Susan G. Komen

Research Grants – Fiscal Year 2015

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Dissecting IRES mediated translation in breast cancer

Investigator(s): Christos Vaklavas, M.D.

Lead Organization: University of Alabama at Birmingham

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Public Abstract:

According to the central dogma of molecular biology, genetic information flows from DNA to RNA (transcription) and from mRNA to protein (translation) with mRNA serving as a template for the protein to be synthesized. While the mechanisms the regulate the first half (transcription) of the dogma have been intensively explored over the past 25 years, the mechanisms that regulate the other half, ie which mRNAs will be translated, how much or even what subtype of protein will be produced, are only now beginning to be investigated.

My research focuses on a special mechanism of protein synthesis that has a rescue or emergency role in breast cancer called IRES-mediated translation. This mechanism allows many mRNAs of oncogenes with unequivocal role in breast cancer to be preferentially translated into proteins under clinically relevant conditions of stress such as those induced by chemotherapy. A group of proteins called ITAFs are responsible for switching to this rescue translational mechanism.

With the proposed research, I intend to investigate how this IRES-mediated translation is involved in triple-negative breast cancer. By virtue of this mechanism serving as a rescue, I hypothesize that IRES-mediated translation will be responsible for the survival of triple-negative breast tumor cells when treated with chemotherapy. This research addresses a critical clinical problem as triple-negative breast cancer that persists after intensive chemotherapy is considerably more likely to come back.

With the first aim, I intend to investigate the role and clinical implications of a set of ITAFs. These ITAFs might ultimately be used for diagnostic purposes and guide treatment planning for individual patients with triple negative breast cancer. Triple negative breast tumors tend to be more primitive and therefore more likely to utilize IRES-mediated translation.

With the second aim, I am adapting a new technology (ribosomal profiling) that relies on next-generation sequencing to provide global views of translation across the entire genome in previously treated and untreated human breast tumor samples. Ribosomal profiling will provide “snapshots” of which mRNAs are being actively translated under each condition. With my adaptation of the ribosomal profiling protocol we can differentiate which mRNAs are preferentially translated by using the IRES mechanism. In doing so, we can gauge at the genomic level the degree to which IRES-mediated translation is responsible for unsatisfactory response to preoperative chemotherapy.

Lastly, using genetically engineered triple-negative breast cancer cells implanted in mice, we will visualize in vivo and real-time how IRES activity varies during tumor development and treatment. Our preliminary studies have indicated that the activation of IRES-mediated translation precedes the transition from a quiet indolent state to an aggressive proliferative cancer.