

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

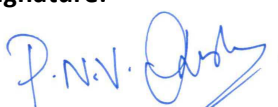
Supervisor: Prof. Konstantin Severinov

Chair of PhD defense Jury: Prof. Yuri Kotelevtsev

Email: y.kotelevtsev@skoltech.ru

Date of Thesis Defense: December 11, 2018

Name of the Reviewer: Naga Vara Kishore Pillarsetty PhD

<p>I confirm the absence of any conflict of interest</p> <p>(Alternatively, Reviewer can formulate a possible conflict)</p>	<p>Signature:</p>  <p>01/12/2018</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 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 PhD candidate Anna Moroz has conducted studies on the development of novel molecular imaging and targeted therapy agents for oncogene RAS driven tumors using in vitro and mouse models of pancreatic cancer by utilizing CUB like domain containing protein-1 (CDCP-1). In order to achieve this goal, she collaborated with Dr. Wells group to use their novel anti-CDCP1 mAb 4A06 and radiolabeling them with zirconium-89 (for imaging) and lutetium-177 (for therapy) and demonstrating that ⁸⁹Zr-4A06 and ¹⁷⁷Lu-4A06 are efficacious for diagnosis and therapy of RAS driven pancreatic tumors. In addition to the main line of work, Anna Moroz has conducted studies on optimizing PET imaging of PD-L1 expression with zirconium-89 labeled Atezoluzumab (⁸⁹Zr-Atezo) in immunocompromized mice models and using zirconium-89 labeled transferrin for studying tuberous sclerosis complex (TSC) and lymphangiomyomatosis (LAM). The problems addressed (RAS driven tumors, PD-L1 imaging optimization and imaging TSC and LAM) by her research are very critical problems requiring serious attention and the solutions developed as part of her research are very elegant and clinically translatable very easily. It is very important to realize that currently (as of late 2018) there are no viable non-invasive diagnostic and therapeutic approaches for treating RAS driven tumors. Therefore the work done as part of the research is ground breaking and attempts to provide a neat solution towards tackling the problem associated with RAS driven tumors.

The introduction to dissertation is very comprehensive and is necessitated by the fact that molecular imaging and targeted radiotherapy problems posed here require multi-disciplinary knowledge, effort and tools to successfully address the problems and find elegant but simple solutions. Overall the structure of the thesis is nicely organized providing details about the RAS family proteins and how CDCP-1 can function as a target for RAS activation and how molecular imaging and targeted radiotherapy can be achieved using antibodies to set the stage for her work being performed. Then followed by the project objectives, methods, results and discussion sections, which are succinct but precise and provide all necessary details. The minor typos and terse sentences in the thesis are arising because Anna is a non-native English speaker and they do not impact the quality of the overall proposal.

To develop solutions for the problems, Anna used both very well established and relevant methods as well as some of the latest techniques that include antibody characterization using reflectance light interferometry, antibody binding assays, small animal PET imaging studies, ex vivo biodistribution studies.

As mentioned in one of the preceding paragraphs, the problems addressed by Anna are very critical both from basic science as well as clinical perspective and the solutions successfully developed by her are of extremely high importance and will achieve high impact and citations after publication.

The solutions developed by Anna are highly relevant for improving outcomes in pancreatic cancer patients. The diagnostic and therapeutic agents developed by Anna can be easily translated to the clinic without much effort after developing GMP production and radiolabeling of antibodies.

During her short time Anna has 4 publications including two first author publications in very good journals. In addition it is my belief that the work done here will lead to multiple high impact publications because they address very important and pestering clinical problems and offer elegant and clinically translatable solutions.

Overall I would rate the PhD work done by Anna Moroz as very important, timely and high quality with a high potential for clinical translation.

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