

Public Abstract

Metastatic triple-negative breast cancer (TNBC) remains a global healthcare problem and greatly impacts women's health. Despite the great advances in surgical techniques and treatment strategies, the treatment efficacy and prognosis of breast cancer patients are far from satisfactory due to metastasis and recurrence after treatment. Immunotherapy has achieved great success in treating multiple types of cancer clinically. However, the relatively low objective response rate and potential side effects significantly dampen its further application. Thus, there is an urgent need for a revolutionized technology that can effectively treat breast cancer with minimized side effects, prolonging the survival and improving the prognosis of metastatic breast cancer patients. Proteolysis targeting chimeras are small bivalent molecules utilizing the ubiquitin-proteasome system to degrade protein target, which revolutionizes the current drug development status by easily targeting and degrading the proteins that are previously recognized as "undruggable". Encouragingly, recent exciting news regarding the phase I clinical trial of proteolysis targeting chimeras treating breast cancer has brought significant promises for clinical translation of this technology. However, several bottlenecks significantly dampen their wider clinical application, including poor pharmacokinetics due to high hydrophobicity and non-specific distribution after systemic administration. In this proposal, we will develop a platelet-based drug delivery system to encapsulate proteolysis targeting chimeras to prolong their blood circulation time and improve the tumor-selective accumulation to enhance their metastatic triple-negative breast cancer treatment efficacy and minimize off-tissue toxicity. Furthermore, the current immune checkpoint blockade strategy will be combined with platelet-based proteolysis targeting chimeras with the hope of eliminating metastatic TNBC. The proposed technology will fulfill unmet clinical needs for metastatic TNBC treatment by extending the circulation time and achieving tumor-targeted delivery of PROTACs through anchoring the PROTACs to endogenous platelets. The successful demonstration of this proposal will not only develop and illustrate a novel treatment method for TNBC therapy but result in a facilitated clinical translation of PROTACs for the treatment of metastatic TNBC, providing great hope for current TNBC-bearing patients who have developed resistance to the current clinical treatment strategies.