Recent studies indicate that local delivery of immunostimulatory adjuvants can activate tumor resident antigen presenting cells (APCs), driving uptake, processing and presentation of tumor neoantigens to T cells that mediate anti-tumor immunity. To overcome challenges associated with intratumoral delivery of such adjuvants, we developed a novel class of systemically delivered TLR immune-stimulating antibody conjugates (ISACs) that comprise a TLR7/8 agonist conjugated to tumor-targeting monoclonal antibodies. In vitro co-cultures of human cancer cell lines and leukocytes revealed that ISACs potently activate primary myeloid APCs, leading to increased co-stimulatory molecule expression and secretion of pro-inflammatory cytokines. Surprisingly, ISACs also induced DC differentiation from monocytes, as measured by changes in cellular morphology and DC-associated surface markers. Finally, we demonstrated in vivo efficacy in xenograft and syngeneic tumor models in which ISAC treatment led to tumor clearance and development of immunologic memory. These results provide a strong rationale for this technology as a platform for cancer immunotherapy.

**Proposed Mechanism of Action**

**Human in vitro Experimental Design**

**Humn in vivo Experimental Design**

**In Vivo Experimental Design**

**NHP Pharmacokinetics**

**Key Findings**

1. ISACs elicit robust myeloid activation and DC differentiation in human cells
2. ISAC treatment leads to anti-tumor efficacy in trastuzumab-resistant models
3. ISAC-mediated anti-tumor immunity supports epitope spreading beyond ISAC-target antigen
4. Tumor clearance following ISAC treatment generates immunologic memory
5. ISAC has acceptable pharmacokinetics and is well tolerated in NHP study