



**Susan G. Komen  
Research Grants – Fiscal Year 2014**

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**Improving response to radio and chemotherapy in triple-negative breast cancer**

**Investigator(s):** Giorgio Seano, Ph.D., Rakesh Jain, Ph.D. (Mentor)

**Lead Organization:** Massachusetts General Hospital

**Grant Mechanism:** PDF Basic and Translational

**Grant ID:** PDF14301739

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**Public Abstract:**

Breast cancer remains a major cause of cancer-related death in women. Unfortunately, five-year overall survival of breast cancer remains at 85%, with a large disparity between different stages and subtypes. Treatments for primary breast cancer have improved dramatically over recent years but long-term survival often remains elusive for triple-negative breast cancer (TNBC) patients, the most aggressive breast cancer subtype. TNBC comprises 13-25% of all breast cancer cases. Sadly, patients with TNBC are often younger and have shorter survival compared to other subgroups and are often refractory to therapy, with an early relapse and metastatic disease progression. Data from my exploratory studies suggests that reduced microvessel density – the density of vascularization – and low intratumor oxygenation reduce therapeutic effectiveness in patients with TNBC. This could make TNBC particularly susceptible to therapies that induce vascular normalization which increase oxygenation and improve response to radio/chemo-therapy as well as inhibit metastatic processes. Matrix metalloproteinase (MMP)-14 plays a fundamental role in metastasis by facilitating the breakdown of extracellular matrix components that otherwise represent a barrier to cancer cells moving across blood vessels. MMP14 expression is strongly associated with breast cancer prognosis and it is a key player in tumor angiogenesis, an important determinant of therapeutic response. Recently, a potent and selective antibody inhibitor of MMP-14 has been developed: DX-2400 is a fully human monoclonal antibody and has the potential to be a powerful tool to study the function of MMP14. This project aims to determine the effect of blocking MMP14 on primary tumor growth, angiogenesis, and response to radio/chemo-therapy as well as the formation of metastases. MMP14 inhibition has the potential to provide a modality to sensitize tumors, by increasing intratumor oxygenation and blood flow perfusion, and could reduce metastases in patients following local radiation therapy or/and systemic chemotherapy. This dual function of DX-2400 could indicate MMP14 as a promising and strategic target for breast cancer therapy of TNBC, highly metastatic and refractory breast cancer subtype. If successful, my findings will form the basis of a clinical trial through our existing collaborations at Dana Faber/Harvard Cancer Center. The proposed research will be conducted under the guidance of my mentor, Dr. Jain. An advisory committee will provide additional guidance throughout my training program: Dr. Dai Fukumura, regarded as an expert in vascular biology; Dr. Yves Boucher, a specialist in pathophysiology and therapy; and Dr. Steven Jay Isakoff, a MGH oncologist specialized in breast cancer. Moreover, I will take advantage of regular meetings with Ms. Marie Artis Levine, an active member of the Dana-Farber/Harvard Cancer Center Patient Advocacy Group, that will help me to understand the "patients' perspective"