Identification of Novel Inhibitor(s) Targeting NLRP3 Inflammasome Activation

Figure 1. Role of CMPK2 in NLRP3 inflammasome activation

Figure 2. Validation of CMPK2 KO effect in pro-inflammatory cytokine production

Figure 3. Bioinformatic analysis suggests correlation of CMPK2 with inflammasome pathway genes.

Figure 4. Identification of hits from CMPK2 biochemical enzyme assay.

Figure 5. Characterization of single-dose hit(s) and controls in dose-response screening.

Table 1. Screening of focused libraries results in the identification of tractable chemical matter

<table>
<thead>
<tr>
<th>Overview of Primary Screening Results</th>
<th>Series 1</th>
<th>Series 2</th>
<th>Series 3</th>
<th>Series 4</th>
<th>Series 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of compounds screened</td>
<td>7500</td>
<td></td>
<td></td>
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<tr>
<td>Number of confirmed hits</td>
<td>1940</td>
<td></td>
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</table>

FUNCTIONAL IMPACT OF HITS ON CYTOKINE PRODUCTION

- Tractable chemical series identified from the biochemical enzymatic assay were subject to further validation in primary human myeloid cells.
- Cellular functional assays monitor the inhibitory effects of compounds on inflammatory cytokine production.
- Several compounds representing diverse scaffolds demonstrated sub-micromolar potency with regard to inhibition of IL-1β.

SUMMARY

- CMPK2 is a key node in the NLRP3 inflammasome pathway and is inducible in primary human cells.
- CMPK2 deletion leads to a dramatic decrease in pro-inflammatory cytokine production.
- An initial screening campaign yielded multiple tractable chemical series from structurally diverse compound libraries.
- Putative lead compounds reduce inflammasome-associated cytokine production.
- Structure-activity relationship studies of compound series with drug-like properties are currently underway.

REFERENCES


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