**\*\*Required for METAvivor’s board: Lay Description of Important Outcomes**

PI Name: Jitesh Pratap

Grant title: Targeting microtubule dynamics and endosomal trafficking for bone metastasis of breast cancer.

RFP name of award: 2022 Translational Research Award (Converted)

Date of submitting the report: 4/01/2024

**Lay Description of Important Outcomes:**

Breast cancer that spreads to the bones can cause severe bone loss and fractures, and over 30,000 people die from it each year. Communication between cancer cells and the bone microenvironment relies on small membrane-bound structures called endosomes. These structures play a crucial role in tumor growth and oncogenic signaling. However, it is not yet clear how metastatic cancer cells control the trafficking of these endosomes on a network of tubes (microtubules). Our goal is to target the regulators of microtubule-dependent endosomal trafficking and study its impact on bone metastatic tumor growth. Our research indicates that Runx2 and HDAC6 proteins regulate endosome distribution and microtubule stability. We are testing the hypothesis that Runx2-HDAC6-mediated endosomal trafficking and microtubule stability promote metastatic tumor growth in the bone microenvironment. Our research has two aims: - Aim 1 is investigating how microtubules support endosomal trafficking and promote oncogenic signaling using patient-derived organoids and breast cancer cells treated with compounds targeting Runx2/HDAC6 and microtubule stability. - Aim 2 is determining effective combinatorial targeting strategies with pharmacologic inhibition of microtubule stability and the endosomal pathway in bone metastatic breast cancer models. Our research aims to uncover novel strategies for targeting metastatic cancer cells in the bone microenvironment and better understand metastatic tumor cell communication in bone.

*Key outcomes from our progress*:

* We have identified specific changes in microtubules and associated endosomal trafficking in bone metastatic breast cancer.
* We discovered how levels of core microtubule components are controlled thereby affecting stability of microtubule network in metastatic breast cancer cells.
* Our results revealed two key components of microtubules that can change how cellular contents are distributed and contribute to the sensitivity of metastatic cells toward chemotherapy agents.
* We found that microtubules respond to the external environment of metastatic cancer cells.
* Year 1 research identified specific changes in microtubules and endosomal trafficking in bone metastatic breast cancer, guiding our targeting efforts in bone metastatic tumor models.

*Highlights*:

* In year 1, we presented our recent discoveries at two international scientific meetings (1: Cancer and Bone Meeting- Eric P. Newman Education Center at Washington University. St. Louis. MO; 2: Annual Meeting of American Society for Bone and Mineral Research- Vancouver Convention Centre, Vancouver, BC, Canada). We are currently preparing manuscripts for submission based on these findings.
* We are also in the process of preparing grant proposals for NIH and the Department of Defense, targeting the submission deadlines in October 2024 and February 2025.

*Clinical relevance of findings and impact on MBC treatment*: Bone is a common site of breast cancer spread, yet current treatments like bisphosphonates have not notably increased patient survival. Our findings offer a novel approach to regulating endosomal trafficking and microtubule stability. When combined with FDA-approved microtubule-targeting drugs, this approach could significantly impact treatment strategies and improve outcomes for stage IV metastatic breast cancer patients.