766 TOWARD SAFE, SYSTEMIC DELIVERY OF SYNTHETIC TLR7/8 AGONISTS USING BOTTLEBRUSH PRODRUGS (BPDS)

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Background Although toll-like receptor (TLR) agonists such as imidazoquinoline derivatives (IMDs) have been well researched and are FDA approved as topical solutions for treatment of skin cancer, their systemic delivery for treatment of metastatic disease has not been successful due to toxicity issues. Therefore, to lessen the degree of the adverse effects of intravenous delivery of IMDs such as resiquimod (R848), a bottlebrush prodrug (BPD) system enabling controlled release of R848 at tunable rates was designed and synthesized. We hypothesized that this approach would allow for minimizing the release of the free drug in serum, allowing for a higher concentration to accumulate in the tumor while minimizing systemic side effects.

Methods R848 was conjugated to a bottlebrush polymer with different linkers designed to precisely tune the R848 release rate. The release rates of the drug delivered through this system were first tested in PBS. These prodrug formulations were validated for drug activity in vitro in mouse and human TLR reporter cells. The maximum tolerable dose was defined by monitoring weight loss and serum cytokine levels upon intravenous administration at multiple concentrations. Finally, anti-tumor efficacy of the BPD system was tested in vivo using the MC38 colon cancer model as a monotherapy and in combination with anti-PD-1 antibody treatment.

Results The in-vitro half-lives of the conjugated drugs varied from a few days to over a month when tested in PBS. The different BPDs demonstrated linker dependent TLR activation upon culturing with TLR reporter cells validating the immunomodulatory activity of R848. It was found that the R848-BPDs, which accumulated at the tumor site over time, significantly delayed tumor growth and improved survival rates, which was further enhanced when used in combination with anti-PD-1.

Conclusions Overall, our research suggests that our R848-BPD platform allows for safe, systemic delivery of TLR agonists to activate the immune system in treatment of cancer.

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