Title:

Discovery and Early Development of Targeted Innate Immune Agonists for Cancer Immunotherapy

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Abstract:

Toll-like receptors 7 and 8 are involved in modulating the adaptive and innate immune responses, and their activation has shown promise as a therapeutic strategy in the field of immuno-oncology. While systemic exposure to TLR7/8 agonists can result in poor tolerance, combination therapies and targeted delivery in a form of antibody−drug conjugates, also called targeted immune agonist or TIA, can help mitigate adverse effects. We identified a novel and potent series of pyrazolopyrimidine-based TLR7/8 agonist payloads that successfully induce the production of various pro-inflammatory cytokines and chemokines from human peripheral blood mononuclear cells. The mechanism of action of TIAs, when conjugated with a targeting antibody, involves tumor antigen recognition, Fcγ-receptor-dependent phagocytosis, and TLR-mediated activation to drive tumor killing by myeloid cells. Several new low DAR anti-HER2 TIAs conjugated with novel TLR7 or dual-TLR7/8 agonists with cleavable and non-cleavable linkers were synthesized and profiled. In vitro studies demonstrated that these TIAs activate myeloid cells only in the presence of antigen-expressing cancer cells. Evaluation in ELISpot-based assays confirmed the low immunogenicity of these constructs. Systemic administration of the novel TIAs in tumor-bearing mice resulted in tumor reduction at low doses. These results provide a strong rationale for further development of the TIAs as a novel class of immunotherapeutics.