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### HPMA copolymer-bound doxorubicin as endogenous vaccine substantially increases therapeutic effect of check-point blockade monoclonals: Acute versus chronic model

DOX<sup>HYD</sup>-HPMA is doxorubicin bound through hydrazone bond to synthetic polymeric carrier based on *N*-(2-hydroxypropyl)methacrylamide. It is effective anticancer polymeric prodrug with decreased side-toxicity and the ability to induce immunogenic cancer cell death releasing site-specific tumor antigen and thus acting as an endogenous vaccine. We have compared chemo-immunotherapy combination treatment of EL4 T cell lymphoma and 4T1 breast carcinoma with DOX<sup>HYD</sup>-HPMA and with immune checkpoint blocking anti-CTLA-4 and anti-PD-1 MAbs either alone or in a mixture. To document the role of intestinal microbiota we use germ-free (GF) mice and GF mice monocolonized with *Bifidobacterium thetaiotaomicron*. Acute model of disease when mice are transplanted once with a lethal dose of tumor cells was compared with chronic model where mice are injected six times every other day with a low number of tumor cells. Healthy mice treated with anti-CTLA-4 and anti-PD-1 mAbs did not show any signs of toxicity while significant co-toxicity was seen in cancer-bearing mice. Treatment with checkpoint inhibitors only exerted a very limited cancer response as no long term survivors (LTS) were recorded. On the other hand more than 60% of mice injected also with therapeutically suboptimal dose of DOX<sup>HYD</sup>-HPMA survived disease-free for more than 100 days. Those suffering from chronic model of cancer showed considerably higher proportion of PD-1<sup>+</sup> cells in tumor microenvironment and reacted substantially better to anti-CTLA-4 or anti-PD-1 treatment than mice with the acute model.

#### Biography

Blanka Rihova is Professor of Immunology, Charles University, Prague, the Czech Republic and Adjunct Professor of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, USA. In 2000–2007 she was a director of the Institute of Microbiology, Academy of Sciences of the Czech Republic. She is president of Czech Immunology Society, vice-president of Czech Learned Society and vice-president of Scientific Council of CAS.

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