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Dear Clinical Cancer Research Editorial Board members,

We are pleased to submit our original research article entitled, "**Mapping the Immune Landscape in Clear Cell Renal Carcinoma by Single-Cell Genomics.**" We feel that this article fits well within the scope of *Clinical Cancer Research*, as it uses cutting-edge approaches to look at the immune microenvironment of renal clear cell carcinoma (ccRCC), with emphasis on clinical and translational elements. Although responsive to immune checkpoint blockade, unlike other immunogenic tumors, mechanisms of ccRCC responsiveness are largely unknown. To this end, we performed single-cell mRNA and T-cell receptor sequencing on 3 ccRCC patients, combining our analysis with IHC, mass cytometry, and bulk mRNA quantifications to better understand the ccRCC microenvironment and clinical implications. Of particular note, in this study we:

- Integrated clonotype and mRNA expression levels using, finding an example of tumor-specific clonotype expansion in later disease that was not seen in peripheral blood of the corresponding patient.

- Identified transcriptional trajectories in $CD8^+$ T cells that corresponding to clonotype with branches furcating to proliferative, exhausted and immunotherapy-responsive states.

- Performed analysis of myeloid cells and found increased and diverging tumor-associated macrophage (TAM) populations with differences in expression of effector and cytokine expression.

- Developed signatures from the proliferative $CD8^+$ T cell and $CD207^+$ TAM subsets that could differentiate survival across the Cancer Genome Atlas cohort ccRCC and corresponding to histological grade of samples.

- Most importantly, we found a gene signature from a subpopulation of CD8 T cells – with proliferative and exhaustion signatures – to be the mostly responsive for the prognostic correlation between CD8 T cells and ccRCC patients. This is further confirmed using CyTOF data at the protein levels.

We strongly believe the manuscript at the current version reflects high scientific values and translational priority. Please let me know if you have more questions.

Sincerely yours,

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