

Lay Abstract

For patients with Stage 4 triple-negative breast cancer (TNBC), the current standard of care is limited to physician-selected chemotherapy without any specific guidance on which drug will minimize further metastatic spread of the disease. Alarming, there is growing evidence that several types of chemotherapy treatment can actually increase the shedding of circulating tumor cells (CTCs) into the bloodstream and enhance metastatic spreading and recurrence in distant tissues. Since patients with Stage 4 triple-negative breast cancer are generally not candidates for surgical resection, it is critically important to understand which chemotherapies will increase further metastatic spread and which chemotherapies could actually reduce further metastatic spread. This project builds off of the discovery in the Martin lab that circulating tumor cells generate unique microtentacles (McTNs) on their cell surface that promote reattachment in distant tissues during metastasis. Earlier studies from the Martin lab showed that microtentacles are supported by a specific type of stabilized microtubule which has a tyrosine amino acid removed (detyrosinated microtubules). Numerous existing FDA-approved chemotherapies target tumor cell growth by stabilizing microtubules (Paclitaxel, Ixabepilone), but this microtubule stabilization actually increases McTNs and promotes tumor cell reattachment. These results indicate that current cancer drugs which aim to reduce metastatic tumor growth could inadvertently be increasing metastatic spread. However, FDA-approved chemotherapies that destabilize microtubules (Vinorelbine, Eribulin) can reduce McTNs and may therefore reduce metastatic risk. It is also important to realize that all 4 of these FDA-approved therapies broadly stabilize/destabilize all microtubules, and therefore have significant toxic effects on normal cells, which also require microtubules for growth and general cell health. The Martin lab has identified that the natural compound, Parthenolide, inhibits only the detyrosinated subset of microtubules that supports McTNs and tumor cell reattachment, without disrupting all microtubules. Parthenolide could therefore target further metastatic spread and potentially have fewer toxic side effects on normal cells. In this METAvivor project, we will compare Parthenolide with the 4 different FDA-approved chemotherapies (Paclitaxel, Ixabepilone, Vinorelbine, Eribulin) to determine which drugs cause further metastatic spread of TNBC tumor cells. Advanced optical imaging will be used to track the spread of metastatic tumor cells in both zebrafish and mice. Exceptionally high-speed microscopy that is possible in the transparent zebrafish will allow us to visualize whether chemotherapy drugs are directly promoting the dissemination of metastatic tumor cells as well as the specific steps of tumor cell reattachment in distant tissues. In mice, metastatic bone tumors will be established to mimic the most common first site of metastasis in TNBC patients. These mice will then be treated with the 4 FDA-approved chemotherapies or Parthenolide to determine whether these treatments can lead to the further shedding of tumor cells from the metastatic bone lesions and seeding of distant tissues (lung, liver). Even though the bone is the most common site of first metastasis in TNBC patients, it is the further metastasis to liver and lung that are the leading causes of patient death. This project will help improve the understanding of how existing chemotherapies could be contributing to the spread of bone mets to additional tissues, and whether novel targeted therapies like Parthenolide can reduce this risk. Since we predict that 2 of the FDA-approved therapies could also reduce metastatic risk (Vinorelbine, Eribulin), it is possible that these drugs could be used as combination therapies to reduce the further spread of metastatic lesions in Stage 4 TNBC patients and be rapidly translated to the clinic, since FDA-approval is already complete.