TARGETED OVARIAN CANCER IMMUNOTHERAPY THROUGH ENGINEERING OF FOLLICLE STIMULATING HORMONE RECEPTOR (FSHR) ANTIBODY TO ENGAGE T CELLS

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Background Ovarian cancer is the deadliest gynecologic malignancy, resulting in the highest mortality among cancers of the female reproductive system. The most prevalent subtype of epithelial ovarian cancer (EOC) is high-grade serous cancer which results in 70–80% of cases. OC is a high need area for novel therapeutic interventions; with a focus on identification of targets for immune therapy approaches expressed in the tumor microenvironment being of particular relevance. Follicle stimulating hormone receptor (FSHR) is one such important target with expression in 50-70% of serous OC cells. To date just handful of studies have targeted FSHR. Here we describe development of biologics targeting FSHR and study their impact against multiple ovarian tumors.

Methods We developed monoclonal antibody clones which target FSHR and focused our studies on a potent FSHR cell binding clone for detailed characterization, including binding and evaluation of its effect on antibody dependent cellular cytotoxicity (ADCC). We expanded this work to develop bispecific T cell engager (TCE) targeting FSHR and evaluated for its specificity, functionality, and efficacy in OC models.

Results We observed that the anti-FSHR clone D2AP11 bound specifically to FSHR positive cells and tissues. D2AP11 IgG2a antibody could induce ADCC in OC cells (IC50: 28.5 μg/ml). We sought to improve on its potential through design of D2AP11-TCE. Besides exhibiting strong bidirectional binding, this TCE induced potent in vitro killing of multiple human OC cells; CaOV3, OVISE, Kuramochi, OVCAR3-FSHR, OVCAR4 and PEO-4 which exhibit resistance to different drugs targeting HDAC, microtubule stabilizer, DNA alkylating agents, mTORC, AKT, PARP etc. (table 1) and tumor lines harboring mutations in BRCA1&2. IC50 values of D2AP11-TCE killing were obtained at 24.7 and 15.9 ng/ml in OVISE-FSHR and OVCAR3 cells respectively, indicating 1000-fold higher efficacy than IgG2a FSHR biologic (figures 1 and 2). In the NSG in vivo tumor challenge studies, this TCE significantly attenuated tumor burden of a model K562-FSHR, and relevant OVISE-FSHR and OVCAR3-FSHR challenged mice. Median survival of D2AP11-TCE treated mice was increased by 10 days compared to control group.

Conclusions These studies extend published data that FSHR appears to be an important target for further study in the context of OC immunotherapy. We present new tools for studying FSHR in OC and report development of a potent TCE with pM activity to impact OC growth in multiple preclinical models. Additional studies of these new tools for different ovarian as well as other cancers expressing FSHR are of high interest.

REFERENCES