TARGETING DEATH RECEPTORS FOR THE TREATMENT OF TRIPLE NEGATIVE BREAST CANCER

MEET THE RESEARCH TEAM

Andres Forero, M.D.
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Dr. Forero’s work focuses on patient focused research with an emphasis on early clinical trials to improve the standard of care and management of breast cancer.

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Co-Principal Investigator
University of Alabama at Birmingham
Dr. Zhou’s work focuses on understanding how to manipulate cellular death/suicide programs (apoptosis) for therapeutic benefit in cancer and autoimmune inflammatory disease.

Drs. Forero and Zhou lead a multi-disciplinary team conducting the research at several academic centers across the U.S. The clinical trials supported by this grant 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.

Triple negative breast cancer (TNBC) is an aggressive subtype which represents 15 to 20 percent, or about 30,000, of all new cases of breast cancer in the US each year. Compared to other subtypes of breast cancer, TNBC is more likely to spread to other organs (metastasize), more likely to recur and occurs more often in younger women and African American women. Breast cancers which have BRCA1 mutations are often TNBC and/or basal-like subtypes.

Estrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor 2 (Her2) receptors are proteins found on the outer surface of cells and bind to other small, specific proteins to signal cells to grow. Most breast cancer cells express one or more of these three receptors. Many “targeted” breast cancer drugs used today interfere with the ER, PR and/or HER2 receptors to prevent the tumor cells from growing.

Since TNBC cells lack ER, PR and HER2 receptors, the available targeted therapies are not considered effective treatment options. Instead TNBC patients are typically treated with conventional cancer treatment options, such as chemotherapy and radiation, which often have severe side effects. Currently, there are no targeted therapies for TNBC.

The Susan G. Komen Promise Grant, co-funded by the Triple Negative Breast Cancer Foundation, supports a five-year, $6.4 million research project to develop new targeted therapies, either alone or in combination with existing chemotherapies, to treat TNBC.

PROJECT SUMMARY

- The Promise Grant research team is focused on identifying potential drug targets in TNBC and developing novel targeted therapies for TNBC, either alone or in combination with existing chemotherapies and/or other agents.
- One potential drug target is a protein called the DR5 death receptor found on certain breast cancer cells. When DR5 is activated (either with a drug or by binding a specific protein) it triggers the death of the cancer cell while sparing normal cells.
- The research team is testing whether targeted therapies, including TRA-8, a drug that targets DR5, can kill basaHlike TNBC cells alone and in combination with chemotherapy drugs and/or other agents that enhance the efficacy of the targeted therapy.
- They are also studying how the targeted therapy TRA-8 transmits its cell-killing signals and what makes TNBC tumor cells sensitive to this drug.
- An early phase II clinical trials will be conducted using the targeted therapy tigatumab (i.e.TRA-8) plus a chemotherapy drug to treat metastatic TNBC.
- These lab-based and clinical studies will help pinpoint biomarkers that could be used to identify which patients are most likely to respond to TRA-8, help the team to develop novel imaging techniques to monitor how a tumor is responding to the drug, and lay the groundwork for future clinical trials testing new drugs or drug combinations for TNBC.

Learn more about Triple Negative Breast Cancer
http://sog.mn/104hJ6G

RESEARCH FINDINGS

The Promise Grant team has made several important findings during the first four years of funding.

THEIR OVERALL FINDINGS ARE:

- The DR-5 death receptor targeted drug TRA-8 can kill basal-like breast cancer cells. This is significant since most TNBC cells are basal-like.

- The combination of TRA-8 and a chemotherapy drug (Adriamycin, Abraxane® or cisplatin) is better than either drug alone.

- Clinical biomarkers to help identify which patients are most likely to respond to TRA-8 were also explored. Two proteins (DDX3 and IAP), which appear to help the targeted drug transmit its cell-killing signal, were found as two potential biomarkers.

- 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 TRA-8. This method will be used in future clinical trials for patients with TNBC.

FUTURE STUDIES PLANNED:

- Studies to look for additional proteins that regulate TRA-8 killing are ongoing, as are studies to analyze the genomic signatures of basal-like breast cancer cell lines that are sensitive or resistant to the targeted drug. These proteins may be potential drug targets in TNBC.

- The research team is developing an additional antibody drug that targets the DR5 death receptor. The drug will be tested in lab-based studies in the next year of the project.

TARGETED DRUG TRIGGERS PROGRAMMEDA CELL DEATH (APOPTOSIS)

A new antibody-based drug called TRA-8 or tigatuzumab can kill breast cancer cells, while sparing normal cells, by binding to the DR5 death receptor on the cell surface.

CLINICAL TRIAL UPDATE

Using findings from their lab-based studies, the research team developed a randomized Phase II clinical trial using tigatuzumab plus the chemotherapy drug Abraxane® to treat metastatic TNBC. 42 received tigatuzumab plus Abraxane® and 22 received Abraxane® alone.

Results so far: The overall response rate, duration of response and progression free survival were similar in both treatment groups. There were no adverse events associated with tigatuzumab. Changes in the tumor’s gene expression in responding and non-responding patients are being analyzed to determine if there are biomarkers that can be associated with response to treatment.

HOW WILL THIS RESEARCH BRING US CLOSER TO THE CURES?

The Susan G. Komen Promise Grant, co-funded by the Triple Negative Breast Cancer Foundation, is supporting a multi-disciplinary research team that is working to develop new targeted therapies to treat TNBC.

The research team is focused on testing an antibody-based drug that targets the DR5 death receptor that is expressed by basal-like TNBC cells, but not in normal cells.

If successful, these studies could lead to the first targeted drug to more effectively treat patients with TNBC who are in urgent need of new ways to fight this aggressive form of breast cancer.

Susan G. Komen 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 TNBC.