

## **Disposition of the reviewers comments/questions and authors point-by-point reply**

for our manuscript entitled “**The chemokine/chemokine receptor pair CCL20/CCR6 in human colorectal malignancy: An overview**” to be published in the World Journal of Gastroenterology.

**ESPS Manuscript NO: 17878**

**Columns: TOPIC HIGHLIGHT**

### **Comments of Reviewer 1:**

This is a well-written and comprehensive review into the role of the CCL20/CCR6 axis in colorectal malignancy. A thorough background is presented, and many relevant studies have been discussed. Some more recent studies should also be included. I have only one major comment. I feel that the authors should include discussion of several more recent studies that are relevant to this review. These studies include:

Nandi B et al. CCR6, the sole receptor for the chemokine CCL20, promotes spontaneous intestinal tumorigenesis. PLoS One. 2014 May 27;9(5):e97566.

Cheluvappa R. Experimental appendicitis and appendectomy modulate the CCL20-CCR6 axis to limit inflammatory colitis pathology. Int J Colorectal Dis. 2014 Oct;29(10):1181-8.

Chin CC et al. Interleukin-17 induces CC chemokine receptor 6 expression and cell migration in colorectal cancer cells. J Cell Physiol. 2015 Jul;230(7):1430-7.

Kryczek I et al. IL-22(+)CD4(+) T cells promote colorectal cancer stemness via STAT3 transcription factor activation and induction of the methyltransferase DOT1L. Immunity. 2014 May 15;40(5):772-84.

### **Answer of authors:**

**We adapted the manuscript according to the reviewer’s comment and consider now several more recent studies in our review. Amongst others also 3 of the studies mentioned above.**

**We did not include the study from Cheluvappa, because we felt that it does not suit our manuscript.**

**We addressed to this subject on page 10, lines 6 to 26 and page 11, lines 1 to 6.**

**The study from Nandi et al. has been also included in table 2, reference 40.**

Minor comments: 1) There are numerous grammatical errors throughout the manuscript. A space is needed in the title. The word “also” is used redundantly in third sentence on page 2. Incomplete sentence in second line on page 5. The sentence on line 7 of page 10 (Recent studied . . .) does not make sense. 2) Is CCL20 specific to CCR6 (i.e. does CCL20 bind only to CCR6)? This was not clear in the top paragraph on page 5.

**Answer of authors:**

**The grammatical errors and the by the reviewer mentioned mistakes have been corrected.**

**In addition on page 6, line 3 to 6, we clarify that CCL20 binds only to CCR6.**

**Comments of Reviewer 2:**

The manuscript by Frick and colleagues summarizes in short some facts on CCL20/CCR6 in colorectal cancer. Although the manuscript is well written and easy to read there are some shortcomings in the article:

1. There are some typos, comma errors, word doublings etc. Thus, a bit of language polishing is necessary. Please revise also Table 2 as it is not easy to read in the current format. It seems that some columns are missing. At least give a hind that this table may also be found in the supplement.

**Answer of authors:**

**The grammatical errors, typos, comma errors and world doublings throughout the manuscript have been corrected.**

**Furthermore I have no explanation, why Table 2 is not displayed in landscape format which corresponds to the format submitted by us. In order that this does not happen again, we will give a hind that the table also is found in the supplement.**

**See page 28, line 1.**

2. Table 1 is far from disclosing 50 chemokines! I agree that this would not make sense; however, the authors should explain the selection.

**Answer of authors:**

**I agree with the reviewer that Table 1 is far from disclosing 50 chemokines.**

**The objective of Table 1 was not to show all existing chemokines and goes in my opinion to far, but to display a selection of chemokines, thereby focusing on the one hand on such chemokines which are involved in inflammation, angiogenesis and homing and on the other hand on chemokines which are the main focus of our research.**

3. The authors wrote that CCR6 is unique as "this receptor can bind only a single chemokine ligand". I agree that this is remarkable, however, I would prefer to write "is found to bind" as there might be additional ligands but not yet identified.

**Answer of authors:**

**It is correct, that by the current state of scientific knowledge CCR6 binds only a single chemokine, namely CCL20.**

**As the reviewer favours another word choice, we adapted the manuscript according to the reviewer's comment.**

**See page 6, line 3 to 6.**

4. Unfortunately the authors ignore the role of the CCL20/CCR6 axis in tumor immunology. CCR6 is expressed on Treg and TH17 cells which are also found in colorectal cancer. Thus, the CCL20/CCR6 axis also affects tumor immunology which might be important for outcome and metastasis.

**Answer of authors:**

**We did not ignore the role of the CCL20/CCL6 axis in tumour immunology, e.g. see page 7, lines 8 to 11, page 10, lines 22-24. We only felt, that concerning this matter we could make it short.**

**But I agree with the reviewer, that more information and discussion on this subject would improve the paper. So we adapted the manuscript according to the reviewer's comments. We address to this on page 7, lines 12-14, on page 9, lines 11-27 and the**

**complete page 10 and also added several new citations (numbers 27, 45-48, 50, 51, 53, 57-61).**

5. The role of CCL20 as a biomarker in colorectal cancer is also missing.

**Answer of authors:**

In the “*CCL20 and CCR6 in tumour metastasis*” section we discuss on the role of CCL20 as a biomarker of colorectal cancer. But we were brief.

To improve the paper, we adapted the manuscript according to the reviewer’s comments. We address to this on page 13, lines 24-26 and page 14, lines 1-9. Again new citations have been quoted (numbers 36 and 89).

**We did not ignore the role of the CCL20/CCL6 axis in tumour immunology, e.g. see page 7, lines 8 to 11, page 10, lines 22-24. We only felt, that concerning this matter we could make it short.**