Human breast cancer (BC) is the most commonly diagnosed cancer in women worldwide and one of the leading causes of cancer-related deaths. Despite the development of new therapeutic agents, Triple Negative Breast Cancer (TNBC), a very metastatic subtype of breast cancer that is prevalent among young women, remains a critical healthcare issue, and new treatments are desperately needed. In healthy tissue, cells are well organized and connected tightly with each other. However, during cancer development and progression, tumor cells undergo the epithelial-to-mesenchymal transition (EMT), a dynamic process that endows epithelial cells with enhanced motility and invasiveness by dynamic changes like loss of connections between epithelial cells. In addition, EMT increases the motility of tumor cells, allowing them to invade surrounding tissue and spread to distant organs. A critical aspect of EMT's role in cancer is its contribution to generating circulating tumor cells (CTCs). CTCs are tumor cells released into the blood and lymphatic vessels that can survive and give rise to metastasis. EMT is also suggested to be important in the formation of so-called cancer stem cells. These cells are more resistant to therapies and can survive in the body for long periods, leading to new tumors and disease recurrence. Recent studies have also shown that cancer stem cells and epithelial-to-endothelial transition (EET), a subtype of epithelial-to-mesenchymal transition (EMT), can promote the process of vasculogenic mimicry (VM), a newly defined pattern of tumor microvascularization by which aggressive tumor cells can form vessel-like structures themselves, independently of angiogenesis involving new blood vessels formation. VM is strongly associated with a poor prognosis in several types of cancer, especially in aggressive metastatic TNBC. However, the biological features of tumor cells that form VM and their role in tumor metastasis remain unknown. Although the molecular mechanisms underlying VM are poorly understood, the epithelial-to-mesenchymal transition (EMT) is believed to play a crucial role in the initial steps of cancer stem cell plasticity. Therefore, we recently developed a reporter system using a human breast cancer model to label and track tumor cells undergoing EMT *in vivo*. Transcriptional analysis of highly invasive cancer cells isolated using this system revealed enrichment in genes essential for cellular movement, cell invasion, and, interestingly, tumor-vasculature interactions. Our analysis of tumors with a reporter system let us identify a rare population of cancer cells with increased plasticity, expressing endothelial marker MCAM and participating in vascular mimicry. We hypothesize that the MCAM-positive breast cancer cells represent cells with stem cell potential, capable of self-renewal and differentiation into endothelial-like, critically involved in tumor vascular mimicry and metastasis. Moreover, specific targeting of this cell population and related molecular pathways could thus provide novel strategies to eradicate cancers currently resistant to conventional therapy. Therefore, this proposed research aims to determine the fundamental molecular mechanisms underlying this phenomenon in the triple-negative breast cancer model to characterize potential targets of VM. We plan to characterize transcriptional markers and signaling pathways and define the epigenetic landscape of the endothelial transition state of the tumor cells undergoing vasculogenic mimicry. Both analyses will allow us to characterize new potential targets of VM that will be tested in the 3D system since anti-angiogenic therapy based on the classical tumor angiogenesis model is not entirely effective. We will also address how cells undergoing vasculogenic mimicry participate in the circulating tumor cells and metastasis formation. We will combine single-cell technology to decipher the importance of MCAM expression in vasculogenic mimicry and tumor spread. This project focuses on the crucial mechanisms by which tumor cells differentiate into endothelial-like cells and on possible therapeutic strategies to combat these alternative tumor vascularization mechanisms since conventional anti-angiogenic agents have little effect on VM-positive tumors due to the absence of typical endothelial cells.