Susan G. Komen
Research Grants – Fiscal Year 2014

This research grant was approved by Komen's national board of directors for FY2014 Research Programs funding. This grant will be funded upon the execution of grant agreements between Komen and the grantee institutions.

Mechanism of PARP inhibitor in breast cancer therapy

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Lead Organization: The University of Michigan
Grant Mechanism: PDF Basic and Translational **Grant ID:** PDF14301538

Public Abstract:
Cancer occurs as a result of mutations, or abnormal changes, in the genes responsible for regulating the growth of cells and keeping them healthy. Normal cells encounter numerous DNA damages induced by environmental and internal hazards. A gene named BRCA1 exists in the cells of breast and other tissue, where it helps repair damaged DNA, or destroy cells if DNA cannot be repaired. If BRCA1 itself is mutated, the damaged DNA won't be repaired properly, which significantly increases risks for cancers. Familial breast cancer cases are often attributed to germline mutations of BRCA1 gene, conferring lifetime risks of up to 90% in the mutation carriers for developing breast cancer. Recent studies suggest that PARPs inhibitors could be the prevalent anticancer drugs for breast cancer chemotherapeutics. However, how PARP1 inhibitors kill breast tumor cells is far from clear. Particularly, it is not clear whether PARP1 inhibitors could kill all the breast tumors bearing BRCA1 mutations or just selectively kill a set of breast tumor cells with specific BRCA1 mutations. Following DNA damage, PARPs catalyze poly-ADP-ribose (PAR), a kind of small molecule polymers, at DNA lesions, which is important for DNA damage repair without elucidated mechanism. Here, we found that PAR recruited the BRCA1 complex to DNA damage sites to fulfill its DNA repair function. Suppression PAR synthesis at DNA damage sites by PARPs inhibitors abrogates partial of BRCA1's function. Since BRCA1 is essential for cell viability and most breast cancer-associated BRCA1 mutations also abolish partial of BRCA1's function, PARPs inhibitors could easily kill breast tumor cells bearing cancer-associated BRCA1 mutations by aggravating the loss of BRCA1-dependent function in cells. However, based on our preliminary results, PARPs inhibitors treatment could not aggravate the loss of BRCA1-dependent function on a small subset of BRCA1 mutations. Thus, in this application, we plan to examine which BRCA1 mutations are sensitive to PARPs inhibitors treatment. These results may have major impact on the design of future breast cancer chemotherapeutics to improve the survival rate of breast cancer patients. As a postdoctoral fellow, I will be trained in the breast cancer research field with a comprehensive training program designed by my mentor. The training program will not only allow me to conduct the research project proposed in this application, but also help me improve my ability and vision in breast cancer research field. After this training, I have strong desire to become an independent investigator to contribute my effort for the irradiation of breast cancer by exploring novel therapeutic strategies for breast cancers.