

Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Artem Mikelov

PhD Program: Life Sciences

Title of Thesis: Dynamics of immunoglobulin repertoires in memory and antibody-secreting B cell subsets in health and disease

Supervisor: Associate Professor Dmitriy Chudakov

Name of the Reviewer: Olga Dontsova

I confirm the absence of any conflict of interest	Date 22 march 2023
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The purpose of this report is to obtain an independent review from the members of PhD defense Jury before the thesis defense. The members of PhD defense Jury are asked to submit signed copy of the report at least 30 days prior the thesis defense. The Reviewers are asked to bring a copy of the completed report to the thesis defense and to discuss the contents of each report with each other before the thesis defense.

If the reviewers have any queries about the thesis which they wish to raise in advance, please contact the Chair of the Jury.

Reviewer's Report

Reviewers report should contain the following items:

- Brief evaluation of the thesis quality and overall structure of the dissertation.
- The relevance of the topic of dissertation work to its actual content
- The relevance of the methods used in the dissertation
- The scientific significance of the results obtained and their compliance with the international level and current state of the art
- The relevance of the obtained results to applications (if applicable)
- The quality of publications

The summary of issues to be addressed before/during the thesis defense

Critical review on Doctoral Thesis by ARTEM MIKELOV (DOCTORAL PROGRAM IN LIFE SCIENCES, Skolkovo Institute of Science and Technology) "DYNAMICS OF IMMUNOGLOBULIN REPERTOIRES IN MEMORY AND ANTIBODY-SECRETING B

CELL SUBSETS IN HEALTH AND DISEASE”

Doctoral thesis of Artem Mikelov focuses on really important issue of analysis of complex sequencing data, namely, sequences of VDJ recombined Ig loci obtained from populations of circulating memory B cells, plasmablasts that undergo class switching and somatic hypermutation and mature plasma cells responsible for production of high affinity antibodies in a case of infection. First of all, it should be noted that circulating cells represent only a thin slice of cells that entered bloodstream, therefore the data obtained from circulating cells are not sufficient to get complete understanding of receptor repertoires of B cells, plasmablasts and plasma cells. The author understands the incompleteness of the analysis and makes a great effort explaining the depth of the problem in quite exquisite literature review.

The body of the study is based on the Ig sequences obtained from FACS-sorted memory B cells, plasmablasts and plasma cells from PBMC fraction collected from 6 relatively young healthy donors: 4 males and 2 females. Blood was collected 3 times at day 0, day 30 and 1 year since the start point. Unfortunately, for one of female donors the blood was collected only once at 1 year point. Therefore, significant gender bias is intrinsically present from the very beginning of the study.

Next, if one would look at the numbers of plasma cells used in the analyses, he would mention that in some preps there are only 200 plasma cells. Despite that, the author states that about 300 sequences were obtained from these samples. It is clear that other samples had more individual cells, but it sounds like overstatement. This point has to be explained to avoid misinterpretation of the data.

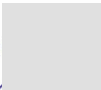
Another minor point is that in the title Artem Mikelov insists on “B cell subsets in health and disease”, but I failed indeed to find any mentions of infectious agents or donors that contracted bacterial or viral diseases. In my opinion, the title should be less ambitious.

All these comments do not suspect the quality and the value of the study, since Artem has made a very good work and essentially improved the way of in silico extraction and analysis of Ig repertoire from circulating antibody-producing cells from healthy donors. He demonstrated that using of his algorithm of analysis is sufficient to get valuable set of data even at relatively low depth of NGS sequencing. That will definitely save lots of time and resources in the nearest future and will allow for great improvement of our understanding of real BCR repertoires.

He has very interesting results concerning the stability or diversity of clonotypes in different types of B cells in a year time, expanding existing knowledge to young individuals. Taking together with the literature data author’s findings allowed to speculate on a mechanism of initial stages of immune response.

The results are published in the very good journals including eLife (first author) and Frontiers in Immunology.

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

The thesis is not acceptable and I recommend that the candidate be exempt from the formal thesis defense