Susan G. Komen
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A structural framework for targeting the HER3 receptor in breast cancer

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Public Abstract:
HER3 is a cell surface molecule that has recently emerged as an important therapeutic target in breast cancer. Increasing evidence implicates HER3 in promoting a wide range of breast cancer types, including triple negative, estrogen receptor-positive and HER2-positive tumors. Currently, the most well understood oncogenic function of HER3 is in HER2-positive breast cancers. HER2 is another cell surface molecule and a close homolog of HER3. In normal cells, interaction between HER2 and HER3 is necessary for initiation of growth factor-induced HER2 signaling, but the molecular details of this interaction remain poorly understood. HER2 levels are elevated in 20-25% of all breast cancers. The scientific data suggest that these HER2-positive breast cancers should be highly responsive to HER2 inhibitors, but in reality even the best agents that antagonize HER2 function fail to cure patients in advanced stages of the disease. This is because in breast cancer cells treated with anti-HER2 agents, inhibition of HER2 is buffered by increased expression of HER3 resulting is sustained HER2/HER3 signaling. Therefore the detailed understanding of HER2/HER3 interaction and the development of direct agents that target HER3 are necessary to stop the advanced HER2-driven cancers. The development of anti-HER3 agents is particularly challenging because HER3 is an intrinsically inactive enzyme and lacks the classical active site pocket that other kinases have. Our recent findings uncovered that HER3 function can be regulated through its unconventional pseudoactive site and present a possibility for the development of the first small molecule inhibitors of HER3. Based on these studies, the goal of this application is to characterize the role of this new regulatory aspect of HER3 function for its signaling with HER2 and for the first time define the structural basis for the interaction between HER2 and HER3. Based on our preliminary evidence, we will also explore how different structural classes of drugs interfere with the function of HER3. To achieve our goals, we designed a multidisciplinary approach that combines structural biology, molecular dynamics and chemical synthesis with the in vitro and cell-based functional assays. Using this approach, we will: (i) obtain an atomic resolution picture of the HER2/HER3 enzymatic complex that will reveal the molecular features of HER2/HER3 interaction interface; (ii) unveil molecular mechanism for regulation of the enzymatically inactive HER3 through its pseudoactive site; and (iii) generate first small molecule inhibitors of HER3 function and test their role in inhibition of HER2/HER3 signaling. The results of our work have the potential to advance the basic knowledge of how HER3 cooperates with HER2 in promoting abnormal cellular signaling that results in breast cancer, and to generate HER3 inhibitors that could become effective therapeutics for the advanced stages of several different types of breast cancer.