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Jury Member Report – Doctor of Philosophy thesis.

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 Professor Dmitriy Chudakov

Name of the Reviewer:

I confirm the absence of any conflict of interest	**Date:** 15-05-2021

Reviewer's Report

This is a strong thesis based on six publications, in two of which (in eLife and Front. Immunol.) the candidate is a first author; the remaining publications are in good journals, including Nat. Comm. and Nat. Immunol. The results have been reported at two reputable international conferences. Hence the formal requirements are met.
The thesis is a collection of published papers preceded by a general review. At that, the papers do form an integrated story, reflected in the dissertation title. Hence, the quality of the results, their state of the art, the relevance of methods are obvious. The contribution of the candidate is specified in each chapter.

Somewhat surprisingly, the candidate has chosen to ignore my comments to the preliminary text of the thesis, so I repeat them here. 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. Some examples follow:

Genes are assembled by the **delicate** process of V(D)J recombination.

The **immense** combinatorial and semi-random diversity of the TCR's CDR genetic sequences allows the T cells to recognize millions of various antigens that an immune system encounters **during a long life** of a human individual.

Transcriptomics represents an indispensable tool for almost every molecular biology laboratory **on the planet**.

The accumulating AIRR data **brings us closer to the future** when we can thoroughly describe the history of diseases and vaccinations from one TCRseq sample… It seems that AIRR has a potential **to enter consumer diagnostics** instead of remaining the status of a fundamental research tool.

Our laboratory's team has been studying the age-related changes in the T lymphocytes compartment of human adaptive immunity **for years**.

Still, it might be a good idea to tone done some of the enthusiasm towards the lab's research and expand description of the more general context.

The first paragraph of section 1.3 (the author's contribution) belongs elsewhere. Moreover, the entire section reads like an advertisement of the methods developed in the lab, not as an academic review, e.g.:

I have been fortunate to work with the same team of bioinformaticians who has developed many unique techniques that **dramatically improve** the quality of immune repertoire sequencing data and data analysis quality.

The **superior quality** of UMI-barcoded data allows using all processed data.

Dr. Shugay and colleagues have developed and maintained **the largest** database of annotated TCR sequences, but it is not enough to annotate a patient's sample yet.

In section 1.6 it is not always clear who is referred to by "we", e.g.:

Our laboratory's team has been studying the age-related changes in the T lymphocytes compartment of human adaptive immunity for years. The total number of T cells is stable throughout life and only slightly decreases with age. But the prominent decrease in the diversity of TCR repertoires is linear and significant [52, 53]. It is associated with the proliferation of memory T cells and the loss of naive T cells due to the continuous thymic involution after puberty [42, 44, 48, 53, 54]. Previously, **we described** the high diversity of T cell receptors in the umbilical cord blood samples and described neonatal immune repertoires' characteristic features [53].

We used peripheral blood samples from healthy donors and umbilical cord blood (UCB) in this project, like most human immunology research. We cannot infer the rules and patterns of development, selection, or aging in the immune cell subsets occurring in peripheral organs from the limited number of blood samples. From studies made primarily on UCB, other authors **and we** assumed that newborns have practically no memory T cells, and the T cell repertoire is composed of naive T cells [53, 55, 56].

- at that, the candidate is not the author of refs. 52-53.

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

Provisional Recommendation

☒ I recommend that the candidate should defend the thesis by means of a formal thesis defense

☐ ~~*I recommend that the candidate should defend the thesis by means of a formal thesis defense only after appropriate changes would be introduced in candidate's thesis according to the recommendations of the present report*~~

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