Intra-tumoral Delivery of Toll-Like Receptor 7/8 Dual Agonist via a Thermosensitive Gel Based Formulation
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Purpose
Toll-like receptors (TLRs) are known as one of the most important regulatory signaling pathways of both innate and adaptive immune responses and TLR agonists have shown efficacy toward a variety of tumors. TLRs are part of emerging cancer immunotherapies as a new option in cancer treatment. TLR agonists are nucleotide analogues that can be used for cancer immunotherapy or vaccination. With systemic administration of TLR agonists, the immune system is stimulated throughout the entire body, potentially causing undesirable side effects. Thus, local administration such as topical delivery of TLR agonists has been introduced to minimize systemic side effects. Intra-tumoral delivery of TLR agonists is being developed as another approach to localize the drug and attempt to limit systemic side effects. Here, the application of a poloxamer 407 thermogel based formulation for intra-tumoral delivery of a TLR7/8 dual agonist is introduced.

Methods
The TLR7/8 dual agonist was formulated with purified poloxamer 407 and the impact of the addition of the drug to poloxamer 407 was evaluated.

Results
The in-vitro release study showed a slight initial burst release followed by sustained release of the TLR7/8 dual agonist from poloxamer 407 thermogel formulations. The pharmacokinetics, efficacy, and systemic cytokine production of the poloxamer 407 formulation incorporating TLR7/8 were conducted in a murine B16-OVA tumor model. The PK study showed an initial slight burst at the 6 hour time point followed by a drop in drug levels in serum. Drug levels in the tumor dropped by ~70% over the 14 days of the PK study indicating retention of the drug in the tumor. Additionally, tumor growth inhibition (TGI), survival, and serum cytokines results for post IT injection of the poloxamer 407 formulation showed that the formulation incorporating the TLR7/8 dual agonist had both better TGI performance and better percent survival when compared to the control group. Finally, the serum cytokines measurement from blood samples indicated that increasing the dose decreased the serum cytokines levels which could be as a result of a reduction of drug diffusion and escape from the tumor site.

Conclusion
Intra-tumoral delivery of TLR7/8 dual agonist via a poloxamer 407 thermogel based formulation was efficacious and could minimize systemic side effects.