



**Karolinska
Institutet**

Institutionen för Onkologi-Patologi

Cancer therapy using viral- and bacterial proteins, as vectors for vaccines or as carriers of cytostatics

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet
offentligen försvaras i Cancer Centrum Karolinskas föreläsningssal R8:00
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av

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ABSTRACT

New cancer therapies are urgently needed, since available treatment options today have negative side effects, and cure only about half of the patients with invasive cancer. One, relatively new, option is to vaccinate against cancer, by introducing an antigen that is present on the tumor cells into the patient to stimulate specific immunity against the tumor. For this purpose viral capsid proteins, which can self-assemble into so called virus-like particles (VLPs), can be engineered to contain tumor antigens in the form of DNA, whole protein or peptides and be used as vaccines. Here, VLPs based on murine polyomavirus (MPyV) and murine pneumotropic virus (MPtV) containing the extracellular and transmembrane part of the breast cancer antigen *Her2/neu*, or the whole prostate cancer antigen PSA, have been produced.

As mentioned above there are side effects with cancer treatment, and the use of the common cytostatic anti-cancer drug Cisplatin has a number of side effects, including; nephrotoxicity (kidney damage); neurotoxicity (nerve damage); and ototoxicity (hearing loss). To possibly inhibit some of this toxicity we attempted to make use of the “enhanced permeability and retention” (EPR) effect that causes macromolecules to accumulate more in tumor tissue than in normal tissue, since tumor blood vessels are leaky, and tumors lack effective lymphatic drainage. The use of a macromolecule as a carrier for Cisplatin would therefore hold the potential to reduce some of its negative side effects. For this purpose it was investigated whether the macromolecule right-handed coiled coil “RHCC” protein from bacterium *Staphylothermus marinus*, that can incorporate heavy metals, would also incorporate cisplatin containing the metal platinum.

The overall aim of the first three papers in this thesis was to develop and determine pre-clinical efficacy of MPyV- and MPtV-VLPs carrying *Her2/neu* or PSA against tumors expressing these tumor antigens. The overall aim of paper IV was to investigate RHCC’s potential to carry cisplatin efficiently to tumors, while retaining the cytotoxic effect of the drug.

In paper I we demonstrated that homologous vaccination with human *Her2/neu*-VLPs was more efficient against outgrowth of human *Her2/neu*-expressing tumors than heterologous vaccination with rat *Her2/neu*-VLPs, while against rat *Her2/neu*-tumors, rat *Her2/neu*-VLPs were more efficient. Furthermore, we observed that vaccination with MPtVLPs was more efficient than vaccination with MPyVLPs, and that Her2MPtVLPs could be used for therapeutic vaccination. In paper II we demonstrated that both CD4⁺ and CD8⁺ T cells are involved in the tumor protective response after Her2MPtVLP vaccination. In paper III immunization with PSA-MPyVLPs, given together with CpG and loaded onto dendritic cells, was shown to protect against outgrowth of PSA-expressing tumor cells. In paper IV RHCC was shown to incorporate cisplatin, and the complex entered human tumor cells, while retaining the cytotoxic potential of the drug both *in vitro* and *in vivo*.

In conclusion, in this thesis it is shown that VLPs based on MPyV and MPtV were efficient vectors for tumor antigens in cancer vaccination, evoking both CD4⁺ and CD8⁺ cell responses. In addition, we show that RHCC can function as a carrier for cisplatin, and that it could potentially reduce some of the negative side effects with cisplatin treatment.