Invasive lobular breast cancer (ILC) is the second most common histological subtype of breast cancer (~27-40,000 new cases annually), after the more common invasive ductal breast cancer (IDC). The hallmark of ILC is loss of E-cadherin, a protein mediating cell-cell attachment. ILC has been chronically understudied but there is increasing evidence for a unique biology of ILC, including many late recurrences and unique sites of ILC metastases. Given this, more research is needed to fully understand this subtype of breast cancer, in order to improve clinical outcomes and identify drug targets for metastatic ILC. ILC often spreads to unique sites in the body including the peritoneum, female reproductive organs such as ovary and uterus, GI tract, eye, and leptomeninges (layers of tissue covering the brain and spinal cord). These organs share a common feature - they are covered by a highly specialized lining of cells called mesothelial cells. These cells produce and secrete sugars and proteins covered with sugars which function as lubricants to generate a slippery, non-adhesive surface for organs to move and slide past one another. We believe that ILC cells gain a unique ability to attach to and then invade through mesothelial cells, potentially as a result of loss of E-cadherin which in turn requires ILC cells to have unique adhesion properties. Our recently completed sequencing studies of patient-matched pairs of primary and metastatic ILC to the ovary identified gene candidate involved in binding to sugars, and in Ca²⁺ signaling that may play a role. We hypothesize that blocking the interaction between ILC cells and mesothelial cells will result in cell death of the ILC cells, thus successfully treating metastases. We propose to identify molecules critical for ILC – mesothelial cell interactions and target these interactions genetically and also pharmacologically. To this end we will establish cell attachment co-culture assays with ILC cells and mesothelial cells to explore cell attraction, attachment and survival, and determine the mechanism of increased ILC cell and mesothelial cell interactions. Finally, we will therapeutically and genetically target the implicated pathways in cell culture and in animal models to validate promising drug targets for the treatment of ILC metastasis.