

Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Julia Piskunova

PhD Program: Life Sciences

Title of Thesis: Structural and Functional Analysis of Ribosomally Synthesized and Post-Translationally Modified Microcins from *Escherichia coli*.

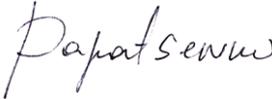
Supervisor: Professor Konstantin Severinov

Chair of PhD defense Jury: Professor Yuri Kotelevtsev

Email: y.kotelevtsev@skoltech.ru

Date of Thesis Defense: October 27, 2017

Name of Reviewer: Asst. Prof. Dmitriy Papatsenko, CDIBB

<p>I confirm the absence of any conflict of interest</p> <p>(Alternatively, Reviewer can formulate a possible conflict)</p>	<p>Signature:</p>  <p>Date: DD-MM-YYYY</p>
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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 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

Thesis work by Piskunova J. " Structural and Functional Analysis of Ribosomally Synthesized and Post-Translationally Modified Microcins from Escherichia coli" is devoted to investigation of properties of bacterial response to antibiotic microcin and its variants, study of the phenomenon of persistence, when certain bacteria are not killed by the antibiotic immediately due to their physiological conditions, which can result in a relapse of infection after antibiotic is removed.

Since the discovery of first antibiotics bacteria have designed many ways to avoid the drugs by either passing on certain plasmids, acquiring mutations and become resistant to treatment. Over time the strains with certain degrees of resistance to treatment became wide-spread and currently there are strains (superbacteria) resistant to nearly any available drug. On top of the regular mechanisms, such as resistance, it has been found that special state of activity caused by some antibacterial drugs prevents bacteria from being eliminated by antibiotics even in the absence of genetic resistance. So, the current goals also include searching for and developing new antibacterial drugs that have a broad spectrum of antimicrobial action and do not cause the development of persistent states.

For the described reasons, the proposed direction of this thesis work and the major goals appear to be on the bleeding edge of current research and technology in biological sciences.

Major results of this thesis work include findings suggesting that microcin C induces persistence in E. coli. McC, an inhibitor of aspartyl-tRNA synthetase, causes production of (p)ppGpp, which activates the (p)ppGpp-dependent persistence formation pathway that is responsible for about 90% of the observed increase in persisters. Based on investigation of McC properties and bacterial responses the author proposed that from the point of view of persistence, McC producing cells seem to contribute to the "public good" of the community, ensuring their own survival and that of others. This property may contribute to the wide distribution of microcinogenicity in phylogenetically diverse bacteria. It appears that this finding, among the others contributes to general view of antibiotic-resistance mechanisms, so this may have impact not only on science but also on medicine.

The dissertation manuscript is very well written and contains substantial backgrounds and clear well-though diagrams and images illustrating major scientific findings. Very deep analysis of the existing literature has been performed and relevant conclusions have been derived from the results. The amount of the work, quality of the performed research and quality of publications, along with significance of the selected research direction fully justify this work as a completed PhD thesis project.

Few minor wishes (which may be addressed at the time of defense) from the side of the reviewer: (a) the dissertation still contains typos, for instance on page 70 there is a sentence: "In this work was show that microcin C induces persistence in E. coli" - the author needs to check the dissertation and fix the language and typos throughout the text. (b) The conclusions are clear, but while in the case of McC there is a clear and very interesting discussion of biological hypothesis, in the case of McB there is a discussion of results and not many biological conclusions. Overall, I think, the conclusions section may be shorten. However, most of these issues may be addressed during 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

