

LAY ABSTRACT

Breast cancer (**BC**) cells (**BCCs**) can survive as sleeping cells at distant organs for years or decades before patients and their doctors know they have BC. The ability for the BCCs to hide as sleeper cells does not only happen before the person knows she/he has cancer. Rather, the process continues at diagnosis and even during treatment. In this case, it is important for the treatment plan to include methods to stop the process that allows BCCs to continue hiding as sleeper cells. When asleep, it is difficult to kill BCCs by current anti-cancer drugs. Also, the sleeper cells can fool the body defense system, allow the cells to survive for decades. These sleeping cells behave as stem cells and this property allows them to be the source of metastatic BC during relapse. Thus, if we kill and/or stop these BCCs from sleeping, we will be able to eliminate BC recurrence, thereby enhancing patient mortality. The organ with clinical challenge is the bone marrow (**BM**), which is the most preferred organ for BCCs. The BCCs find a friendly place in the BM because they can instruct BM cells to help them survive. The oncologists are aware that dormant BCC are hiding inside the BM at diagnosis and also, when the patient is in remission. However, killing these sleeping BCCs in BM is a major hurdle because they take on properties of stem cells and become similar to the normal stem cells in BM that are responsible to make all blood cell types. Thus, scientists are faced with the following challenge: How can they kill sleeping BCCs in BM without harming the stem cells that make blood? This study will answer this question and in doing so, make the following positive steps towards eliminating the mortality associated with metastatic BCCs: 1) Identify how BM cells help BCCs to lie dormant for years or decades only to re-emerge into metastatic cancer; 2) We will be able to prevent recurrence into metastatic BCCs. We know which population of BM cells help the BCCs to hide. They are called mesenchymal stem cells (**MSCs**) and they release small particles stuffed with important information to change the BCCs into sleeper cells. We will test this with experiments in the laboratory and mouse model. All types of BCCs enter the BM and hide, making this study benefit all BC patients. Interestingly, we have noted that the BCCs are strategic in their journey towards a sleeper phase. They first take up the small particles from MSCs and then instruct the MSCs that they need additional small particles. If we can stop the first step, we will prevent the second step. We have established the studies in such a way that the findings will stop BCCs from sleeping and if cells are already asleep, they will be flushed out and killed. *We are confident that we will kill the sleeping BCCs thereby preventing lethal recurrence to significantly improve the mortality associated with metastatic BC.* **AIM 1** will identify how the cargo from MSCs begin to change BCCs entering the BM into sleeper cells by helping them to repair their well-being at the level of the gene. **AIM 2** will identify how the repair occurs to get the BCCs into their final sleeper cells. We have assembled two oncologists who will include their patients as well as two other survivors (mother and daughter) to follow our progress. This will ensure rapid movement of our findings into the clinic. Overall, this study will have a significant impact to all patients with the hope that BC will not recur as metastatic cells.