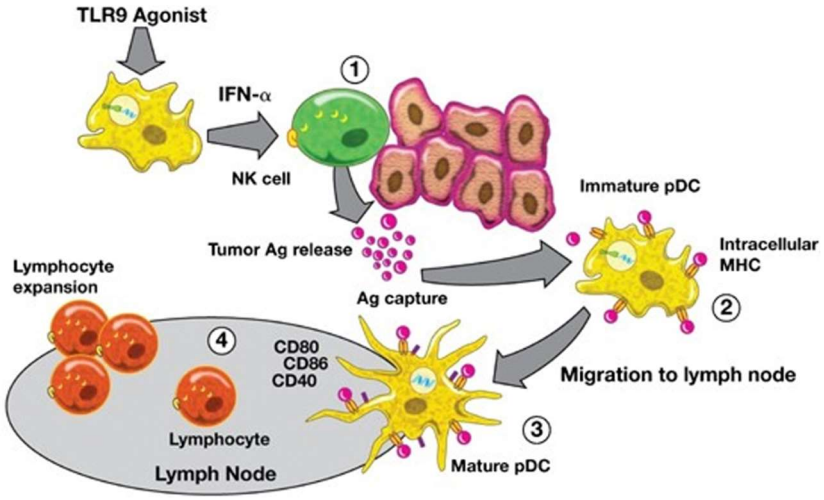
TLR9 Agonists Emerges as a Promising New Partner for Checkpoint Inhibitors

The 2011 Noble Prize in Physiology or Medicine was awarded to groundbreaking discoveries on Toll and Toll-like receptor (TLR) activation of the first line of defense of the immune system against viruses and bacteria as well as cancerous cells. That part of the immune system, the innate immune response can prime the induction of long-lasting adaptive immunity, which both fights off the first attack and retains memory of the encounter to react to future attacks.

TLRs alert the body to potential danger by recognizing specific molecules derived from bacteria, viruses, or damaged cells. TLRs essentially act like a smoke alarm, warning the body when trouble is detected. Toll-like receptor 9 (TLR9) is one of the most promising targets for increasing the response and reversing the resistance to current cancer immunotherapies. TLR9 agonists have been developed to inhibit tumor growth by converting immunologically "cold" tumors to immunologically "hot" tumors and make them susceptible to different cancer treatments, such as breast cancer, lung cancer, melanoma, colon, cervical, pancreatic cancer, lymphoma et cetera.



In a recently published review article in *OncoTargets and Therapy*, written by Lilit Karapetyan, Jason J Luke and Diwakar Davar, the authors have discussed and reviewed the results of preclinical studies and ongoing clinical trials of TLR9. According to Karapetyan et al., TLR9 agonists are well tolerated as monotherapy and do not appear to increase the toxicity of chemotherapeutic, targeted, radiation, and other immunotherapy agents as part of combination therapy. The main adverse effects are injection site reactions and flu-like symptoms, of mild to moderate severity and typically well managed with symptomatic treatment – and have resulted in treatment discontinuation in only a small number of patients in clinical trials. In terms of efficacy, preclinical studies of TLR9 agonists suggested efficacy both as monotherapy and in combination with several agents, which led to clinical trials in patients with advanced cancer with antitumoral responses in both treated and untreated tumors. Intratumoral administration showed better local and distant responses in comparison to intravenous or subcutaneous administration. According to the article, the greatest excitement has been seen in combinations of TLR9 agonists with immune checkpoint inhibitors.

The need for repeated intratumoral injections when using standard formulated TLR9 agonists poses a risk for the patients and increases the costs for the healthcare systems. As a response to that, LIDDS has developed a NanoZolid-formulated TLR9 agonist that only requires a single injection, resulting in continuous TLR9 activation at an optimal intratumoral concentration over an extended period of time. LIDDS has completed a preclinical data package on its NZ-TLR9 project showing that a single NZ-TLR9 injection is reducing tumor growth and improves the survival of mice. The TLR9 agonist is released during at least 6 weeks with equal efficacy as with repeated standard TLR9 agonist injections. NZ-TLR9 is therefore an optimal choice for treating deep lying tumors needing weekly injections. LIDDS is planning a clinical Phase I trial of NZ-TLR9 treating solid tumors with intratumoral NZ-TLR9 targeting head and neck cancer, melanoma, sarcomas and lymphomas combining 2 million diagnosed patients each year.

To find out more please visit:

https://www.dovepress.com/toll-like-receptor-9-agonists-in-cancer-peer-reviewed-article-OTT

https://liddspharma.com/pipeline/#nz-tlr9