Susan G. Komen
Research Grants – Fiscal Year 2014

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Tracking intratumor heterogeneity in triple negative breast cancer

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Public Abstract:
Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer that is initially sensitive to chemotherapy but has a worse prognosis than hormone receptor- or HER2-positive breast cancers. Although very sensitive to chemotherapy initially, there is evidence of escape from or resistance to chemotherapy: TNBC recurs at a rate of 10-15% per year for the first several years after initial surgery, while hormone receptor-positive breast cancer recurs at a rate of 3-5% per year. Additionally, TNBC is more likely have distant (lung, brain) rather than local (breast, lymph nodes) recurrence, suggesting a failure of systemic chemotherapy rather than local therapy. Overcoming chemotherapy resistance could reduce the rate of relapse and significantly impact patient outcomes. While nearly every tumor is derived from a single cell, cancer cells evolve over time, resulting in many unique sub-populations within a single tumor. The impact of this tumor heterogeneity on TNBC treatment is poorly understood, e.g. how different sub-populations are affected by distinct chemotherapy regimens, which subpopulations expand during relapse, and whether the subpopulations communicate with each other to limit therapy effectiveness. To study the dynamics of tumor subpopulations in response to therapy, we have developed technologies that make it feasible to grow unique subpopulations derived from human TNBC, a significant advance over established cell line-based experiments. We will tag each subpopulation with an inert DNA 'barcode' to be able to track each individual population over time, then establish tumors in mice made up of a mix of subpopulations. We will treat the mice using chemotherapy agents used in clinical TNBC management to mirror care of patients with breast cancer. We will then study what specific sub-populations remain after treatment, how this compares to the composition of untreated tumors, and also whether the same subpopulations are present as tumors re-grow (i.e. 'relapse'). After identifying the most resistant clones, we will look for mutations or changes in their genetic program which may mediate resistance. We will also selectively eliminate resistant clones within tumors and re-assess sensitivity to chemotherapy, hypothesizing that removing this 'instigator' population will render the entire tumor more chemosensitive and give insight into communication among subpopulations. This proposal offers a unique approach to a well-known clinical problem – why a subset of patients with TNBC show remarkable initial response to chemotherapy then rapidly relapse - and directly studies cells derived from patient samples with treatment approaches used in the clinic. This study design offers a close connection to the biology of TNBC in patients and should expose relevant opportunities to improve existing therapies.