



**Susan G. Komen**

**Research Grants – Fiscal Year 2015**

This research grant was approved for FY2015 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

**Therapy of triple negative breast cancers by targeting the TPX2 mitotic regulator**

**Investigator(s):** Julia Rohrberg, Ph.D.; Andrei Goga, M.D., Ph.D. (Mentor); Zena Werb, Ph.D. (Co-Mentor)

**Lead Organization:** University of California, San Francisco

**Grant Mechanism:** PDF Basic and Translational

**Grant ID:** PDF15331114

---

**Public Abstract:**

The aim of my study is to find novel targeted therapies against triple negative breast cancer (TNBC), the subtype with the poorest patient outcome for which no therapeutic strategies are currently available. As it is the most difficult-to-treat form, there is an urgent need to deepen our understanding of this aggressive breast cancer and to identify clinically relevant targets for therapeutic intervention. Our lab recently found an oncoprotein called MYC that is highly elevated in TNBC and associated with poor prognosis. We seek to take advantage of this distinctive molecular feature to identify effective treatment strategies. Unfortunately, no small molecule inhibitor for MYC is available for clinical use. An alternative approach to selectively kill MYC-driven tumors is to inhibit those proteins that are indispensable for the viability of such tumors but are not essential in non-tumorigenic cells. We were successful in identifying such a protein, called CDK1, and in translating this concept into a clinical trial at UCSF. However, CDK1 is also an important engine for normal cells to divide. Thus, its inhibition could potentially lead to toxicity and limit the usefulness in the clinic. In my proposal, I seek to find a novel, non-toxic, efficacious targeted therapy based on our lab's success of CDK1 inhibition.

I analyzed patient data to find CDK1 substrates that are specifically elevated in TN tumors. I discovered the CDK1 substrate TPX2 to be required for the TNBC tumor cell to survive. Using bioinformatics analyses of several clinical cohorts, we found that patients with elevated TPX2 have a dramatically worse prognosis than those with low TPX2 expression.



In my proposal, I will study how the tumor cells die after depletion of TPX2 and why TPX2 is indispensable for MYC overexpressing TNBC tumors. I will further evaluate the preclinical efficacy of targeting TPX2 function and its influence on the metastatic process.

I will use various cell based assays and the best pre-clinical mouse model of TNBC to date to address these proposed aims. I will screen drugs that are currently being evaluated in clinical trials, thus my proposal harbors a high potential to translate into clinic. The understanding of the underlying biology will help to identify the patient population with the strongest response, which will make an existing drug much more powerful and efficacious (while limiting toxicity) in personalized therapy. My study aims to identify a compound that can readily go into early phase clinical trials here at UCSF to evaluate its effectiveness against a selected patient population with breast cancers that have elevated MYC and TPX2 expression.

