Inflammatory eye diseases such as non-infectious posterior uveitis and dry eye syndrome can be debilitating and in severe cases lead to visual impairment.

Corticosteroids (CS) are one of the primary treatment options for these patients however long-term CS use is limited by ocular side effects of cataract and intrageneric glaucoma.

NSKIs have been developed to target p38-α, Src and Syk, key kinases involved in signalling cascades of innate and adaptive immunity.

Here, NSK TOP1106 is compared to CS in primary retinal epithelial cells and an acute in vivo model of eye inflammation.

**In Vitro Results**

- TOP1106 is a potent inhibitor of p38-α, Src and Syk kinases, key kinases involved in inflammatory signalling cascades (Table 1).

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>IC50 (nM)</th>
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<tbody>
<tr>
<td>p38-α</td>
<td>61</td>
</tr>
<tr>
<td>Src</td>
<td>10</td>
</tr>
<tr>
<td>Syk</td>
<td>17</td>
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- TOP1106 potently inhibits pro-inflammatory cytokine release from cells of the innate (LPS stimulated PBMCs and primary macrophages) and the adaptive (α-CD3/CD28 stimulated CD4⁺ T lymphocytes) immune response (Figure 1).

- TOP1106 achieves marked inhibition of pro-inflammatory cytokines from primary RPE cells and is superior to CS (Figure 2).

- TOP1106 is a potent NSKI, which inhibits key kinases involved in inflammatory signalling cascades, leading to broad anti-inflammatory effects across cells of both the innate and adaptive immune response as well as primary RPE cells.

- This study highlights the potential of NSKIs as a novel treatment option for inflammatory eye disease.

**In Vivo Results**

- TOP1106 is superior to dexamethasone in the EIU model.

**Methods**

- Inhibitory effects on recombinant p38-α, Src and Syk kinases were assessed in an ATP dependent ZLYTE™ assay.

- Cellular assays were performed after 2hr pre-incubation with compound or vehicle. Peripheral blood monocytes (PBMCs) and primary human monocyte derived macrophages (HMDM) were stimulated with lipopolysaccharide (LPS). CD4⁺ isolated lymphocytes were stimulated with anti-CD3/CD28. Primary human retinal pigmented epithelial (RPE) cells were stimulated with TNFα/IL-1β. Inflammatory cytokine release was measured by R&D ELISA.

- In vivo efficacy was assessed in an endotoxin induced inflammatory model (EIU) where LPS was administered IVT into the eye of Lewis rats. Compound or PBS control was administered as a eye drop at -1hr, 0hr, 1hr, 2hr & 4hr relative to LPS exposure. Inflammatory cytokine levels in eye tissue homogenates were assessed 6 hours post LPS stimulation.

**Conclusions**

- TOP1106 is a potent NSKI, which inhibits key kinases involved in inflammatory signalling cascades, leading to broad anti-inflammatory effects across cells of both the innate and adaptive immune response as well as primary RPE cells.

- In the EIU model, following topical administration, TOP1106 effectively inhibits inflammatory cytokine release in both anterior and posterior eye tissue and is superior to corticosteroid.

- This data highlights the potential of NSKIs as a novel treatment option for inflammatory eye disease.

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