Biomimetic nanoparticles for lymphe node focused immune activation

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Agonists of Toll-like receptors are potent activators of the innate immune system and hold promise as vaccine adjuvant and for anti-cancer immunotherapy. Unfortunately, in soluble form, they readily enter systemic circulation and cause systemic inflammatory toxicity. Here we demonstrate that by covalent ligation of a small molecule imidazoquinoline-based TLR7/8 agonist to 50 nm sized degradable polymeric nanoparticles, the potency of the agonist to activate TLR7/8 in *in vitro* cultured dendritic cells is largely retained. Importantly, imidazoquinoline-ligated nanoparticles focused the *in vivo* immune-activation on the draining lymph nodes whilst dramatically reducing systemic inflammation. Mechanistic studies revealed a prevalent passive diffusion of the nanoparticles to the draining lymph node.

Clinical relevance of this therapeutic strategy is demonstrated as vaccine adjuvant and for tumour immunotherapy. Immunization studies in mice show that, relative to soluble TLR7/8 agonist, imidazoquinoline-ligated nanoparticles induce superior antibody and T cell responses against an admixed antigen. Currently, we are evaluating the potential of imidazoquinoline-ligated nanoparticles for co-delivery of tumour-associated peptide antigens.

On the other hand, we also demonstrated that imidazoquinoline-ligated nanoparticles are capable to reduce tumour growth upon peri-tumoral injection by activation of DCs in the tumour-draining lymph node.

In summary, our approach opens avenues to enhance the therapeutic benefit of small molecule TLR agonists for a variety of applications in anti-cancer immunotherapy.