PRECLINICAL IN VIVO MODEL DEVELOPMENT: HIGHLIGHTING SUCCESS AND DISCUSSING XENOGRAFT ADVANCEMENTS, A STEP CLOSER TO PREDICTING PATIENT OUTCOMES

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Background Immunotherapy, in particular chimeric-antigen receptor (CAR) T-cells, has been shown as an effective strategy for the treatment of cancer. However, the full therapeutic potential of these innovative therapies has not yet been fulfilled. This is particularly true of complex solid tumors. In comparison with hematologic tumors, solid tumors are more complex with unique three-dimensional structures, an immune-suppressive microenvironment and cellular heterogeneity that extends to the expression of tumor-associated antigens. Therefore, robust preclinical models with a high degree of fidelity towards the clinical presentation of the tumor are required for the accurate evaluation and translation of next-generation immunotherapies, including advancement of in vivo xenograft mouse models that more closely recapitulate disease as it is observed in the clinical setting.

Methods We have developed an orthotopic, mammary fat pad #4 (MFP#4) xenograft model utilizing an engineered tumor cell line based on the MDA-MB-231 triple negative breast cancer (TNBC) to assess epithelial cancer progression. Using this anatomically implanted human tumor model, we evaluated tumor growth kinetics, body weight, metastases and control of tumor with bioluminescence imaging.

Results The established MFP#4 xenograft model yields consistent, uniform tumor growth that produces disease progression and secondary metastases in vivo. Importantly, the model produced secondary tumors in both the lung and liver, recapitulating human disease in distal sites where 31.4% and 26% of patients show metastases. Moreover, we observed metastases in the axillary lymph node, a hallmark sign for diagnosing and staging breast cancer in patients. In the initial proof of concept study, administration of induced pluripotent stem cell-derived CAR T (CAR iT) cells, which had been successful in demonstrating tumor growth inhibition in various other disseminated and subcutaneous in vivo tumor models, significantly reduced the size of the primary tumor burden and the secondary tumor nodes.

Conclusions This work demonstrates that our engineered TNBC cell line in the MFP#4 xenograft model recapitulates much of the human disease phenotype. Importantly, the model demonstrated metastatic disease consistent with clinical presentation. Furthermore, administration of CAR iT-cells resulted in a decrease in overall tumor burden, validating the use of the orthotopic tumor xenograft as a preclinical model of TNBC with a high degree of clinical translatability.

REFERENCE

Ethics Approval All animal studies were conducted under the approval of the IACUC at Fate Therapeutics.