



Susan G. Komen

Research Grants – Fiscal Year 2015

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Overcoming resistance to treatment of brain metastases from HER2 positive breast

Investigator(s): Gino Ferraro, Ph.D.; Rakesh Jain, Ph.D. (Mentor)

Lead Organization: Massachusetts General Hospital

Grant Mechanism: PDF Basic and Translational

Grant ID: PDF15331878

Public Abstract:

Scientific rationale: Patients with metastatic breast cancer have a median survival of two years, and account for 40,000 deaths, annually, in the US alone. Human Epidermal Growth Factor 2 (HER2)-positive breast cancer represents about 20-25% of all breast cancer, and is a particularly aggressive subtype that is associated with a poor prognosis. Up to 50% of patients with metastatic HER2-positive breast cancer will eventually develop brain metastasis. Unlike HER2-amplified breast cancers in extra-cranial locations, brain metastases do not respond to HER2-targeted therapies. The standard treatment option for patients with brain metastases, whole-brain irradiation, provides only a limited survival benefit at the cost of high morbidity. The mechanisms behind the differential response of brain metastases from HER2-expressing breast cancer to these agents, compared with extra-cranial disease, remain unknown. My project is dedicated to identifying the resistance mechanisms of breast cancer brain metastases, and then developing clinically translatable strategies to overcome this resistance – ultimately to prolong survival and increase the quality of life of breast cancer patients with brain metastases.

My objective is to design and undertake clinically relevant experiments to reveal and block the mechanisms of metastatic progression and resistance to current therapies. The training plan I propose here will allow me to develop an in depth understanding of clinically relevant research and expose me to new cutting edge experimental techniques. The research proposal I describe here has been designed to



remain as clinically relevant as possible throughout the study. This is an invaluable opportunity to me, as a basic scientist, not to stray too far from clinical relevance while performing basic research. Together, my proposed fellowship plan will allow me to strengthen my chances of becoming an independent scientist performing clinically relevant research to improve treatment of metastatic breast cancer patients.

Impact of research: My project focuses on HER2 positive breast cancers, which often metastasize to the brain. There are limited treatment options for patients with these metastatic lesions. I plan to use our pre-clinical animal model to develop a combinatorial therapeutic approach to block resistance in the brain, while selectively targeting HER2 positive tumor cells with currently approved therapies. We have gathered preliminary data demonstrating that a protein related to HER2, HER3, is present in brain metastases and that inhibiting its function could improve HER2 targeted therapies. We have collaborations with breast oncologists who are eager to begin clinical trials studying the therapeutic outcome of these combinatorial treatment approaches.

