Name of Award: METAvivor Research Award

Name: Fumito Ito, MD, PhD

Title: Associate Professor of Oncology

Address: Roswell Park Comprehensive Cancer Center

Elm and Carlton Streets, CCC-539, Buffalo, NY 14263

Phone number: (716) 845-1300 ext. 6240

Descriptive title of project: “In situ radio-immunotherapy to maximize the engagement of Batf3 dendritic cells to treat metastatic breast cancer”
Fumito Ito, MD, PhD  “In situ radio-immunotherapy to maximize the engagement of Batf3 dendritic cells to treat metastatic breast cancer”

SIGNIFICANCE: This project is significant because 1) in situ radio-immunotherapy (ISRI) may be a useful treatment for patients with unresectable and metastatic breast cancer; 2) ISRI may generate tumor-specific T cells without the need for identification of patient- and tumor-specific cancer antigens such as neoantigens, or isolation, modification, or ex vivo expansion of patient- and tumor-specific T cells (e.g. chimeric antigen receptor (CAR) T cells or neoantigen vaccine therapy); 3) we will significantly improve our understanding of Batf3 DC biology; and 4) this research will broaden our knowledge about systemic immunity elicited by radiation therapy (RT)

IMPACT: Despite significant advances in chemotherapy and targeted therapy, metastatic breast cancer remains challenging to treat. Revolutionary immunotherapy that unleashes patients’ T lymphocytes to attack cancer can cause long-lasting immune responses in significant number of cancer patients (1-5). One major limitation of immunotherapy for breast cancer patients; however, is lack of T lymphocytes in the tumor for immunotherapy to be effective (6-9). Our new strategy is to convert tumors into cancer vaccine manufacturing factories, and educate T lymphocytes to attack widely metastatic cancers. Successful completion of the proposed study should provide a solid foundation for the future development of clinical trial with large cohorts of patients, and for the generation of more effective personalized cancer treatment targeting unresectable and metastatic breast cancer.

BACKGROUND: Batf3+ dendritic cells (Batf3 DCs) display enhanced abilities to phagocytose dead cells and prime tumor-specific T cells among various DC subsets (10-16). We hypothesized that the induction and activation of tumor-residing Batf3 DCs would facilitate the priming, expansion, and infiltration of tumor-specific T cells into the non-T cell-inflamed tumors. To test this hypothesis, we developed a novel combinatorial in situ radio-immunotherapy (ISRI) regimen (Fig. 1) comprised of intratumoral administration of 1) Fms-like tyrosine kinase 3 receptor ligand (Flt3L) to mobilize Batf3 DCs to the TME; 2) RT to promote immunogenic death of cancer cells and maturation of DCs; and 3) dual TLR3/CD40 stimulation to activate Batf3 DCs for priming and expansion of CD8 T cells. Excitingly, our research has revealed that this regimen can trigger priming of tumor-specific T cells, increase T cells in the tumor, mediate rapid and robust regression not only of primary, but also untreated distant tumors, render non-T cell-inflamed breast tumors responsive to anti-PD-L1 therapy, eradicate large tumors, and develop tumor-specific systemic immunological memory (data not shown). Furthermore, this strategy significantly decreases distant metastatic tumor burden, and improves survival (Fig. 2).

APPROACH: In Aim 1 and 2, we will determine the critical immunological mechanisms generating abscopal effects by ISRI, and potential synergy with anti-PD-1 therapy in orthotopic mouse models of spontaneous and established breast cancer lung/brain metastasis. In Aim 3, we would like to propose a first in human phase I clinical study to evaluate safety and treatment activity of ISRI. We will treat unresectable and metastatic stage IV breast cancer patients with four cycles of in ISRI: intratumoral injection of Flt3L (CDX-301) for 5 days (D1-5), RT (9 Gy x 1) on day 8, and administration of TLR3 (Poly-ICLC)/CD40 agonist (CDX-1140) on day 9. [A similar combination without CDX-1140 was tested for lymphoma recently (17).] To validate conversion of non-T cell-inflamed tumors to T-cell inflamed tumors, we will obtain serial tumor biopsies, and examine alteration of tumor-infiltrating immune cells in the non-T cell-inflamed TME by high-dimensional single-cell RNA sequencing, imaging mass cytometry, and TCR sequencing.

Fig. 1: Graphical working model.

Fig. 2 (A) AT-3 expressing luciferase (AT-3-luc) cells were orthotopically implanted to mammary fat pad, and injected i.v. to establish primary tumors and lung metastases. Primary tumors were untreated (NT) or treated with intratumoral (i.t.) injection of Flt3L, radiotherapy (RT) (9Gy) and i.t. TLR3/CD40 agonists (ISRI), followed by resection to evaluate growth of lung metastases. (B) Representative bioluminescent imaging on day 60. (C) Survival curves in AT-3-luc tumor bearing mice treated with NT or ISRI (n = 9-10 per group).
REFERENCES: