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Thesis Changes Log

Name of Candidate: Sofya Kasatskaya

PhD Program: Life Sciences

Title of Thesis: Origin of T cell subsets studied through the lens of TCR repertoires

Supervisor: Associate Prof. Dmitriy Chudakov, Dr. Olga Britanova, IBCH RAS

Chair of PhD defense Jury: Prof. Mikhail Gelfand

Date of Thesis Defense: 17/06/21

The thesis document includes the following changes in answer to the external review process.

Dear Jury members,
I am grateful for your comments, insightful critique, and for taking the time to evaluate my work. Thank you for your suggestions on how to improve my thesis. Here is the list of changes I made in the final version of the thesis text to follow your suggestions.

Reviewer: Prof. Mikhail Gelfand

- *While the introduction / review chapter is generally well-written and logically structured, I feel that the balance between the general literature review, the lab's contribution, and the candidate's research has not been maintained. The style seems to be a bit too dramatic, but it is a matter of taste.*

  Answer: Thank you for the suggestion. The revised thesis version aims for a more academic style both in the introduction and conclusions sections. To tone down the style, the adjectives were changed at the indicated sites of the text.

- *The first paragraph of section 1.3 (the author's contribution) belongs elsewhere.*

  Answer: Section 1.3 was partially rewritten following the suggestions from Prof. Gelfand and Prof. Kedzierska. The first paragraph is moved to the end of the section to keep an explanation on candidate's contribution.

- *In section 1.6 it is not always clear who is referred to by "we". <...> At that, the candidate is not the author of refs. 52-53.*

  Answer: The citing of references 52-53 was partially incorrect as the candidate is a co-author only in ref.53 but not 52. The text was changed to clarify that the references belong to the earlier projects in the laboratories led by Dr. Chudakov and Dr. Britanova throughout section 1.6. Moreover, to define the candidate's contribution clearly, a section is designated before each of the chapters.

- *The final editorial note: sequences, motifs etc. are "conserved", not "conservative"; the latter applies to politicians and parties.*

  Answer: Corrected in the final version of the thesis. The author is grateful for pointing out this recurring error.

Reviewer: Prof. Katherine Kedzierska

- *Please explain differences observed between your PhD data using the broad TCR analyses of non-antigen specific T cells, especially with respect to shortening of CDR3 length in the elderly and published reports on CDR3 elongation within antigen-specific T cells in the older individuals?*
  Answer: A short paragraph with a discussion of this question was added to the conclusions section of the thesis. The question is included in thesis defense presentation.
- *Abstract: "..multivariate subset-specific differences in physicochemical TCR* features. ." one full stop too many
  Answer: Changed in the text to "We show that even among unrelated donors, functional T cell subsets share the same patterns of prominent physicochemical TCR features."
- *Publications: Journal of hepatology: Hepatology should start with a capital letter*
  Answer: Corrected in the text.
- *Page 29, "conventional ab T cells" ab should be* αβ
  Answer: Fixed in the text. This mistake frequently appears if the documents are merged in Microsoft Word.
- *Please briefly outline different TCR sequencing approaches and discuss their benefits and disadvantages.*
  Answer: Thank you for this comment. A brief paragraph on benefits and disadvantages of various TCR sequencing protocols is now included in the thesis introduction, section 1.3.

Reviewers: Prof. Benny Chain, Dr. Grigory Efimov

- **Prof. Benny Chain:** *«In addition, more extensive TCR sharing is observed between TH22/TH2/TH17 and TH1/TH17 – _the authors interpret this as increased plasticity of these subsets, although it would be interesting to discuss the alternative hypothesis that these types share precursors.»*
- **Dr. Grigory Efimov:** *«Besides that, the authors showed that some TCRBs were present in two distinct T-cell subsets. From this observation they draw a conclusion of the certain plasticity of helper T cell population. This term is used multiple times in the paper and in the abstract of the thesis to describe the underlying reason for the observed overlap in repertoires. Albeit T cell plasticity is one of the possible explanations, in their work the authors did not strictly show that T cells can and do transit from one phenotype to another. Neither it was feasible to demonstrate by the used methodology. Another possible interpretation is that some clones just do exist in more than one subpopulation (in this explanation the fate of the cell progeny diverges rather than phenotype of individual changes over time). This notion is in my opinion is no less significant than the plasticity.»*

  Answer: The convergent comments by two reviewers raise an important point. An explanation of the possible reasons for the observed clonotype sharing besides clonal transition is added in the revised thesis text both in section 2 and conclusions section.

Reviewer: Prof. Benny Chain

- *Issues which could be discussed during the thesis defense. 1. The difficulty of comparing and harmonizing different TCRrep data sets. 2. The biological significance of TCR publicity, and why it should change with age. 3. The biological importance of the physical changes in TCR observed with aging, and in Tregs. 4. The evidence for T cell subset plasticity and how this might be maintained. 5. The balance between innate and adaptive responses in gamma/delta T cells. 6. The perspectives for gamma/delta cells in immunotherapy of cancer. More general discussion could focus in the candidate's views about the current challenges to TCR repertoire studies; and the impact of single cell RNAseq on the study of the repertoire.*

  Answer: No changes are taken in the thesis text, but these important points are included in the presentation for the thesis defense in the Supplementary materials.

Reviewer: Dr. Asaf Madi

- *The conclusion paragraph at the end of the thesis is satisfactory in terms of limitations and future directions but lacks some meta-analysis interpretation. I would ask Sofya to add both a paragraph that gives the reader some meta interpretation, a conclusion she can draw from her vast experience as well as, a short paragraph describing the ethical implications of her work specifically but not limited to the immune-aging.*

  Answer: A paragraph summarizing the conclusions on TCR repertoire from different studies and its implications to T cell-based therapy is present in the conclusions section. A short paragraph about ethical implications of TCR immune profiling in aging is added to conclusions section as well.