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Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Mikhail Moldovan

PhD Program: Life Sciences

Title of Thesis: HERITABLE MODIFICATIONS OF TRANSMITTED BIOLOGICAL INFORMATION AS POSSIBLE SOURCES OF ADAPTATION

Supervisor: Professor Mikhail Gelfand

Name of the Reviewer: Petr Sergiev

I confirm the absence of any conflict of interest	**Date: 07-09-2021**

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

As was wisely stated by Theodosius Dobzhansky, "Nothing in Biology Makes Sense Except in the Light of Evolution". The presented thesis is devoted to a particular aspect of evolution, namely a role which is played by the systems of RNA and protein modification in a particular set of species.

The first system studied is deamination of adenines with formation of inosines in coleoids, exemplified by two octopuses *Octopus vulgaris* and *O. bimaculoides*, *Sepia esculenta (cuttlefish)*, and *Loligo pealei* (squid). While adenine deamination with the help of ADAR enzymes is widespread in nature, coleoids have an unusually large number of editing sites. At the same time, their genetic variability is low. In the presented thesis Mikhail questioned the role and evolution of the modification system and whether it can to some extent “substitute” direct mutagenesis of the target site. To make a long story short, Mikhail demonstrated that indeed, deamination of adenine what change the pairing properties of A go that imitating G is somewhat like “soft” form of mutation. Edited adenines are on average more frequently substituted by guanines. The most intriguing question is why the mutation of a particular “A” context which would make such a position prone to editing would happen or fixed more frequently than mutation of the target site *pre se*? Hypothetical answer provided by the author is that since editing efficiency depends on the secondary structure there might be much more mutations creating the site of editing in comparison with the single mutation which convert A to G. Thus, contextual mutations would be more probable. While this explanation sounds valid, there are no direct proofs, if I haven’t overlooked it. Have you considered a possibility that massive A deamination might be a way to deal with probable dC to dU deamination in the genomes of coleoids? I don’t know whether it is indeed the case. Sometimes nature uses “general” cure to overcome the consequence of massive damage to the genome happening in too many places, which make it impossible to correct via random mutational restoration.

The continuation of the editing story was about the clustering of editing sites and the order of editing in double edited adenines. This part is more focused on mechanistic aspects of editing and might be useful for “wet” biologists studying enzymology of deamination.

The second part of the thesis is devoted to modification of proteins, such as the most common phosphorylation. The idea behind the study is that sites of phosphoserine and phosphothreonine formation are frequently mutated to negatively charged aminoacids. This process is more frequent in the intrinsically disordered regions containing clusters of phosphorylation sites. To my view, it is not really a surprise, but anyway, the strict computational proof of something which might be predicted on the basis of common physical-chemical sense is a good thing.

As a summary, I have to state that the work of Mikhail Moldavan which was included into his thesis is a significant advancement of our understanding of evolution in relation to the systems of post-transcriptional and post-translational modification. The results were published in two papers in PeerJ and a paper in Scientific reports. It is absolutely clear that Mikhail Moldavan should defend the thesis by means of a formal thesis defense.

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*