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. Yuri Kotelevtsev

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 of Anna Moroz (Pavlova) devoted the development of radiolabeled antibodies for diagnostics and treatment of tumors (theranostics approach). It combines spatial *in vivo* visualization with radio ablation of malignancies. Tumors expressing RAS oncogenes were chosen as a model because no reliable theranostic platform is available at the moment for this marker. The author has chosen the new promising target CDCP1 which is differentially expressed on the tumor cells with oncogenic mutations of RAS oncogenes. The author carefully characterized the mouse model and described CDCP1 as a potential tumor specific antigen. Several antibodies with different complex on ligands bearing radioactive elements were developed.

The research benefits from parallel evaluation of xenografts (PDX) developed from biopsy materials of clinical patients with pancreatic cancer. Radiolabeling of the anti-CDCP1 antibodies with isotopes 89-Zirconium and 177-Lutetium allowed the use of both positron emission tomography (with Zr) and single photon emission computed tomography (with Lu). Significant decrease of tumor growth and extended overall survival of experimental mice (n=80) was demonstrated in groups treated with anti-CDCP1 with ^{177}Lu. For the first time imaging with ImmunoPET with ^{89}Zr anti-CDCP1 abs was achieved. The work underpins CDCP-1 abs as a perspective platform for diagnostics and treatment of RAS driven tumors.

In the second part of the study, investigation of ^{89}Zr labeled transferrin has revealed the remits for specific activity necessary for quantitative measurement of tumor-associated PD-L1 in tumors with low to medium antigen expression. Proposed new molecular imaging approach will improve the detection of clinically problematic samples arising from TSC and/or LAM.
The thesis addresses a very important topic as RAS itself has been proven to be a very difficult therapeutic target. According to the thesis results expression of CDCP1, controlled by RAS, may be a strategic target for diagnostics and therapy.

The thesis is performed with the cutting edge experimental approaches, including in vivo experiments with heterologous transplants in nude mice. Several modified radiolabeled abs were used which allowed detection high sensitivity detection with PET and gamma tomography. CDCP1 abs also have been proven to have therapeutic properties in mice when carrying emitters. Such experiments are still possible only in very advanced laboratories

addressing the high demand for discovery of new therapeutic approaches.

The thesis has a traditional structure contains 8 tables and 26 figures. The literature review is comprehensive and well written. The materials and methods chapter provides sufficient detail for reproduction of experiments. Representation of results are accurate. Analysis of the results are critical and conclusions are based exclusively on the reported data.

The results of the thesis are novel, original and have provided the basis for high impact publications which will be of interest not only to the specialists in molecular imaging and radiotherapy but also to a broader medical and biological audience.

Provisional Recommendation

X☐ *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*