Susan G. Komen
Research Grants – Fiscal Year 2014

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Development of selective Grp94 inhibitors for the treatment of breast cancer

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Public Abstract:
Breast cancer is one of the most common cancer affecting women and ranks second as a cause of cancer death in women with approximately 40,000 deaths last year in the United States. Despite recent advances in the diagnosis and treatment of breast cancer it is predicted that the number of deaths will remain unchanged in 2013 with an estimated addition of more than 250,000 new cases (American Cancer Society, Cancer Facts & Figures 2012 and 2013). Breast cancer is a complex disease in which during the early stages, highly abundant cancer causing proteins referred to as onco-proteins (e.g. HER2, EGFR etc.) in the tumor cells are responsible for the transformation into the breast cancer cells. Upon progression of the disease, tumors become highly diverse and are driven by a complex mechanism regulating cellular proliferation, survival and metastasis. Because of these complexities, there is currently a critical need to find clinically relevant targeted therapies for aggressive subtypes of breast cancer, which can overpower the large number of abnormal cellular processes. There is strong biological data that suggests the direct correlation between increased expression of Grp94 and tumor progression. Thus there is an important role of Grp94 inhibitors in the treatment of cancers. While the discovery of Grp94 inhibitors has been a challenge thus far, this landscape is about to change as work from our laboratory provided small molecules with high selectivity for Grp94, and this work was recently disclosed in Nature Chemical Biology (Patel et al., Nat. Chem. Biol. 2013), and further selected to be highlighted in the "Research Watch" section of Cancer Discovery. With the help of these selective ligands, we observed that selective Grp94 inhibition led to increased killing of breast cancer cells overexpressing HER2 and EGFR at the plasma membrane. The fact that the initial molecules discovered show potent activity against cancer cells offer a promising avenue for their further development into molecules with improved drug-like features, with the ultimate goal being their clinical translation into potent anti-cancer agents. This work proposed here, while focused primarily on the aspect of drug discovery, given my organic and medicinal chemistry background, is also part of a larger effort of my laboratory and of my colleagues within the Breast Cancer Medicine Service at Memorial Sloan-Kettering Cancer Center. Together, we are rigorously evaluating ways for the rational translation of these agents for the treatment of breast cancer. We believe that the expertise and experience of our large team in the translation of drugs from bench-to-bedside augurs well for our combined endeavors towards the development of a novel targeted drug to be added to the armamentaria to fight breast cancer. Thus, this work will pave the ground towards the development of a potentially novel treatment paradigm for patients afflicted with breast cancer.