AB045. Turning-off the survivin stimulus: overcoming retinoblastoma drug resistance *in vitro*

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Background: Cancer is the leading cause of death in Canada. One of the major challenges in the cancer therapy is chemoresistance, which plays a critical role in cancer dissemination, relapse and patient clinical outcome. In retinoblastoma, the most common cancer affecting children eyes, refractory cases are treated by enucleation in order to avoid brain metastasis. Overexpression of the oncogene survivin is recurrent in many cancer types, including in retinoblastoma. Survivin upregulation results in apoptosis inhibition, cell mitosis stimulation and DNA repair. Therefore, survivin silencing through small-interfering RNA (siRNA) technology has emerged as a powerful approach in cancer therapy to overcome chemoresistance. However, the efficacy of siRNA mainly relies on its successful delivery, limited by its highly hydrophilic nature and rapid nucleases degradation. We have recently developed lipid nanoparticle able to protect siRNA in the systemic circulation and release it within the cell in a pH-sensitive fashion. Here we propose to downregulate the survivin oncogene, *in vitro*, through a liposome-mediated siRNA delivery to improve drug's effectiveness in a retinoblastoma cell line model (Y79).

Methods: Firstly, we formulated a survivin-targeted nanocomplex (STN) composed of pH-sensitive liposomes and survivin-targeted siRNA. STN was characterized regarding size, polydispersity index and zeta potential. The survivin silencing efficiency in retinoblastoma cells (Y79) was assessed through RT-qPCR and Western blotting assays. Then, we evaluate the impact of survivin-silencing on Carboplatin, Topotecan, Teniposide and Melphalan's effectiveness in Y79 cells through a cell viability assay.

Results: A novel STN was formulated within desired nanoscale parameters. Survivin was efficiently depleted at both mRNA (RT-qPCR) and protein levels (western Blot). Furthermore, survivin downregulation synergistically improved chemotherapeutics' effectiveness *in vitro* in Y79 cells. Interestingly, survivin downregulation did not modify carboplatin's effect in a non-tumoral human retinal cells (ARPE-19).

Conclusions: Those results demonstrate the cancer specific expression of the oncogene survivin and highlight the survivin-silencing as a promising retinoblastoma-specific therapy. This strategy holds a promising clinical translational application, encouraging further experimentation *in vivo*.

Keywords: Retinoblastoma; chemoresistance; survivin; siRNA; pH-sensitive liposomes

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