Award ID:
RP100475

Project Title:
Evaluation of the utility of two-dimensional RNA biomarker analysis in classification of human cancers.

Award Mechanism:
High Impact/High Risk

Principal Investigator:
Neilson, Joel R

Entity:
Baylor College of Medicine

Lay Summary:

In the dawn of personalized medicine, global measurements of gene expression are a cutting-edge tool for disease diagnosis and prognosis. These measurements are generally made by assessing the amount of a particular RNA transcript (mRNA) that is produced from each gene. However, a majority of genes encoded in the DNA utilize more than one set of building blocks to produce the mRNAs coding for protein production. While invisible to commonly used genomic platforms, these variations in mRNA composition can change the function of protein that is produced by the gene, and in fact may dictate whether a protein is produced from the transcript at all; We recently demonstrated that proliferative cells, and in particular human cancer cell lines, produce mRNAs with an altered back, or “3'” end, as compared to normal, quiescent cells (Science 320:1643-7). These changes occur independently of the amount of RNA that is produced from any given gene. Another study demonstrated that this might result in activation of known oncogenes in breast cancer cell lines (Cell 138:673-684). We believe that these programs of RNA variation profoundly impact gene expression and cellular events leading to cancer; To extend these observations, we developed a novel high-throughput sequencing approach that simultaneously assesses both the copy number of the mRNA and the composition of the 3' end of the transcript. We will test the hypothesis that tumor classification approaches taking into account both of these parameters will significantly increase our ability to prospectively identify tumors of unknown origin, as compared to approaches using either parameter independently. If successful, the new approach will be markedly more cost-efficient that “shotgun” high-throughput mRNA sequencing approaches, and could potentially be adapted for clinical use in a relatively short amount of time. The study also has the potential to identify novel targets for downstream therapeutic development.