Increased Serum Levels of EBI3 Are Associated with Poor Outcome in Hepatocellular Carcinoma Patients and SRF388, a First-in-Class IL-27 Blocking Antibody, Inhibits the Growth of Murine Liver Tumors

Matthew R. D. Devapregasan Moodley,1 Marisa O. Peluso,1 Seclí Kosgeo,1 Jing Hua,2 Gege Tang,2 Ricard Masía,1 Benjamin H. Lee,1 Isabella Coussineau,1 Simon Turkote,1 John Stagg,1 Vito J. Palombella,1 Pamela M. Holland,1 Jonathan A. Hill1

1Surface Oncology Inc., Cambridge, MA, USA; 2Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Quebec, Canada

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Background

- IL-27 is a heterodimeric member of the IL-12/IL-23 cytokine family that consists of 2 subunits: p28 and Epstein-Barr virus-induced gene 3 (EBI3).
- IL-27 signals through a heterodimeric receptor composed of glycoprotein 130 (gp130) and IL-27 receptor subunit alpha (IL-27RA/WSX-1), which activates the JAK-STAT pathway to limit the duration and intensity of T cell-mediated immunity leading to:
  - Altered immunoregulatory receptor expression
  - Decreased proinflammatory cytokine secretion (TNF-α, IFN-γ, and IL-17)

- SRF388 is a first-in-class p28 antibody that blocks the interaction of IL-27 with IL-27RA and inhibits IL-27 signaling in primary human immune cells.

Given the expression profile and immunoregulatory interaction of IL-27 with IL-27RA and inhibits IL-27 SRF388 is a first-in-class p28 antibody that blocks the interaction of IL-27 with IL-27RA and inhibits IL-27 signaling in primary human immune cells.

Conclusion

- p28 transcript levels are elevated in tumors from patients with HCC.
- Circulating levels of the EBI3 subunit of IL-27 are elevated in a subset of patients with HCC and inversely correlated with overall survival.
- SRF388 enhances proinflammatory cytokine production in combination with PD-1 blockade in PBMC from healthy donors and patients with HCC.
- SRF388 demonstrates single-agent activity in a murine orthotopic model of HCC in vivo.
- SRF388 altered the mRNA transcriptional landscape of orthotopic Hepa1-6 tumors in mice including inhibition of immunoregulatory receptors (PD-L1 and TIGIT).
- SRF388 reduced AFP expression.
- SRF388 increases histologic infiltrates.

EBI3 Levels in Patients with HCC Predict Poor Outcome

**EBI3 Levels Are Elevated in Patients with HCC**

<table>
<thead>
<tr>
<th>Cohort 1</th>
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<tr>
<td>p28</td>
<td>EBI3</td>
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<tr>
<td>p28 low</td>
<td>EBI3 low</td>
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<tr>
<td>p28 high</td>
<td>EBI3 high</td>
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**EBI3 is Highly Expressed in Liver Cancer**

- EBI3 is highly expressed in liver cancer.
- Elevated EBI3 is not correlated with viral infection status or alpha fetoprotein (AFP) level.

**SRF388 Increases Proinflammatory Cytokine Production in Combination with PD-1 Blockade**

**SRF388 Significantly Inhibits Tumor Growth**

**SRF388 Inhibits the Growth of Orthotopic Hepa1-6-luc Tumors**

**SRF388 Significantly Modulates Gene Expression in the Hepa1-6 Mouse Model of HCC**

**SRF388 Significantly Inhibits Immuno-Inhibitory Genes**

**SRF388 Increases Histiocytic Infiltrates**

**Conclusion**

- SRF388 is being evaluated in a Phase 1 clinical trial (NCT03478487) in patients with advanced solid tumors.