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Nanoparticles co-delivering doxorubicin and PD-L1 inhibitor to induce immunogenic cell death and enhance anti-cancer immune response in lung cancer

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Abstract

Non-small cell lung cancer (NSCLC) accounts for one in five of all cancer deaths worldwide. Most patients are diagnosed at advanced stages, resulting in a 5-year survival rate of less than 20%. Recently, immune checkpoint inhibitors (ICIs) for PD-L1 and PD-1 have received FDA approval for the treatment of NSCLC. However, only a small subset of patients (15-20%) respond to ICIs, and many of these responders eventually relapse. Doxorubicin (DOX) is an FDA-approved chemotherapeutic used in treating many cancers, including lung cancer. However, it has dose-dependent toxicity and patients develop resistance to DOX over time.

We have developed a new therapeutic based on our patented nanoparticle platform (Pdx-NPTM) for the co-delivery of DOX and the PD-L1 antibody avelumab, each at 4% by weight. The construct, named A-DOX-NP, has a size of about 100 nm in saline. PD-L1 blockade experiments showed that avelumab-loaded NPs significantly reduced PD-L1 expression compared to NPs alone. DOX-NP treatment also showed a greater reduction of lung cancer cells' viability than free DOX treatment. Flow cytometry analysis of A-DOX-NP treated cells indicated approximately 21 and 8-fold higher signal of calreticulin (an immunogenic cell death marker) than cells treated with free DOX and avelumab-loaded NPs, respectively. Evaluation of A-DOX-NP in lung cancer mouse models is underway.

In conclusion, A-DOX-NP offers a rational combination therapy that enhances immunogenic cell death via DOX, releases cancer antigens to train CD8+ T cells to recognize cancer, while inhibiting immune checkpoint molecules on cancer cells with the PD-L1 antibody, thereby allowing T cells to effectively attack the cancer cells. In addition to its synergistic effects, A-DOX-NP as a single agent may reduce patient burden by requiring fewer doses and shorter infusion times.