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Skolkovo Institute of Science and Technology

Jury Member Report – Doctor of Philosophy thesis.

Name of Candidate: Anna Moroz

PhD Program: Life Sciences

Title of Thesis: Preclinical testing of new modalities for PET visualization and treatment of RAS-driven cancers

Supervisor: Prof. Konstantin Severinov

Chair of PhD defense Jury: Prof. Yuri Kotelevtsev *Email: y.kotelevtsev@skoltech.ru*

Date of Thesis Defense: December 11, 2018

Name of the Reviewer: Yury Likar, MD, PhD, Dr. Sci.

I confirm the absence of any conflict of interest (Alternatively, Reviewer can formulate a possible conflict)	**Signature:** **Date: 27-11-2018**

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

- ***Brief evaluation of the thesis quality and overall structure of the dissertation.***

The thesis of Anna Moroz entitled «Preclinical testing of new modalities for PET visualization and treatment of RAS-driven cancers» applies a combination of experiments in cell biology, molecular imaging and therapeutic to examine new modalities which can be used for theranostics or just for molecular imaging. Specifically, this research presents novel ways to diagnose and treat cancers that bear RAS oncogenes, using radiolabeled antibodies against CDCP1, ^{89}Zr labeled transferrin as a new molecular imaging approach that may improve detecting and monitoring procedures of clinically problematic cells arising from TSC and/or LAM, measuring PD-L1 with non-invasive imaging. Work presented by Dr. Moroz in this thesis is concentrated on the fusion of molecular imaging and cancer research and generally of high quality in both fields.

- ***The relevance of the topic of dissertation work to its actual content***

The title of the thesis reflects its content.

- ***The relevance of the methods used in the dissertation***

The work looks quite modern. Anna Moroz uses a powerful combination of different methods for *in vitro* and *in vivo* experiments to explore questions that are highly relevant to understanding how new modalities can be properly used for PET visualization and treatment. The methods chosen for the study match the goals and demonstrate wide panel of author skills acquired during her work.

- ***The scientific significance of the results obtained and their compliance with the international level and current state of the art***

Her work was published in good international journals as well as presented on multiple conferences, resulted in several first author abstracts. Some unpublished work is also very likely going to result in publications in the nearest future.

- ***The relevance of the obtained results to applications (if applicable)***

This research has several novel contributions to the field. Namely, it applies newly developed antibody against CDCP1 and provides much needed and highly clinically relevant assessment not only in pure animal model, but also in patient derived xenografts format. It is also beneficial and relevant to combine, by means of using radioisotopes with different properties, two different clinical imaging modalities – SPECT and PET in one application for this purpose. Treatment data for experiment with $Lu^{177}$is both novel and promising for patients with pancreatic and, possibly, other RAS positive cancers. In addition to this data, thesis presents encouraging results on novel Zr^{89}-transferrin and Zr^{89}-Atezolizumab applications that further the advancements in diagnostic and therapy of various cancers. The methods chosen for the study match the goals and demonstrate wide panel of author skills acquired during her work.

At the same time, the reviewer has the following comments and suggesting to the actual content of the thesis and possible future development of this work:

1. While work is concentrated in pancreatic cancer and touches the lung cancer models, it makes overall conclusion regarding the RAS positive cancers, which also include colorectal cancers (up to 55% of which is RAS+). It would be interesting to see of this results will hold true for these cases as they are very frequent in clinic.
2. Overall logistics of procuring requires isotopes and conduct labeling is expensive and complex. It would be valuable for successful translation of this method into Russian clinic to explore way to simplify the approach and make it more robust.
3. For translation of these results into wider use – the procedure of actual antibody development and purification should be discussed in more details and possibly simplified. However I do admit that it was not the focus of the thesis specifically as the antibodies were received from elsewhere.

Minor points:
1. Page 81; Does this sentence belong here?
DFO-atezo was radiolabeled via incubation with 89Zr-oxalic acid for 120 min and purified using size exclusion chromatography. The radiochemical yield was consistently >95%, the radiochemical purity >98%, and the specific activity was ~ 3,35 μCi/μg.
2. Page 82; Figure 19: In the figure captions we have A and B but images unmarked.
3. Page 84; Figure 20: Images unmarked but in figure captions we can see A,B, C and D
Moreover, in legend B. **CT and PET/CT images** showing the biodistribution of 89Zr-4A06 48 hours after injection in *nu/nu* mice bearing PDX derived from two different patients with PDAC but in reality both images are PET/CT.
4. Page 90; All these values were compared favorably to those we achieved and reported for 89Zr-C4, including a specific activity of **~7 mg/mg.** Should be 7 **μCi**/μg?

The comments above do not concern overall value of the candidate's work and I agree that this is a strong doctoral thesis. I have no doubt that it has novelty and quality to be accepted by any institution working in fields of cancer research and molecular imaging.

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*