Metastasis is responsible for most cancer deaths. The Tavazoie laboratory employs a systems biology approach that integrates molecular, genetic, cellular, organismal, and clinical observations to discover and characterize key molecular regulators of metastasis, with the goal of developing new therapeutics for its prevention and treatment. This work has also unexpectedly uncovered surprising fundamental insights into mechanisms of gene regulation.

Metastatic disease is the primary cause of cancer mortality but remains poorly understood at the molecular level. The Tavazoie lab studies the molecular and cellular mechanisms underlying this process. Their work has also uncovered novel roles for transfer RNAs (tRNAs) in gene regulation.

The lab employs genome-wide technologies to identify recurrent molecular alterations associated with enhanced metastatic capacity. Molecular and genetic studies in mice are used to implicate critical genes that regulate this process, with clinical association studies confirming human relevance and biochemical studies implicating signaling pathways involved. This has led to the discovery that modulation of tissue-specific sets of small non-coding RNAs (microRNAs) drives metastasis formation in distinct cancer types by altering expression levels of critical downstream genes. These genes activate pathways that alter the cellular, metabolic, or matrix composition of the metastatic microenvironment; such changes to the microenvironment enhance the survival, immune-evasive, and invasive capacity of cancer cells. Major efforts in the lab aim to understand how metastases initiate in end-organs, how metastatic cells reprogram surrounding host cells and metabolism, how immune-evasion occurs, and how extreme metastatic gene expression states are established. Recent work uncovered the first evidence for an inherited genetic basis for human metastasis formation—providing a powerful genetic foundation for future studies. Scientists in the lab have applied these insights toward the development of two first-in-class metastasis-targeting therapeutics, which have been advanced into national clinical trials. Their long-term goal is to develop broadly curative metastasis-preventive regimens for common cancers.

Furthermore, by studying how rare cancer cells achieve extreme gene expression programs during metastasis formation, Tavazoie and his colleagues have revealed that modulation of specific transfer RNAs (tRNAs) is a gene regulatory process that alters the expression of specific downstream proteins in a codon-dependent manner to causally drive cancer progression. This has led to the delineation of specific tRNA-driven pathways as well as demonstration that deprivation of specific amino acids can govern codon-dependent translation of specific genes. Such tRNA modulation responses have been observed in a variety of cells and systems and are increasingly recognized as a key mode of gene regulation.