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Skolkovo Institute of Science and Technology

Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Sergey Shmakov

PhD Program: Life Sciences

Title of Thesis: Computational approaches for discovery of novel CRISPR-Cas systems

Supervisor: Professor Konstantin Severinov

Chair of PhD defense Jury: Professor Mikhail Gelfand ***Email:*** ***mikhail.gelfand@gmail.com***

Date of Thesis Defense: October 16, 2017

Name of Reviewer:

I confirm the absence of any conflict of interest (Alternatively, Reviewer can formulate a possible conflict)	**Signature:** **Dmitri Pervouchine** **Date: 25 Sep 2017**

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 forward a completed copy of this report to the Chair of the Jury 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 relevancy of the topic of dissertation work to its actual content
- The relevancy 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

The manuscript by Sergei Shmakov describes a classic bioinformatic endeavor into the evolutionary history of genes and pathways, in the particular case of Class 2 CRISPR-Cas systems. The author uses Cas1, the most conserved gene among CRISPR-Cas families, as a seed to locate CRISPR-Cas modules across bacterial and archaeal genomes, and proceeds synthetically within each genome to identify and characterize open reading frames that encode other members of the CRISPR-Cas system. The results of the work were presented at international scientific conferences and published in high profile scientific journals.

The manuscript consists of literature review, materials and methods, results and discussion, conclusions, results outline, and reference list. In literature review, the author describes the mechanistic aspects of CRISPR action, describes the classification of CRISPR-Cas systems (figure 4), argues on their evolutionary origin, and lists numerous applications. Materials and methods summarize datasets and the annotation pipeline. In Part 1 of results and discussion, the author focuses on novel Class 2 CRISP-Cas systems, provides an updated classification scheme (figure 8), an updated phylogeny of effector proteins and their domain architecture, the strength of purifying selection, and other results related to novel functional annotations. In the parts that follow, he focuses on the census of Class 2 CRISPR-Cas systems in bacteria and archaea, evolutionary origins of novel CRISPR-Cas systems, and possible applications. In conclusion, the author points to a remarkable diversity of Class 2 CRISPR-Cas systems and argues about their evolutionary emergence.

The manuscript is written fairly well. I have only a few stylistic comments. On page 4 the author presents the list of acronyms, but these abbreviations are repeated in what follows, e.g., "double-strand break (DSB)" on pp. 11 and 27. This does not create any inconvenience for the reader, but conflicts with the idea of the list of acronyms. Second, before going into the narrative, it is advisable to have a "roadmap" of the of the thesis, in which the reader could get an idea where in the manuscript (s)he should look when asking a particular question. Overall I find the manuscript is an excellent work and the author Sergei Shmakov should be awarded the phD degree.

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*