

Veronika Benson, PhD
Laboratory of Molecular Biology and Immunology
Institute of Microbiology CAS
Víteňská 1083
142 20 Prague 4

Review of PhD thesis entitled “Targeted biocompatible nanoparticles for therapy and cancer diagnostics” submitted by Jitka Neburková, MSc.

The PhD thesis submitted by Jitka Neburková, MSc. focuses on the surface modification of nanoparticles in order to improve their colloidal stability and uptake by cancer cells, while reducing non-specific interactions with normal cells.

The achievements are presented in the form of commented research papers to which the author has contributed. Out of the total 10 publications (published and submitted), the author chose 7 research papers to be commented on within this thesis.

Formal quality and description of the thesis

The thesis (in total 78 pages) comprises a general introduction to the problematic use of nanoparticles with regards to different surface modifications, overall thesis aims, a list of the methods employed, a summary of the results in regard to each publication, specific contributions of the author to each of the commented papers, discussion of the results achieved in the selected publications in regard to the field priorities, and conclusions remarking the answers to the specific aims of the thesis. It is followed by a list of the ten published research papers and four book chapters, a list of the cited literature (over 90 references), and seven attached publications including their supporting data.

The introduction well describes the current approaches and methodology in the development of nanoparticles useful in cancer theranostics. The author clearly explains the achievements as well as pitfalls and weaknesses of the mentioned approaches, including also her own thoughts and brief commentary. The text is fluent and easy to read for a broader audience, even without deep knowledge in colloidal and polymeric chemistry. All statements are properly supported by current

references. Generally the thesis exhibits high quality graphically and good readability, and the author uses correct terminology and current literature citations. The author's English is for the most part very good; however some sentences have confusing wording for example statements on pages 22 (before the Figure 4) and 41 (specific x non-specific interaction/one/-), and thus are a bit harder to understand quickly. Furthermore some abbreviations of the cell lines involve designation of the tissue origin and some do not (for example HeLa vs. LNCap).

Topicality of the research

The main hypothesis questioned in this work, the specific aims, and experimental approaches all reflect the contemporary challenges emerging in the nanomaterial and nanomedicine fields. The author has good orientation in the chosen problematics, including possibilities and weaknesses of individual approaches that are well documented by her discussion and comments within the thesis, as well as the numerous publications.

Thesis Aims, Methods, and Results

The main goal of the thesis was to improve surface properties of nanoparticles in order to eliminate non-specific interaction with neighboring cells and support the targeting and the interaction with cancer cells.

In the main hypothesis, the author has questioned if distinct surface modifications lead to an increase in the specificity of nanoparticles-cancer cells interactions, and she has divided that broad topic into 6 specific aims. These specific aims discussed recent problematics in the field such as colloidal stability of nanoparticles after surface coatings, biocompatibility and cellular uptake of different nanoparticles, the effect of the size and shape of nanoparticles, and specific-cell targeting via ligand-decorations of the nanoparticle surface. The author also discusses the usefulness of nanodiamonds for biomedical applications.

In summary, the author has successfully answered all specific aims / hypotheses she pointed out in the beginning of her thesis.

Specifically:

She has revealed that the differences in nanoparticle colloidal stability do depend on nanoparticle size, shape, surface modification including polymers types, or methods of polymer-NP coatings. She has improved the targeting nanoparticles systems to be more cancer-cell specific with minimal non-cancerous cell interactions – important for both, diagnostic as well as therapeutic use of the systems in the future. Here she has developed targeting systems based on polymer coatings as well as on

cancer-cell specific markers.

Finally, the nanoparticles she has modified and characterized were used in killing HeLa cancer cells via thermoablation or as programmable pH and redox potential nanosensors.

The specific surface modifications performed in this thesis are undoubtedly new contributions in the field and because of that they are also published in research journals with moderate impact factors.

Requirements of independent research work

The thesis submitted fulfills the requirements of independent research work. The results of the research obtained during Ph.D. studies were published in 8 full papers and 2 communications, and another paper has been submitted recently. Out of that, Jitka Neburková, MSc. is the first author in 5 of them. The average impact factor of her publications equals 6.1.

Conclusion

I have thoroughly reviewed the submitted thesis, and I believe it fulfills the requirements of the author to independent experimental research and obtaining the title PhD.

Supplementary Questions:

1. What are the applications that benefit from non-specific adsorption of proteins to ND surface?
2. You mention that NP decorated with Tf showed 175x higher specific interaction; however then you used the decoration with glutamate carboxy-peptidase exhibiting only 75x higher specificity of interaction. From the text flow it seemed that you preferred the glutamate carboxy-peptidase decoration, even though it had lower specificity than Tf. Why?
3. Why have you chosen mouse polyomavirus particles when they exhibit such a high nonspecific interaction with cells? Was that a control system to evaluate the NDP efficacy and selectivity?

Prague, August 22, 2018



Veronika Benson, PhD.