



**Development of a novel nanoparticle immunotherapeutic for the treatment of cancer**

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**ABSTRACT:**

Cancer continues to be one of the leading causes of death worldwide in spite of the recent development of more effective treatment options. One interesting avenue in cancer treatment is the development of innovative immunostimulants that can promote killing of the cancer cells by cytotoxic T lymphocytes (CTLs) while also disrupting the local immunosuppressive tumor microenvironment. In a continuous effort to fight cancer, our group has developed a novel glycoliposome containing muramyl dipeptide and a low dose of the chemotherapeutic agent cytarabine (Ara-C/DS). The immunostimulatory properties of Ara-C/DS nanoparticles were evaluated in peripheral blood mononuclear cells (PBMCs) isolated from healthy donors and cancer patients *in vitro*. Antigen-specific CTLs were expanded using a pool of standard immunogenic peptide antigens (CEF) with or without Ara-C/DS and IFN-gamma producing CTLs were measured by flow cytometry upon antigen re-stimulation. The effects of Ara-C/DS on antigen-presenting cells (APCs) were also investigated by western blot analysis of the stimulator of interferon gene (STING) pathway and flow cytometry analysis of macrophage surface markers. We demonstrated that Ara-C/DS displays strong anticancer immune properties. It stimulated the production of pro-inflammatory cytokines IFN-gamma, TNF-alpha and IL-12p40, but not the anti-inflammatory IL-10 in PBMCs from both healthy donors and cancer patients, and increased CEF-specific CTLs producing IFN-gamma from  $6.8 \pm 5.0$  % to  $19.1 \pm 3.0$  %. Ara-C/DS also activated the STING pathway, a known enhancer of CTLs, in APCs, as well as downregulated CD163 and upregulated CD80 in M2 differentiated macrophages suggesting a shift towards the beneficial immunogenic M1 phenotype. Not only are these findings the first to show that cytarabine possesses immunostimulatory properties at low doses, but its activity is also greatly improved with the use of our novel nanoparticle system. Ara-C/DS is an interesting and innovative anticancer immunostimulant which warrants further studies.