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**Christina S Leslie\*** ([cleslie@cbio.mskcc.org](mailto:cleslie@cbio.mskcc.org)), 1275 York Ave, Mail Box #460, New York, NY 10065. *Inferring transcriptional and microRNA-mediated regulatory programs in glioblastoma.*

Large-scale cancer genomics projects are profiling hundreds of tumors at multiple molecular layers, including copy number, mRNA and miRNA expression, but the mechanistic relationships between these layers are often excluded from computational models. We developed a sparse regression framework for integrating molecular profiles with regulatory elements to reveal mechanisms of dysregulation of gene expression in cancer, including miRNA-mediated expression changes. We applied our approach to 320 glioblastoma tumors and identified key miRNAs and transcription factors as common or subtype-specific regulators. We confirmed that target gene expression signatures for proneural subtype regulators were consistent with in vivo expression changes in a relevant mouse model. We tested two predicted proneural drivers, miR-124 and miR-132, both underexpressed in proneural tumors, by overexpression in neurospheres and observed a partial reversal of corresponding tumor expression changes. Computationally dissecting the role of miRNAs in cancer may ultimately lead to small RNA therapeutics tailored to subtype or individual. (Received September 22, 2011)