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Praha, 15.5.2018

## **Review of the PhD thesis: Anti-tumor activity and toxicity of HPMA copolymer conjugates bearing cytotoxic drugs**

In her PhD thesis Barbora Tomalova follows up on the longterm research focus of her research team and extends preclinical findings of the work focused on the development of high molecular weight modifications of classical chemotherapeutic drugs, such as doxorubicin and docetaxel.

PhD thesis is structured according to the instructions for the shorter version of the thesis. The introduction focuses on the description of the history and current status of HPMA copolymer based chemotherapeutics and it's then followed by three fulltext papers describing work of dr.Tomalova in this fiels.

The introduction is concise, easy to follow but rather brief. I would appreciate a more in depth overview of the history and translational activities on HPMA conjugates and more elaborate sections on the ability of HPMA conjugates to induce longterm protective immunity in treated mice models.

At the same time, I acknowledge that the study complies with the criteria for the shorter version of the PhD thesis and that there is lots of additional information in the introductory sections of included research papers. I fully acknowledge that dr. Tomalova has exceeded the criteria set for the defense of the PhD thesis having five scientific papers in peer reviewed journals, one of them as a first author:

Etrych T., Strohalm J., Sirova M., Tomalova B., Rossmann P., Rihova B., Ulbrich K. and Kovar M.: High-molecular weight star conjugates containing docetaxel with high anti-tumor activity and low systemic toxicity *in vivo*. Polym. Chem. 6: 160-170, **2015**.

IF = 5,52

Tomalova B., Sirova M., Rossmann P., Pola R., Strohalm J., Chytil P., Cerny V., Tomala J., Kabesova M., Rihova B., Ulbrich K., Etrych T. and Kovar M.: The structure-dependent toxicity, pharmacokinetics and anti-tumour activity of HPMA copolymer conjugates in the treatment of solid tumours and leukaemia. JCR 223: 1-10, **2016**.

IF = 7,44

Pechar M., Pola R., Janouškova O., Sieglöva I., Kral V., Fabry M., Tomalova B. and Kovar M.: Polymer Cancerostatics Targeted with an Antibody Fragment Bound via a Coiled Coil

Motif: *In Vivo* Therapeutic Efficacy against Murine BCL1 Leukemia. *Macromol. Biosci.*

Published online, ahead of print, **2017**.

IF = 3,23

Tomala J., Kovarova J., Kabesova M., Votavova P., Chmelova H., Dvorakova B., Rihova B. and Kovar M.: Chimera of IL- 2 Linked to Light Chain of anti-IL- 2 mAb Mimics IL-2/anti-IL- 2 mAb Complexes Both Structurally and Functionally. *ACS Chem. Biol.* **2013**.

IF = 5,356

Skopova K., Tomalova B., Kanchev I., Rossmann P., Svedova M., Adkins I., Bibova I., Tomala J., Masin J., Guiso N., Osicka R., Sedlacek R., Kovar M. and Sebo P.: Cyclic AMP-Elevating Capacity of Adenylate Cyclase Toxin-Hemolysin Is Sufficient for Lung Infection but Not for Full Virulence of *Bordetella pertussis*. *Infection and Immunity* 85 (6): e00937-16, **2017**

IF = 3,593

Rather than discussing experimental aspects of the individual papers that successfully passed the peer review process, I would like to ask several more conceptual and general questions to better understand the context of the experimental work:

- There is now a renaissance of the clinical development of antibody drug conjugates approach combining targeting of the tumor cells by monoclonal antibody conjugated to various forms of toxic payloads. How would you compare the antibody drug conjugate approaches to the approach using HMPA conjugation?
- Could you please briefly review the history and current status of the translational activities around the HPMA bound chemotherapeutics? What is the IP status of the technology? Are the novel modifications of the HMPA backbone eligible for new IP generation?
- What was the reason for the selection and testing of doxorubicin and docetaxel? Is the presented approach also applicable to other chemotherapies?
- Have you investigated in more details the potential of doxorubicin-HPMA conjugates to induce immunogenic cell death?

Judging from the PhD thesis manuscript, I conclude that during her PhD studies Barbora Tomalova gained proficiency in the vast number of experimental methods as documented by five original articles in respected scientific journals. The results of her scientific projects clearly show that she meets the requirements set by the Immunology board of PhD program and she can be awarded the PhD degree.

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