Skoltech
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: Prof. Konstantin Lukyanov

I confirm the absence of any conflict of interest	**Signature:**  **Date: 30-11-2018**

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

The thesis “Preclinical testing of new modalities for PET visualization and treatment of RAS-driven cancers” by Anna Moroz aims at developing preclinical models for Immuno-PET/SPECT imaging and therapy of RAS-driven and some other cancers. Using *in vivo* tumor mice models, Anna demonstrated that radioactively labeled (^{89}Zr or ^{177}Lu) 4A06 human recombinant antibody against CDCP1 can be used to visualize and treat RAS-driven cancer cells.

In addition, Anna succeeded in developing PET/SPECT-based molecular imaging approach for detecting and monitoring clinically problematic cells arising from Tuberous Sclerosis Complex (TSC) and lymphangioleiomyomatosis (LAM).

The present work has clear perspectives for future applications in clinics to monitor tumor progression and assess tumor burden, as well as a therapeutic potential.

Main results were published in two papers in Bioconjugate Chemistry (IF 4.5), including one with the first author of Anna, and one paper in JCI Inside (a peer-reviewed journal founded in 2016 by the American Society for Clinical Investigation).

Overall, this is an excellent work; the thesis is well written and illustrated. The author used fully appropriate modern methods to achieve the goals. The literature review is very helpful for the readers and describes everything you should know to understand the present experimental work. I am confident that Anna Moroz should defend the thesis by means of a formal PhD thesis defense; but it would benefit from minor corrections as listed below.

Minor criticism and questions:

A general problem of using radiotracers such as ^{89}Zr and ^{177}Lu is their rather fast radioactive decay, so that half-life values are comparable to the duration of some experiments. Thus, it is important to clearly state in each case (Figs. 19, 20, 21, 23, 27) whether images and corresponding histograms were corrected for decay or not (e.g., in the figure legend). It might be also helpful to show (or at least discuss) both corrected and raw data, since at late stages a high percentage of accumulation can actually correspond to a very low absolute value.

Fig. 2B (page 23): I think that in the protein names in the alignment - “HRAS (aa1-169)”, *etc.* – “1-169” aa numbers are not appropriate as only 20 residues are shown.

Figures 19 and 20 have no letters designating the panels (A, B, C, …). In the images in Figs. 20D and 26C, size of the scale bar rather than “20X magnification” should be noted.

Page 83: “DAR images clearly showed high levels of ^{89}Zr-4A06 in sections from each PDX that overlapped with regions of viable tissue (defined by H&E)”. It is not evident from the low-magnification images shown in Fig. 20. It would be helpful to show some regions at higher magnification to illustrate the above statement.

Formatting issues:

Tables and Figures with their legends should be placed on the same page whenever possible; obviously, it is inconvenient for reader to see it split onto two pages. Also, a common formatting is to place table title above the table, not below.

To easy find any particular abbreviation, “List of Symbols and Abbreviations” should be in alphabet order. FACS is Fluorescence-Activated Cell Sorter, not “Flow Cytometry Analysis and Sorting”. “EGFP – Epidermal growth factor receptor” (-> EGFR). “PTM” commonly designates Post-Translational Modifications, but

here is used for “Translational Lipid Modifications” (Abbreviation list) or “Post-translational lipid modifications” (text, p. 23). “TSC – Tuberoslerosis Factor” in the Abbreviation list but “Tuberous sclerosis complex” in the text (p. 68).

Misprint (page 90, end of 1st par): “… for ^{89}Zr-C4, including a specific activity of ~7 µg/µg” (-> µCi/µg).

Reference list contains citations in different formats. Ref. 171: no commas between author names. Some needless parentheses in many references (e.g., 1, 3, 10, 12, 135, 172).

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*