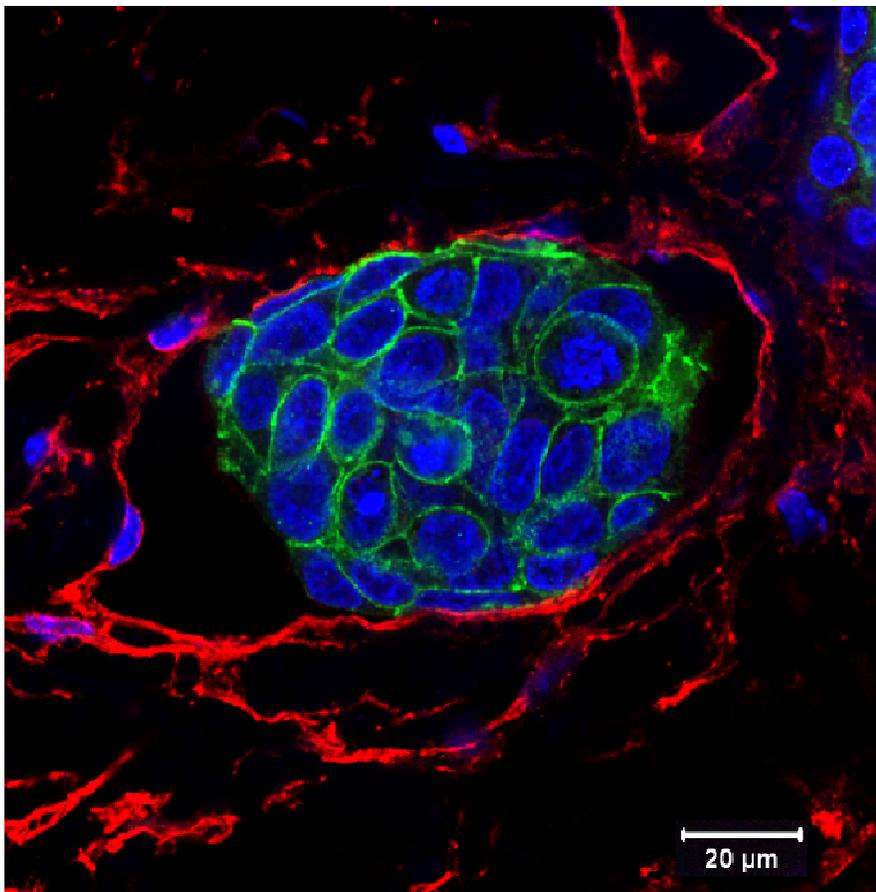


Novel Targets for Treatment and Detection of Inflammatory Breast Cancer

PROJECT SUMMARY AND PROGRESS REPORT

Although it is less common than other types of breast cancer, inflammatory breast cancer (IBC) is one of the most lethal forms of the disease. Because IBC does not typically occur as a lump, does not look like other breast cancers (the cells grow as sheets or nests), and may not easily be detected by mammography, it is often misdiagnosed, leading to delays in treatment. Conventional therapies developed for other types of breast cancer are used to treat IBC, but they are largely ineffective. Although there have been major advances in the detection and treatment of breast cancers overall, there have not been any significant changes in the diagnosis, treatment, and overall median survival rate for IBC patients in over 30 years.

The **American Airlines Susan G. Komen for the Cure[®] Promise Grant** provides full support, totaling \$7.5 million, for a 5-year research project to develop a new method for the earlier detection and more accurate diagnosis of inflammatory breast cancer and specific, targeted therapies to more effectively treat this relatively rare but aggressive form of breast cancer.



Clumps of tumor cells, called emboli, spread through lymph vessels. Image of inflammatory breast cancer tumor emboli (shown in green) that reside within lymphatic vessels (shown in red). This is the mechanism—called lymphovascular invasion—by which IBC metastasizes through lymphatic vessels, to lymph nodes and then to other tissues. The green fluorescence identifies the protein E-cadherin, which is a marker of IBC as well as a potential drug target that the team is currently pursuing.

Courtesy of Dr. Fredika Robertson

THE RESEARCH TEAM



Fredika Robertson, PhD, Professor in Experimental Therapeutics at The University of Texas M.D. Anderson Cancer Center and Director of Translational Research at the Morgan Welch Inflammatory Breast Cancer Research Program, Houston, TX

Massimo Cristofanilli, MD, FACP, G. Morris Dorrance Jr. Endowed Chair in Medical Oncology and Chairman of the Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA



Drs. Robertson and Cristofanilli, Promise Grant Co-Principal Investigators, have assembled a team of experienced investigators—breast medical oncologists, breast surgeons, imaging specialists, pathologists, radiation oncologists, translational researchers, physician scientists and basic scientists—who are working together with IBC patient advocates. The project involves the first clinic specifically focused on the diagnosis, treatment, and research of IBC—The Morgan Welch Inflammatory Breast Cancer Research Program and Clinic at The University of Texas M.D. Anderson Cancer Center—as well as the Fox Chase Cancer Center. In addition, the group has assembled a panel of internal advisors with expertise in IBC to help the team focus its efforts to improve the diagnosis and treatment of IBC.

THE RESEARCH PROJECT

The research funded by this American Airlines Susan G. Komen for the Cure® Promise Grant is focused on studying the cellular and molecular hallmarks of IBC. The insights gained about the biology of this disease will be used to develop a novel, more effective method to accurately diagnose IBC and to develop new therapies that target the ways in which this aggressive cancer grows, forms new blood vessels (a process called angiogenesis), and spreads to other organs (or metastasizes). This multi-disciplinary research team is also developing new preclinical models of IBC to study the characteristics of IBC and learn more about how it develops and metastasizes.

These strategies have led to a clinical trial of a new agent, rapid development of other therapeutic agents, and identification of several potential biomarkers...all with the goal to diagnose IBC more rapidly and accurately and to develop targeted therapies that will significantly improve survival for IBC patients.

—Dr. Robertson

The project aims to:

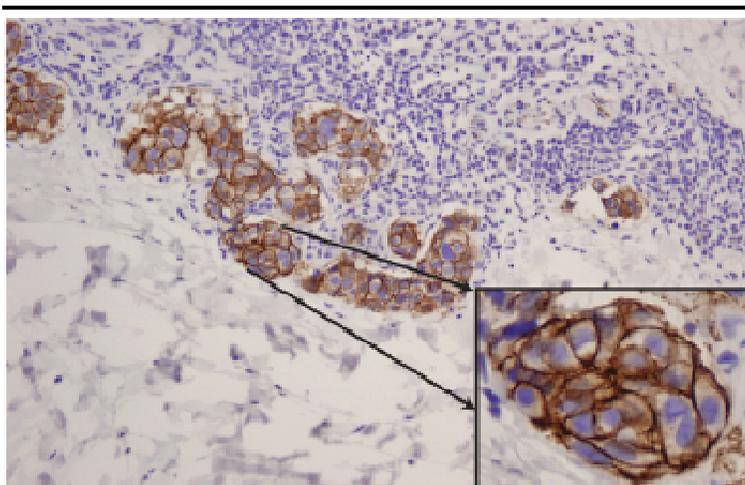
1. Define the molecular signatures of IBC tumor cells and identify the signaling pathways they use to grow, invade and metastasize. The signatures will help identify potential molecular targets for drugs and biomarkers that could be used to better distinguish IBC from other breast diseases (e.g., infectious or autoimmune mastitis).
2. Conduct preclinical studies to validate the molecular targets identified above. These studies will test whether drugs that selectively target the distinct molecular signatures of IBC can disrupt the cells' critical biological functions (e.g., growth, invasion, metastasis, angiogenesis). The studies will determine which drugs or drug combinations should be evaluated in clinical trials for patients with IBC.
3. Fast-track suitable FDA-approved agents (i.e., drugs that match IBC-specific targets and have been confirmed in preclinical studies) into clinical trials.

RESEARCH PROGRESS

During the first two years of funding, the Promise Grant research team has made significant progress toward defining the molecular signatures of IBC tumor cells and determining which molecules and pathways are critical for IBC tumor cells to grow, invade, metastasize and form new blood vessels. They have found that:

- IBC has molecular hallmarks of a process that promotes rapid metastasis to the chest wall and other organs.
- IBC is a distinct disease with different molecular subtypes, and different biological processes are associated with the different subtypes, suggesting treatments could be tailored to match patients' specific tumors.

These studies have also helped identify potential drug targets (including two proteins named E-cadherin and JAK2/Stat3), and these targets have been validated in IBC patient tissues and cells. The targets have been matched with drugs (which are already FDA-approved or are entering into clinical trials) that specifically target these proteins and are being used to treat other cancers or diseases.



The protein named E-cadherin is found in IBC tumor cells, and researchers are searching for ways to target it with medicine. E-cadherin (brown stain) on the surface of IBC tumor emboli in a skin punch biopsy from an IBC patient.

*Courtesy of Dr. Fredika Robertson
and Dr. Savitri Krishnamurthy*

The research team is now focused on conducting preclinical studies to evaluate the effect of these targeted drugs on the growth and metastatic spread of IBC tumors. To accelerate progress, they have developed two new preclinical models of IBC with which to study and evaluate potential targeted drugs, and collected tissue/cell samples from patients so their preclinical findings can be validated in IBC tissues.

As described above, the researchers identified the JAK/Stat pathway as a target, based on the molecular signatures of IBC tumors, and tested drugs that block this pathway. Following these studies, the research team started a Phase I clinical trial at Fox Chase Cancer Center using one of these drugs. This is the first example of the utility of the research team's approach to identify potential IBC-targeted drugs and move them to clinical trials for patients.

HOW WILL THIS RESEARCH BRING US CLOSER TO THE CURES?

In the U.S., IBC affects about 1 to 5 percent of women with breast cancer. Globally rates vary but are thought to be as high as 17% in some regions, and unlike other types of breast cancer, IBC incidence rates are on the rise. Although relatively rare, IBC is highly aggressive, with only about 50% of patients surviving five years after initial diagnosis. This is likely due to the current lack of effective ways to accurately diagnose it early and the lack of therapies developed specifically for IBC.

If successful, this research will lead to earlier and more accurate diagnosis of IBC and will provide the first therapies specifically designed to treat IBC, both of which are critically important to improve overall survival of patients with this lethal form of breast cancer.

Susan G. Komen for the Cure® is proud to partner with American Airlines to fund the fight against this rare and aggressive form of breast cancer and to offer great promise to patients with inflammatory breast cancer.