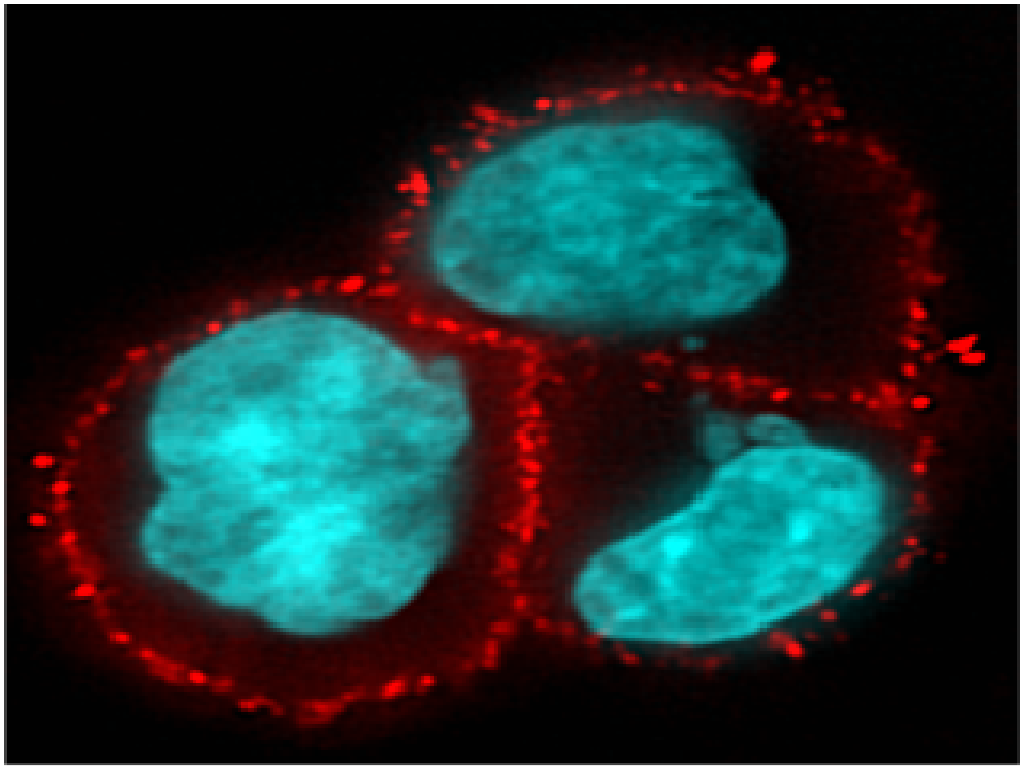
Targeting Death Receptors for the Treatment of Triple Negative Breast Cancer

PROJECT SUMMARY AND PROGRESS REPORT

Triple negative breast cancer (TNBC) accounts for 15-20% of all breast cancers in the U.S. and it is often more aggressive, more likely to spread to other organs (metastasize), and more likely to recur than other types of breast cancer. The majority of TNBC tumors are "basal-like" (based on the genomic classification of breast cancer), and by definition, they lack the three receptors that fuel most breast cancers: estrogen receptors, progesterone receptors and human epidermal growth factor receptor 2 (HER2). As a result, TNBC generally does not respond to drugs that target those receptors and are used to treat other types of breast cancer. Instead, chemotherapy and radiation—conventional therapies that often have severe side effects—are the most effective treatments for TNBC. There is very little known about the biology of TNBC, and because of this, targeted therapies that specifically disrupt these critical biological functions do not yet exist.

The Susan G. Komen for the Cure® Promise Grant, Co-funded by the Triple Negative Breast Cancer Foundation supports a promising five-year, $6.4 million research project to develop new targeted therapies to treat this aggressive form of breast cancer, which doesn't respond to currently available targeted therapies.



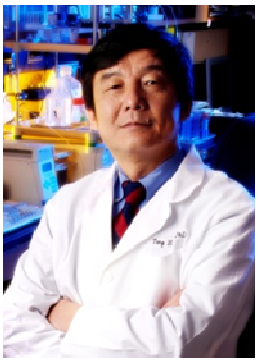
Basal-like breast cancer cells express the death receptor DR5 on their surface. *An antibody named TRA-8 or tigatuzumab targets (binds to) the death receptor DR5 (shown in red) on the surface of 2LMP breast cancer cells (cell nuclei shown in blue). Researchers are studying this drug as a new targeted therapy for triple negative breast cancer.*

Courtesy of Dr. Andres Forero

THE RESEARCH TEAM

Andres Forero, MD, Professor of Medicine in the Division of Hematology/ Oncology at the University of Alabama at Birmingham (UAB), and Co-Leader of the Experimental Therapeutics Program and Director of the Clinical Studies Shared Facility at the UAB Comprehensive Cancer Center.

Tong Zhou, MD, Professor in the Division of Clinical Immunology and Rheumatology at the University of Alabama at Birmingham, and Senior Scientist at UAB's Arthritis and Musculoskeletal Center and the UAB Comprehensive Cancer Center.



Drs. Forero and Zhou, Promise Grant Co-Principal Investigators, have assembled a unique team of experienced investigators—medical oncologists, basic researchers, pathologists, and imaging specialists—who are working together with patient advocates to develop a new treatment for triple negative breast cancer. The University of Alabama at Birmingham (UAB) team will collaborate with researchers from the University of North Carolina and the University of Michigan, and clinical trials will be conducted through the Translational Breast Cancer Research Consortium (TBCRC), a group of 16 leading academic institutions (including UAB) from across the country working together to expedite early phase breast cancer clinical trials.

THE PROJECT AND PROGRESS

The research funded by this Promise Grant is studying a new drug (an antibody named TRA-8, also called tigatuzumab) that may be an effective targeted therapy for triple negative breast cancer. This drug, developed in partnership with the Daiichi-Sankyo Co. Ltd. of Japan, targets a "death receptor" (the human death receptor 5, or DR5) found on the surface of basal-like breast cancer cells, triggering apoptosis (programmed cell death) of the cancer cells, while sparing normal cells. Specifically, the project aims to:

1. Study the effectiveness of TRA-8, alone or in combination with chemotherapy drugs, to kill basal-like tumor cells. These laboratory studies will determine which drug combinations should be evaluated in clinical trials as possible therapies for TNBC.

2. Determine how TRA-8 transmits its cell-killing signal and what makes basal-like tumor cells ultra-sensitive to this drug. This work will provide clues into the biology of TNBC and pinpoint molecules that could be used as biomarkers to help identify which patients are most likely to respond to this targeted therapy.

3. Develop novel imaging techniques to help monitor how a tumor is responding to the targeted therapy.

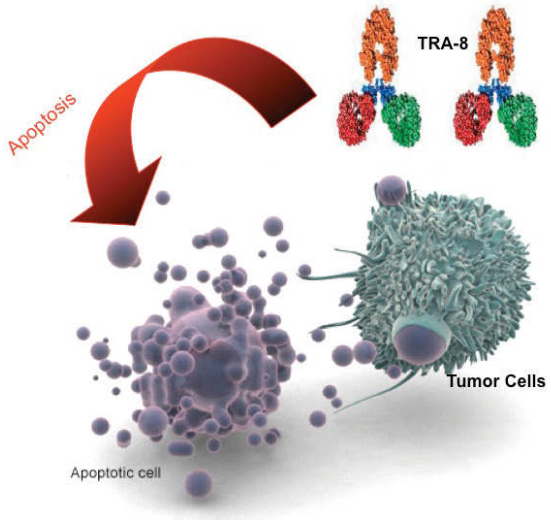
4. Conduct early (Phase II) clinical trials using tigatuzumab, a special form of TRA-8, plus a chemotherapy drug as a new therapy for patients with metastatic TNBC and in the future as a possible neoadjuvant therapy in newly diagnosed TNBC patients.

Preclinical research shows that there are some markers in the MRI images of metastatic lesions that may be used to predict response to tigatuzumab; this technology will be used for the patients who will participate in the clinical trial.
—Dr. Andres Forero

The Promise Grant team has made progress towards each of the research goals during the first year of funding. They have found that TRA-8 can kill basal-like tumor cells, and the combination of TRA-8 and a chemotherapy drug is better at killing basal-like tumor cells than either drug alone. From these studies, the team has developed a Phase II clinical trial using TRA-8 (a targeted therapy) plus the chemotherapy drug Abraxane to treat metastatic TNBC. Fourteen of the 16 institutions of the TBCRC, including UAB, are enrolling patients on the clinical trial, which opened March 2011.

The research team developed a novel imaging method using MRI that detects early signs of cells dying to help monitor how well tumor cells respond to the treatment. This method will be used in the clinical trial for patients with TNBC.

Preliminary studies have revealed two proteins that help TRA-8 transmit its cell-killing signal. Basal-like tumor cells with low levels of these proteins are sensitive to TRA-8, and cells that are resistant to TRA-8 express high levels. These proteins may be used as biomarkers to help identify which patients are most likely to respond to this targeted drug.



A new targeted drug triggers apoptosis (or programmed cell death) of basal-like breast cancer cells. *This diagram shows how a new drug (an antibody named TRA-8 or tigatuzumab) can kill basal-like tumor cells, while sparing normal cells, by binding to the death receptor DR5 on the cancer cell surface.*

Courtesy of Dr. Tong Zhou

All of the integrated research projects will continue into the second year.

HOW WILL THIS RESEARCH BRING US CLOSER TO THE CURES?

Approximately 30,000 U.S. women are diagnosed with TNBC each year. This aggressive disease represents about 15 percent of all new breast cancer cases but accounts for as much as 25 percent of all breast cancer deaths. Most drugs available today target three receptors that TNBC cells do not express, making it difficult to treat. There are no specific, targeted therapies for TNBC, leaving conventional treatments, which often have severe side effects, as the most effective way to treat patients with TNBC.

The multi-disciplinary research team funded by this Promise Grant is collectively focused on the goal of developing a drug that targets the death receptor DR5 expressed on basal-like breast cancer cells but not normal cells. If successful, these studies will provide the first targeted therapy to more effectively treat patients with triple negative breast cancer who are in urgent need of new ways to fight this aggressive disease.

Susan G. Komen for the Cure® is proud to partner with the Triple Negative Breast Cancer Foundation to fund the fight against this aggressive form of breast cancer and support the discovery of promising new treatments for patients with this disease.