The elimination of immunosuppressive cells, such as myeloid cells and neutrophils, to allow the reactivation of effector cells, is a hallmark of synergy in immunotherapy. Indeed, C5aR2 (C5L2). C5aR1 blockade is thus a potentially powerful means for controlling myeloid suppressive cells in the TME. We developed IPH5401, a fully human monoclonal anti-C5aR1 blocking antibody that prevents binding to C5a. C5aR1 is upregulated in patients with NSCLC displaying progression after an initial response to anti-PD-(L)1 therapy (IO) [1].

We first explored the expression profile of C5aR1 in the TME further, focusing on both mRNA and protein levels, in several solid cancers displaying various levels of infiltration with C5aR1 mRNA (Zilionis, 2019 [2]).

**References**

1. Massard et al.
2. Zilionis et al.
3. Pio et al.
4. Wada et al.
5. Tsuchiya et al.

**Conclusion**

- Anti-C5aR1 antibodies target suppressive myeloid cells in the TME via a direct and indirect mechanism.
- The inhibition of C5aR1 signaling increases CD8 T-cell infiltration and function, thereby enhancing the efficacy of anti-PD-(L)1 antibodies.
- C5aR1 is expressed by TME-infiltrating myeloid cells. IPH5401, a fully human anti-C5aR1 antibody, inhibits C5a-mediated effects on neutrophils [3]. We confirm the expression of C5aR1 in several primary tumor types and its correlation with poor prognosis [4-7].

**Mechanism of action**

**FIGURE 4A**: IPH5401 inhibits C5a-induced neutrophil migration in vitro. C5a (A: 3 nM, B: at indicated concentrations) for 20 min at 37°C. CD11b surface expression on neutrophils was then quantified by flow cytometry. (A) The purple line on the right panel is the fitted concentration of C5a with IPH5401. C5a-induced neutrophil migration is dependent on C5aR1.

**FIGURE 4B**: IPH5401 efficiently blocks the C5a-induced expression induced by supra-physiological concentration of C5a in vitro.

**TABLE 1**: The effects of IPH5401 on CD11b expression on neutrophils in vitro.

<table>
<thead>
<tr>
<th>Concentration of C5a (ng/ml)</th>
<th>% of Neutrophils with CD11b+</th>
<th>P-value</th>
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<td>0</td>
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<td></td>
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<td>75</td>
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</tr>
<tr>
<td>200</td>
<td>50</td>
<td>0.001</td>
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**FIGURE 3C**: Examples of staining for C5aR1 protein in liver and lung cancers

**FIGURE 2B**: Levels of the PD-L1 and C5aR1 mRNA in primary lung adenocarcinoma and primary liver hepatocellular carcinoma; COAD, colon adenocarcinoma; DLBC, lymphoid neoplasm grade glioma; LIHC, Liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell adenocarcinoma; READ, rectum adenocarcinoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; THCA, thyroid carcinoma; UBQUIT, uterine corpus endometrial carcinoma; UVM, uveal melanoma; (n=34450) for patient lung tumor biopsies (n=7). Data from lionis2019/human/NSCLC_immune are shown on the left and C5AR1 expression in primary tumors /low-expression groups and the p-values are indicated on the right. Patients. The HR and its confidence interval; the number of patients in high-expression group.

**FIGURE 3B**: C5aR1 protein may be highly expressed in tumor infiltrating lymphocytes.

**FIGURE 2A**: The C5AR1 transcript is found in all primary tumors (TGCA).

**FIGURE 2C**: C5aR1 expression in primary tumors is associated with poor clinical outcome (TGCA).

**FIGURE 2D**: scfMMF showing that lung tumor-infiltrating myeloid cells, except DC, contain C5aR1 mRNA (Zilionis, 2019).

**FIGURE 2B**: C5aR1 mRNA expression in various types of cancer. Thickness of grey line indicates low and high expression levels. The graph indicates the number of tumors with red expression levels. The mRNA and protein levels of C5aR1 are strongly correlated in primary tumors (100% correlation). C5aR1 is expressed by TME-infiltrating myeloid cells. IPH5401, a fully human anti-C5aR1 antibody, inhibits C5a-mediated effects on neutrophils [3]. We confirm the expression of C5aR1 in several primary tumor types and its correlation with poor prognosis C5aR1 is expressed by TME-infiltrating myeloid cells. IPH5401, a fully human anti-C5aR1 antibody, inhibits C5a-mediated effects on neutrophils [3]. We confirm the expression of C5aR1 in several primary tumor types and its correlation with poor prognosis.

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