206 CpG anti-PD-L1 Immunoconjugate for Cancer Therapy

Asset Overview

Product Type	CpG anti-PD-L1 Immunoconjugate
Indication	Oncology
Current Stage	Lead Identification/optimization
Target(MoA)	ADC
Brief Description	The antibodies are conjugated to CpG, a Toll-like receptor 9 agonist, which activates innate immune cells. Preclinical studies showed that CpG-conjugated antibodies delay tumor growth and improve survival. Chemical conjugation of CpG to checkpoint inhibitors may sensitize cold tumors to ICI treatment.
Organization	University of Southern California

Differentiation

□ **Unmet need of immune check point inhibitor (ICI)**

- Immune checkpoint inhibitors (ICIs) have demonstrated unprecedented success in treating several types of cancers
- The therapeutic effectiveness of ICIs, is limited to "hot" tumors which bear large neoantigen burden that can activate adaptive immunity through induction of T cell response. Improving the ability of ICIs to treat "cold" tumors with reduced neoantigen burden, therefore, will expand their therapeutic potential.

□ **CpG-conjugated anti PD-1**

- CpG contain motifs of unmethylated cytosine-phosphate-guanosine dinucleotides that mimic bacterial and viral DNA, and are known to stimulate dendritic cells, B cells, and natural killer cells
- CpG therapy has been shown to elicit a Th1-like pattern of innate immune activation and inhibit immune suppressor cell populations like myeloid-derived suppressor cells
- These immune effects are mediated through TLR9-dependent and -independent pathways, and appear to be varied across species and the route of administration
- Researchers at USC have generated antibodies which enhance adaptive anti-tumor immune response by eliciting innate immunity. The antibodies are conjugated to CpG, a Toll-like receptor 9 agonist, which activates innate immune cells
- Preclinical studies showed that CpG-conjugated antibodies delay tumor growth and improve survival
- Chemical conjugation of CpG to checkpoint inhibitors may sensitize cold tumors to ICI treatment

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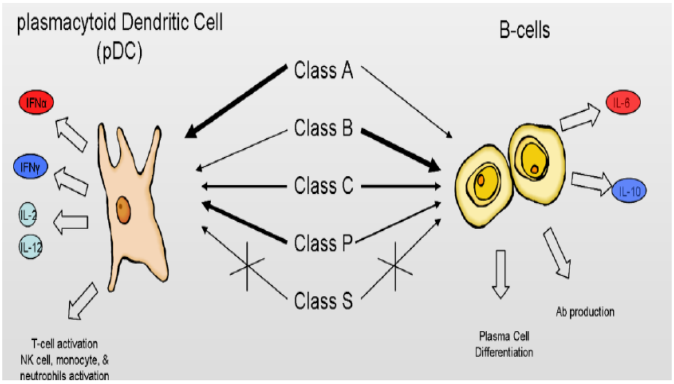
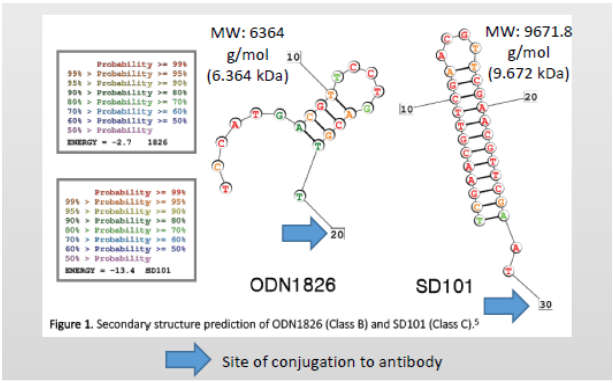
Key Data

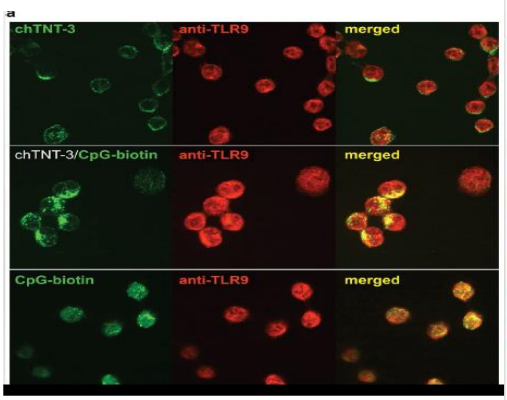
Structure and Function of CpG ODN (TLR9 Agonists)



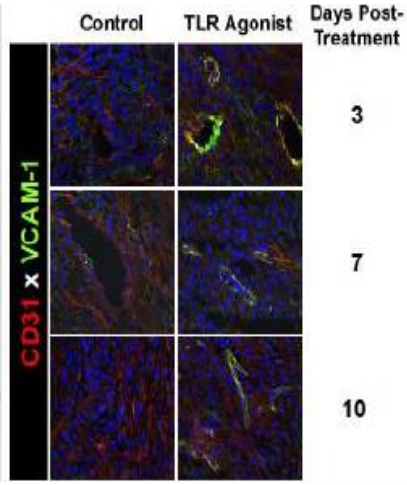


CpG oligodeoxynucleotides (or CpG ODN) are short single stranded synthetic DNA molecules that containa cytosine triphosphate deoxynucleotide ("C") followed by a guanine triphosphate deoxynucleotide ("G"). The "p" refers to the phosphodiester link between consecutive nucleotides, although some ODN have a modified phosphorothioate (PS) backbone instead. When these CpG motifs are unmethylated , they act as immunostimulants . CpG motifs are considered pathogen associated molecular patterns (PAMPs) due to their abundance in microbial genomes but are rare in vertebrate genomes. The CpG PAMP is recognized by the pattern recognition receptor (PRR) Toll Like Receptor 9 (TLR9), which is constitutively expressed only in B cells and plasmacytoid dendritic cells (pDCs) in humans and other higher primates . This receptor is found in the endosome of antigen presenting cells and some tumors.

ICC analysis of CpG-conjugated Ab



Co-localization of CpG Moiety with TLR 9 Receptor in Cytoplasmic Endosome.



Targeted CpG alters tumor vasculature to express adhesion molecules required for translocation of immune cells into tumor. CD31 is marker for tumor vessels. VCAM is marker for adhesion molecule expression.

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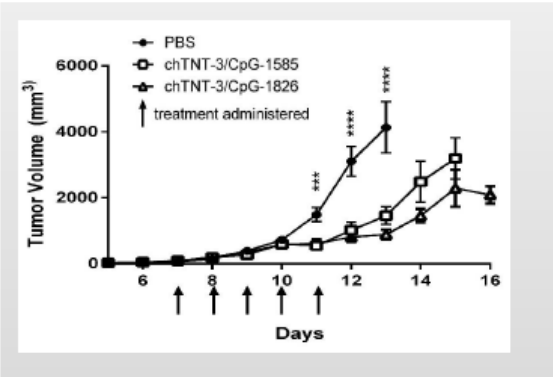
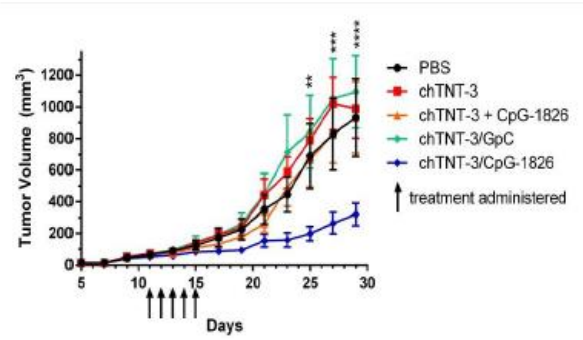
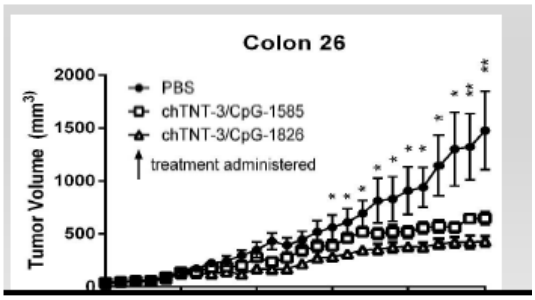
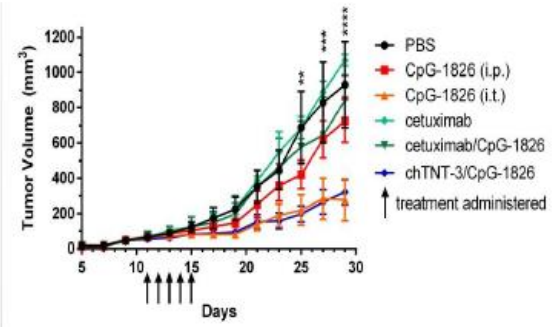
Therapeutic Effect of CpG /chTNT 3 on Cold (B16 Melanoma) And Hot (Colon 26) Tumor Models

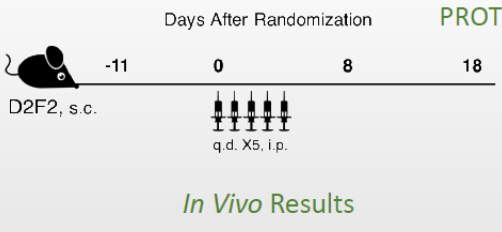




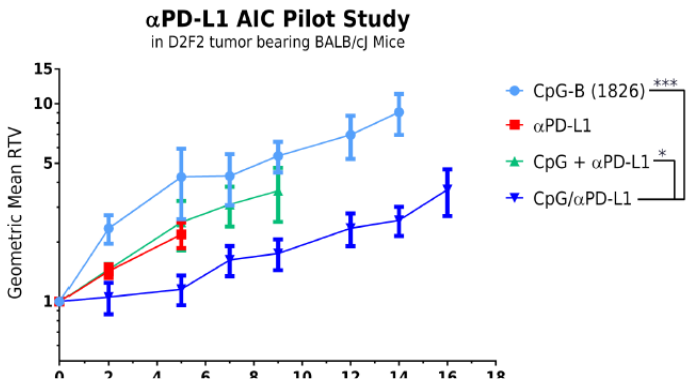




Control Experiments: Anti tumor effect requires active CpG (not scrambled) to be conjugated to tumor



In Vivo Results



Using the triple negative breast imurine tumor model D2F2 in BALB/c mice, the immunoconjugate CpG /PD L1 blue line) which targets tumor cells and myeloid derived antigen presenting cells was found to be less toxic than PD L1 therapy alone (red line) and produced better suppression of tumor growth compared to a mixture of both CpG and antibody (green).

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Intellectual Property

Patent No.	
Application Date	
Status	
Country	

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URL	