Susan G. Komen

Research Grants – Fiscal Year 2015

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Targeting basal-like breast cancer via CRISPR-mediated multiplex gene knockout

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Lead Organization: Broad Institute

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Public Abstract:

Basal-like breast cancer (BLBC) is the most malignant form of breast cancer. An effective targeted therapy for this breast cancer subtype remains unavailable to date. Combination therapy that co-targets multiple oncogenic signaling has emerged as an appealing therapeutic approach. However, an integral approach for comprehensive investigation of combination therapies is still lacking. Identifying optimal combination options has become a pressing need in medical oncology to reduce the mortality rate of BLBC. Inspired by this clinical challenge, this proposal intends to take a rational approach and establish a systematic platform for developing combinatory strategies. The project aims to develop a multiplexed CRISPR-based gene perturbation system to investigate and model combination therapies for BLBC. CRISPR is a cutting-edge technology that allows us to abolish gene functions by editing DNA sequences of specific genes. It is more accurate and versatile than previous tools. The novel multiplex design here allows this approach to screen gene combinations faster than current one-by-one methods. From a defined set of genes that are functionally relevant to BLBC malignancy, the project aims to identify optimal gene targeting combinations against BLBCs in clinical relevant experimental models. Based on the identified genetic combinations, the project will move forward to find whether small molecule inhibition of the target genes can achieve the same effects as CRISPR editing. In-depth mechanism investigation and detailed characterization of the cancer lesions undergoing the combination treatment will be performed to reveal the molecular underpinnings of its therapeutic efficacy as well as potential toxicities. Collectively, these efforts aim to establish a pipeline of mechanism-based combination

therapy for BLBC that is translatable to the clinic, from uncovering cancer vulnerabilities to developing novel therapeutics.