DEVELOPMENT OF TLR7- AND STING-CONJUGATABLE AGONISTS FOR IMMUNOSTIMULATORY ADC-BASED CANCER THERAPIES

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Background Immunostimulatory agents such as TLR7 (Toll-like receptor 7) and STING (Stimulator of interferon genes) agonists have emerged as attractive cancer immunotherapy targets. They play a key role in the activation of tumor resident antigen presenting cells and drive anti-tumor immunity by promoting antigen cross-presentation and direct killing of tumor cells. However, the enhanced immune activation following systemic administration or local delivery of these agonists has several limitations, including off-target and toxic effects. Antibody-drug conjugates (ADCs)-based therapies offer the great advantage of tumor-targeted compound delivery, thus abolishing these drawbacks. A novel class of ADCs, in which TLR7 or STING stimulatory ligands (payloads) are linked with tumor-targeting monoclonal antibodies (mAbs), constitutes a promising new and safe therapeutic approach.

Methods InvivoGen has developed two sets of TLR7 or STING agonists conjugatable to antibodies through two different methods. These agonists, TL7-887 & TL7-975 (TLR7) and STG-982 & STG-968 (STING) were first evaluated on TLR7- or STING-expressing reporter cells. Then, they were conjugated to the tumor-associated antigen (TAA)-targeting Anti-HER2 (trastuzumab) and Anti-TROP2 (sacituzumab) mAbs, both used in FDA-approved ADCs. The activity of these immunostimulatory ADCs was validated using in vitro co-culture models mimicking the tumor microenvironment.

Results All of the aforementioned TLR7 and STING payloads were able to activate TLR7- or STING-expressing reporter cells similar to well-known TLR7/STING agonists. Their conjugation to Anti-HER2 and Anti-TROP2 mAbs was achieved with a drug-to-antibody ratio between 4 and 6. In HER2/TROP2-expressing cells, these ADCs induced a stronger TLR7-/STING-mediated immune response in comparison with the free agonists or control ADCs. In vitro co-cultures of immune cells with HER2- or TROP2-expressing cancer cells showed a significant higher production of IL-6 and CXCL10 cytokines in response to TLR7- and STING-ADCs, respectively.

Conclusions We have successfully developed synthetic conjugatable TLR7 and STING agonists to generate anti-tumor antibody conjugates. Our data show that these pattern recognition receptor (PRR)-ADCs elicit robust myeloid cell activation compared to the unconjugated ligands or negative control ADCs. Additionally, these PRR-ADCs are only functional in the presence of both a TLR7/STING agonist and TAA cell surface expression, indicating their specificity. Ex vivo whole blood-based assays and in vivo studies in a murine cancer model are ongoing to evaluate their efficacy and safety. Taken together, our results highlight the potential of these original conjugatable PRR-agonists to be used with clinically relevant TAA-targeting mAbs for the treatment of a large panel of tumors.

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