Inflammatory Breast Cancer (IBC) is a type of breast cancer that is characterized by the rapid onset of swelling and redness of the breast. Compared to other subtypes of breast cancer, it often occurs in younger patients and has an aggressive course, including increased likelihood of early spread to distant sites and an association with worse outcomes. As a result, although IBC accounts for only ~2% of breast cancer incidence, this disease is responsible for ~10% of breast cancer mortality, and new therapies for metastatic IBC are urgently needed. IBC research has been hampered by a lack of sufficient models for study in the laboratory. We are addressing this need by using a new technique for growing tumors in the lab to generate patient-derived cultures of IBCs, termed patient-derived organoids. Organoids are grown in a medium that contains factors that mimic the environment in the breast, and growth occurs in three dimensions using a gel that simulates tissue architecture. We have found that tumors can be grown efficiently using this method, and the method preserves key features of the original tumor to a greater extent than traditional culture methods. We have generated a set of IBC patient-derived organoids and characterized the cultures for key molecular features of IBC. In addition, we have used a drug screening approach to identify compounds that enhance the efficacy of chemotherapy specifically in IBC, with results encompassing multiple promising classes of drugs, including drugs that inhibit the bcl-2 pathway that blocks cell death in cancers. Candidate compounds which have been identified through this screen, including bcl-2 inhibitors, will undergo rigorous validation across our biobank of IBC and non-IBC organoids, with a focus on triple-negative breast cancer that is enriched in IBC. In addition, molecular determinants of sensitivity and resistance to these drugs will be assessed at the RNA and protein levels. The ultimate goal of these studies is to identify new therapeutic strategies that will facilitate the development of clinical trials for this particularly challenging type of metastatic breast cancer.