Background: Toll-Like Receptors (TLR) and Interleukin-1 Receptors (IL-1R) play a critical role in the innate immune response as microbial sensors, providing a bridge between the innate and adaptive immunity (1). Interleukin receptor associated kinases (IRAk) 1 and 4 are serine/threonine kinases that are essential for signaling downstream of most TLRs and IL-1Rs and the resulting production of pro-inflammatory cytokines (2). Suppression of TLR and IL-1R signaling through inhibition of IRAK1/4 kinases is a promising therapeutic approach for the treatment of inflammatory and autoimmune diseases.

Objectives: The aim of the study was to characterize the effects of R835, a novel small molecule inhibitor of IRAK1/4, on TLR4 signaling.

Methods: R835 was identified in cell-based assays measuring cytokine production induced by LPS (TLR4 ligand). Inhibition of IRAK1 and IRAK4 kinases by R835 was confirmed in biochemical assays and cell lysates. The ability of R835 to inhibit TLR4 signaling was further evaluated in humans and mouse whole blood assays. R835 was tested in a mouse model of LPS-induced cytokine release. Mice were pre-treated orally with vehicle or R835 prior to challenge with LPS and serum cytokine levels were monitored over a 24-hour period.

Results: We have identified R835, a selective small molecule inhibitor of IRAK1 and IRAK4. R835 blocked LPS/TLR4 signaling and the resulting production of proinflammatory cytokines in both human and mouse cells and whole blood. R835 suppressed serum cytokine elevation in mice challenged with LPS.

Conclusion: Our study demonstrates that R835, through inhibition of IRAK1/4 kinase activity, blocks LPS-induced cytokine production in vitro and in vivo. In a recent phase 1 study, R835 substantially reduced the increase of serum cytokines after an intravenous LPS challenge in healthy volunteers. Importantly, this shows that the pharmacological inhibition of IRAK1/4 pathway by R835 in humans mirrors the results obtained in mice. To our knowledge, R835 is the first dual IRAK1/4 inhibitor to enter clinical development and demonstrate inhibition of TLR4-induced cytokines in both mice and humans. R835 is a promising clinical candidate that will allow the exploration of IRAK1/4 inhibition in the treatment of cytokine-driven rheumatic and autoimmune diseases.

References:

Disclosure of Interests: C. Lamagna1, C. Gundel1, M. Chan1, C. Young1, S. Braselmann1, R. Frances1, S. Yi1, Y. Chen1, G. Park1, L. Chou1, E. Masuda1, V. Taylor1. Rigel Pharmaceuticals, South San Francisco, United States of America

Table 1. Demographic data and clinical features of patients with TAK

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Gender (male/ female)</th>
<th>Disease durationa (months)</th>
<th>ESR (mm/h)</th>
<th>hs-CRP⁎ (mg/L)</th>
<th>Interleukin 6 (ng/mL)</th>
<th>TNFαFog/ml</th>
<th>used/ non-used</th>
<th>Dosage (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated (n=20)</td>
<td>39.37±9.27</td>
<td>1/19</td>
<td>43 (12, 103)</td>
<td>14.60±8.94</td>
<td>1 (0.55, 5.625)</td>
<td>2.1 (2, 3.95)</td>
<td>7.56±4.39</td>
<td>18/2</td>
</tr>
<tr>
<td>Active (n=11)</td>
<td>39.30±7.889</td>
<td>1/10</td>
<td>116 (18, 166.5)</td>
<td>16.82±10.81</td>
<td>5.63 (1.49, 8.33)</td>
<td>3.15 (2.05, 8.42±5.57)</td>
<td>10/1</td>
<td>10 (10, 15)</td>
</tr>
<tr>
<td>Nonactive (n=9)</td>
<td>39.44±10.59</td>
<td>0/9</td>
<td>40 (12, 44)</td>
<td>11.89±6.41</td>
<td>0.84 (0.31, 1)</td>
<td>2 (2, 2.4)</td>
<td>6.60±2.11</td>
<td>8/1</td>
</tr>
<tr>
<td>P value</td>
<td>0.89</td>
<td>—</td>
<td>0.16</td>
<td>0.34</td>
<td>0.02</td>
<td>0.08</td>
<td>0.65</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 2. Demographic data and clinical features of patients with TAK

Prednisone

* median (min, max)