Despite the widespread use of immunotherapy, the poor clinical response by immune-cold tumors is a current challenge. Triple negative breast cancer (TNBC) is the most aggressive mammary carcinoma subtype. Although a PD-L1 inhibitor has been FDA approved for the treatment of metastatic TNBC, the majority of TNBC patients show limited responses, particularly when their tumors are “cold” or “non-inflamed”. In contrast with “hot” tumors, these immune-cold tumors are characterized by a scarcity of T lymphocyte infiltration, commensurate with their failure to elicit anticancer immunity. Our endeavor to identify suitable targets for improving anticancer immune responses against TNBC therapy has drawn our attention to B7-H4.

Using combinatorial approaches, we unravel a novel regulatory mechanism by which B7-H4 protein turnover is governed by asparagine (N)-linked glycosylation. N-linked glycosylation is a co- and post-translational modification important for protein stability, folding, trafficking, and physiological function. Glycosylation of B7-H4 catalyzed by specific glycosyltransferases (STT3A and UGGG1) antagonizes the B7-H4 ubiquitination by E3 ligase autocrine motility factor receptor (AMFR), thereby preventing the degradation of B7-H4 and hence stabilizing the protein. Abundant B7-H4 can inhibit the phosphorylation of eIF2α, CALR exposure, and cancer cell immunogenicity. We designed a strategy for inhibiting the oligosaccharyltransferase (OST) complex that stabilizes B7-H4, thus reducing its expression and enhancing the immunogenicity TNBC cells in the context of immunogenic cell death-eliciting chemotherapy and PD-L1-targeting immunotherapy. We are currently under the process to develop new small molecule inhibitor that could specifically target the glycosylated B7-H4 for cancer treatment.