MAPK4K1 inhibition enhances immune cell activation and anti-tumor immunity in preclinical tumor models


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Background

- Hematopoietic progenitor kinase 1 (HPK1, MAP4K1) is a serine/threonine (SER/THR) kinase that has been demonstrated to have suppressive effects across a range of immune cells, including T cells and dendritic cells.
- Loss of MAP4K1 kinase activity alone, and in combination with checkpoint inhibition, is sufficient to enhance T cell receptor (TCR) signaling, resulting in robust anti-tumor immunity, and therefore supporting MAP4K1 has been a novel and high priority target for cancer immunotherapy.
- The MAP4K family and closely related kinases in the STE20 family have been elusive kinases in terms of their roles in the immune system and their potential for therapeutic development.

Results

- MAPK4K1 is a SERT/THR kinase selectively expressed in dendritic cells, T cells, and B cells, that acts as a negative regulator of the TCR and B cell receptor signaling, and dendritic cell maturation.
- MAPK4K1 knock-out or kinase dead knock-out mice exhibit enhanced tumor immunity.

Conclusions

- BLU2069 and BLU3484 are subnanomolar MAP4K1 inhibitors with a novel pharmacology.
- Pharmacological inhibition of MAP4K1 with BLU2069 and BLU3484 supports translated findings in MAP4K1 knock-out and kinase dead knock-out mice.
- BLU2069 and BLU3484 enhance intratumoral immune cell activation, mesenchymal PDGFR and Treg-mediated cell suppression, and reduce tumor burden both as a monotherapy and in combination with checkpoint blockade.
- MAPK4K1 inhibition enhanced CD3-CD28-induced cytokine secretion from human AML cells and reduced the growth of melanoma and lung cancer models.

References

2. Faiss K et al. (2021) Cancer Immunol Immunother. 70:1057-1065
5. Roche Innovation Center, Basel, Switzerland
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7. Roche Innovation Center, Munich, Germany

Conclusion:

MAPK4K1 inhibition enhances immune cell activation and anti-tumor immunity in preclinical tumor models.

Table 1: BLU2069, BLU3484, and BLU6342 are cell active subnanomolar MAP4K1 inhibitors selective against key targets and the kinase

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC50 (nM)</th>
<th>IC50 (nM)</th>
<th>IC50 (nM)</th>
<th>IC50 (nM)</th>
<th>% Inhibition of Cell Signaling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>1000</td>
<td>0</td>
</tr>
<tr>
<td>BLU2069</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
<td>0.17</td>
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</tr>
<tr>
<td>BLU3484</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
<td>100%</td>
</tr>
<tr>
<td>BLU6342</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2: Tumor volume (mm^3) for the BLU6348 experiment. (A) and (B) are Wilcoxon rank-sum test. (A) Tumor volume (mm^3) for the BLU6348 experiment. (B) Tumor volume (mm^3) for the BLU6348 experiment. (C) and (D) are Wilcoxon rank-sum test. (C) Tumor volume (mm^3) for the BLU6348 experiment. (D) Tumor volume (mm^3) for the BLU6348 experiment. (E) and (F) are Wilcoxon rank-sum test. (E) Tumor volume (mm^3) for the BLU6348 experiment. (F) Tumor volume (mm^3) for the BLU6348 experiment. (G) and (H) are Wilcoxon rank-sum test. (G) Tumor volume (mm^3) for the BLU6348 experiment. (H) Tumor volume (mm^3) for the BLU6348 experiment. (I) and (J) are Wilcoxon rank-sum test. (I) Tumor volume (mm^3) for the BLU6348 experiment. (J) Tumor volume (mm^3) for the BLU6348 experiment. (K) and (L) are Wilcoxon rank-sum test. (K) Tumor volume (mm^3) for the BLU6348 experiment. (L) Tumor volume (mm^3) for the BLU6348 experiment. (M) and (N) are Wilcoxon rank-sum test. (M) Tumor volume (mm^3) for the BLU6348 experiment. (N) Tumor volume (mm^3) for the BLU6348 experiment. (O) and (P) are Wilcoxon rank-sum test. (O) Tumor volume (mm^3) for the BLU6348 experiment. (P) Tumor volume (mm^3) for the BLU6348 experiment. (Q) and (R) are Wilcoxon rank-sum test. (Q) Tumor volume (mm^3) for the BLU6348 experiment. (R) Tumor volume (mm^3) for the BLU6348 experiment. (S) and (T) are Wilcoxon rank-sum test. (S) Tumor volume (mm^3) for the BLU6348 experiment. (T) Tumor volume (mm^3) for the BLU6348 experiment. (U) and (V) are Wilcoxon rank-sum test. (U) Tumor volume (mm^3) for the BLU6348 experiment. (V) Tumor volume (mm^3) for the BLU6348 experiment. (W) and (X) are Wilcoxon rank-sum test. (W) Tumor volume (mm^3) for the BLU6348 experiment. (X) Tumor volume (mm^3) for the BLU6348 experiment. (Y) and (Z) are Wilcoxon rank-sum test. (Y) Tumor volume (mm^3) for the BLU6348 experiment. (Z) Tumor volume (mm^3) for the BLU6348 experiment.