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Summary

A group led by Dimitris Anastassiou applied their novel attractor metagene methodology to the 2,000 breast cancer sample METABRIC data set and won the Sage Bionetworks–DREAM Breast Cancer Prognosis Challenge, topping 353 other participants. The attractor metagene method is an iterative process that converges to one of several precise sets of genes ["attractors"] defining signatures representing molecular features which were found to be correlated with important clinical-pathologic parameters such as tumor grade and stage. The single most prognostic molecular feature of the winning model was a newly identified metagene defined as the average expression of two genes, FGD3 and SUSD3, which are directly adjacent to each other at chromosome 9q22.31. Loss of expression of the genes was strongly predictive of poor survival; much more so than loss of expression of the estrogen receptor (ER). Little is known about either gene, but the available literature suggests a likely significant cellular phenotype to altered FGD3 and/or SUSD3 expression. Using published data sets of gene expression in breast cancer cell lines we have confirmed the positive correlations between expression of FGD3 and SUSD3, and between the FGD3-SUSD3 metagene and the estrogen receptor, establishing the rationale for initial *in vitro* testing. In addition, the cell line MDA-453 has homozygous deletion of both genes, consistent with it having the lowest metagene score of any cell line. We hypothesize that decreased expression of one or both of these highly prognostic genes, FGD3 and SUSD3, results in an altered cellular phenotype corresponding to hallmarks of cancer.

Specific Aim 1: Determine whether selective inducible knockdown of FGD3, SUSD3, or both genes, alters the phenotype of selected breast cancer cell lines with relatively high baseline expression of the genes.

Specific Aim 2: Assess the protein expression of these genes in a pathologically and clinically annotated cohort of breast cancer specimens.

Given the discovery of the FGD3-SUSD3 metagene as the single most prognostic molecular feature in breast cancer, characterizing the functional significance of altered expression of these genes is a high priority. In addition, it is important to know if protein analysis can used as an alternative biomarker for these prognostic genes. Our proposed studies will lay the groundwork for understanding how loss of expression of one or both of these genes leads to a worse prognosis in breast cancer.