

Delta Opioid Receptor Ligand and Checkpoint Inhibitor Conjugates for Targeted Immunotherapy of Lung Cancer



The Delta Opioid Receptor (DOR) is overexpressed in all three major subtypes of lung cancer. Conjugates of the DOR ligand (DORL) and anti-PD1 checkpoint inhibitor antibodies were designed and synthesized to target and concentrate checkpoint inhibitors in lung tumors that express the target DOR. This invention is a targeted delivery of checkpoint inhibitors to malignant tissues while reducing the systemic dosages needed, resulting in lower systemic toxicity. Xenograft mouse experiments demonstrated efficacy at lower dosing compared to anti-PD1 alone. Additionally an anti-metastatic response and enhanced survival was observed.

COMMERCIAL OPPORTUNITY

- The Delta opioid receptor is G-protein-coupled receptor (GPCR) that is overexpressed in some cancer types but not in normal tissue. DOR is overexpressed in all major lung cancer subtypes, for example DOR is overexpressed in 73% of NSCLC. The ACS estimates there will be 234,030 new cases of lung cancer in 2018 of which approximately 85% will be NSCLC. DOR is also overexpressed in liver and breast cancer, with 2018 estimates of 268,670 new cases of breast cancer and 42,220 new cases of liver cancer.
- The DORL-anti-PD1 immuno-conjugates are structurally similar to existing antibody-drug conjugates and mechanistically similar to bispecific antibodies (BiTes).
- Using DOR to target immunotherapy results in improved efficacy at lower dosing, which can potentially decrease systemic toxicity, decrease costs and increase clinical efficacy. The DORL-PD1 conjugate is retained at higher concentrations in DOR positive tumors compared to negative controls, and conjugates circulate for greater than 148 hours.
- Most narcotics used for pain management bind mu, delta, and kappa opioid receptors, but the DORL exclusively binds DOR. DOR is expressed in the brain, but immuno-conjugates do not cross the blood brain barrier and so do not target DOR behind the BBB.

TECHNOLOGY

Anti-PD-1 efficacy is conserved following conjugation of DORL. Intravital confocal imaging of a dorsal window chamber (DWC) using syngeneic 344/mDOR tumor showed DORL-PD1 rapidly penetrating throughout the tumor 3 hours post i.v. injection. DORL-PD1 is retained at higher concentrations in DOR positive tumors compare to negative controls, and conjugates circulate for >148 h. In a xenograft mouse model, PD-1 efficacy and α PD1-DORL efficacy in DORL-tumors is due to enhanced permeability and retention (EPR). Tumor growth delay was observed in refractory DOR tumors by α PD1-DORL. A growth delay was observed at half of the clinical dose (40 nmol/kg vs 80 nmol/kg) following a single administration relative to the clinical 3-administration regimen. A significant anti-metastasis response (peritoneal metastasis) was observed after a single dose, and the treated mice exhibited dramatically enhanced survival.

PUBLICATION/PATENT

- PCT patent application filed March 5, 2017 for Dr. Mark McLaughlin, Dr. Amer Beg and Dr. David Morse

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