG
  - Any of 7 adrenergic receptor subtypes
  - Any remaining assays included in the panel

Proof of Principle Data

- PL-8177 was evaluated in a cannulated rat model of bowel inflammation.
  - Dinitrobenzene sulfonic acid (DNBS) was administered rectally as a solution in male, 200g Wistar rats to induce inflammation of the bowel lumen.
  - The rats were implanted with a catheter in the proximal part of the ascending colon, which exited out the nape of the neck for dosing access.
  - In groups of 10, the rats were dosed at: 0.5 µg and 5.0 µg PL-8177 and vehicle (sterile water) via intracolonic injection at 24 h, 12 h, and 2 h before and 6 h after DNBS challenge, followed by twice-daily dosing for 5 consecutive days through day 7.
  - Non-cannulated control rats were administered sulfasalazine (positive controls), and vehicle (untreated controls)

Conclusions

- PL-8177 is a highly selective MC1 receptor agonist with in vitro actions similar to those of endogenous MC1 receptor agonists such as α-MSH and ACTH.
- In a cannulated rat model of DNBS-induced bowel inflammation, PL-8177 administered via catheter reduced inflammation and colon weight scores to a similar degree as sulfasalazine.
- An orally administered capsule formulation of PL-8177, released in the colon, also improved inflammation scores in rats with DNBS-induced bowel inflammation, without systemic exposure.
- Based on these data, a per-oral colon release formulation of PL-8177 will be developed for clinical evaluation.

Disclosures

Carl Spana, Marie Mahklina, Wei Yang, and John Dodd are employees of Palatin Technologies, Inc.

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References