Introduction

Biological Role of Melanocortin-1 (MC1) Receptor Agonists

• MC1 receptor agonism is an endogenous mechanism that downregulates inflammatory immune responses

• MC1 receptor antagonists are upregulated in inflammatory bowel disease (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, and melanocortin-3, -4, and -5), and was shown in numerous animal models to prevent and reverse intestinal inflammation

• α-MSH is also constitutively expressed in the healthy eye, stimulates regulatory actions, and has been shown to suppress experimental uveitis (uveitis)

• The MC1 receptor has the highest affinity for α-MSH

• PL-8177 and PL-8331 (Palatin Technologies, Inc.) are potent MC1 receptor agonists that demonstrate binding characteristics similar to those of α-MSH

Table 1. In Vitro MC1 Receptor Activity of Endogenous Melanocortins and Palatin (PL) MC1 Receptor Agonists

<table>
<thead>
<tr>
<th>Action</th>
<th>Melanocyte Stimulating Hormone (α-MSH)</th>
<th>ACTH</th>
<th>PL-8177</th>
<th>PL-8331</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC50 (nM) binding affinity</td>
<td>0.095</td>
<td>4.0</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>IC50 (nM) functional activity</td>
<td>0.22</td>
<td>980</td>
<td>0.39</td>
<td>0.033</td>
</tr>
</tbody>
</table>

[Note: IC50 values are included.]

Objectives

• A series of preclinical studies was conducted to determine whether PL-8177 and PL-8331 exhibit actions and efficacy similar to those of α-MSH in preventing and reversing intestinal and ocular inflammation

Studies Overview

• PL-8177 and PL-8331 — MC1 receptor lead profile in vitro assays

• PL-8177 — Experimental IBD

• MC1 receptor in vitro activity

• Preclinical in vivo proof of principle

• Experimental (murine) autoimmune uveitis (EAU)

• EAU scores by fundus examination

• Confoirametric Histology

• PL-8331 — Experimental (murine) dry eye

• Corneal fluorescein score

Studies/Results

PL-8177 and PL-8331 In Vitro Assays

• In a Eurofins lead profile (Eurofins Scientific 2018), PL-8177 and PL-8331 demonstrated no activity in any of 72 in vitro assays at 10 μM

• PL-8177 and PL-8331 exhibit actions and efficacy similar to those of α-MSH in reducing parameters of bowel inflammation (colonic weight and inflammation scores)

• In the DBN rat model of bowel inflammation, PL-8177 was as active as α-MSH (standard of care), and superior to untreated controls, in reducing parameters of bowel inflammation (colonic weight and inflammation scores)

• In comparison with healthy retina from non-EAU mice, retinas of untreated EAU mice featured (Figure 4)

• Cellular infiltrate, uneven nuclear layers with folding, and loss of the outer limiting membrane

• Missing retinal intervening plexiform layer between the inner and outer nuclear layers

• Thinner photoreceptor layer, suggesting photoreceptor dropout

• Vasculitis of central retinal vessels

• In contrast to retinas of untreated EAU mice, retinas of PL-8177-treated EAU mice showed (Figure 4)

• Retention of even layers of retina with little evidence of photoreceptor loss

• Some retention of outer limiting membrane

• Clear outer plexiform layer between the inner and outer nuclear layers

• No evidence of vasculitis

Figure 4. Histology of Retinas From Healthy Mice, EAU Mice Treated With PL-8177, and Untreated EAU Mice

Conclusions

PL-8177 and PL-8331 are potent MC1 receptor agonists with in vitro actions similar to those of endogenous MC1 receptors α-MSH and ACTH

• In a rat model of bowel inflammation, PL-8177 administered via catheter reduced inflammation and colonic weight scores to a similar degree as α-MSH

• In a mouse model of autoimmune uveitis, PL-8177 administered via intraperitoneal injection significantly reduced retinal inflammation versus untreated controls, and to a similar degree as α-MSH

• Based on these data, PL-8177 appears to have anti-inflammatory actions across body systems, similar to those observed with α-MSH

• PL-8331 demonstrated reduction (significant at dose of 1×10–5 mg·mL–1) in corneal epithelial damage due to dry eye, and efficacy similar to Restasis®

Disclosures

• Andrew Taylor conducted the PL-8177 uveitis study supported by a sponsored research agreement between Palatin Technologies, Inc., and the study site (the University of California, San Francisco). Wei Yang, John Doddi are employees of Palatin Technologies, Inc. David Weigelt hasnothing to disclose.

References


Mountjoy KG. The human melanocyte stimulating hormone receptor has evolved to become super-sensitive to melanocortin peptides. Mol Cell Endocrinol. 1994;101:97-111.