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Target Validation and Drug Development with Aptamers for Basal-like Breast Cancer

This proposal seeks to develop and apply a new strategy of cancer therapy through the use of aptamers against target proteins and cells. It focuses on the Basal-like Breast Carcinoma (BLBC), which is a particularly aggressive subtype of breast cancer refractory to conventional therapy. The poor prognosis of BLBC patients is partly due to the lack of estrogen receptor expression and HER2 gene amplification, thus they are not treatable by biologically-based drugs. Using microarray gene expression data and bioinformatic analyses we have identified genes specifically or predominantly expressed in BLBC. Here we choose a subset of these genes as potential drug targets. To determine whether they are indeed responsible for the aggressive behavior of BLBC and therefore can serve as points of intervention, we will create aptamers in the form of stable modified RNA to modulate their activity and to examine the effects of these aptamers on the malignant phenotypes of cancer cells in tissue culture. Moreover, we propose to augment the potency of these target-binding aptamers so that the targets are not only neutralized but also destroyed or damaged. We will develop bi-functional composite aptamers that simultaneously bind the target molecules and the activated complement protein C3b/iC3b, thereby tagging the target molecules and associated cells as “foreign” in the process of opsonization. Aptamer-mediated opsonization of secreted proteins would lead to their clearance through endocytosis by phagocytes. A salient feature of our approach is that once validated the targets are immediately druggable by the aptamers. The general strategies being developed and principles being uncovered in this project are applicable to other types of cancer.

Statement of Public Health Relevance

This study is designed to improve the means of treating a form of aggressive and recalcitrant breast cancer, the Basal-like Breast Carcinoma. The proposed strategy represents a conceptual and technological advance, which transcends the classical pharmacodynamics of antagonism.

Specific Aims

Aim 1 Creating one or more aptamers for extracellular protein targets and one or more aptamers for membrane protein targets.

Aim 2 Investigating effects of the aptamer(s) for extracellular target(s) and/or membrane target(s) on malignant phenotypes and gene expression patterns of tumor cells.

Aim 3 Developing and testing bi-functional opsonizing aptamer(s) for extracellular target(s) in cell-based assays.