Removing Brakes of Tumor-Resident Myeloid Cells as a Novel Cancer Immunotherapy

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Recent approaches in cancer immunotherapy revolve around encapsulating immunostimulatory molecules within nanoparticles and using systemic delivery to deliver them into the tumor, generating powerful antitumoral immune responses. Previous work sought to develop a nanoparticle with synergistic action by coloading an agonist of the stimulator of interferon genes pathway (STING) and a Toll-like receptor 4 (TLR-4) agonist. The STING agonist was cyclic diguanylate monophosphate (c-di-GMP), and the TLR-4 agonist was monophosphoryl lipid A (MPLA). However, one of the challenges of immunotherapy is identifying a rational dose and in particular, the minimum effective dose. It is essential to strike a balance between pro-inflammatory immune stimulation and overactivation/tolerance. In order to efficiently achieve this, this project utilizes in silico modeling. In order to model in vivo transport of the immunostimulatory nanoparticle, this system will be studied using a compartmental-model-based approach. Transport from the microcapillary system of the tumor into the perivascular space is modeled as a one directional system and the rate constant for this transfer was assumed to be static. A system of non-linear ordinary differential equations was constructed and solved in Python, using SciKitLearn's in-built routine, solve_ivp. The resulting equations successfully modeled existing in vivo data and were capable of predicting and optimizing the in vivo behavior of the immunostimulatory nanoparticle. Ongoing work seeks to expand the compartmental model to include further constraints and ultimately optimize and test these conditions in in vivo models.

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