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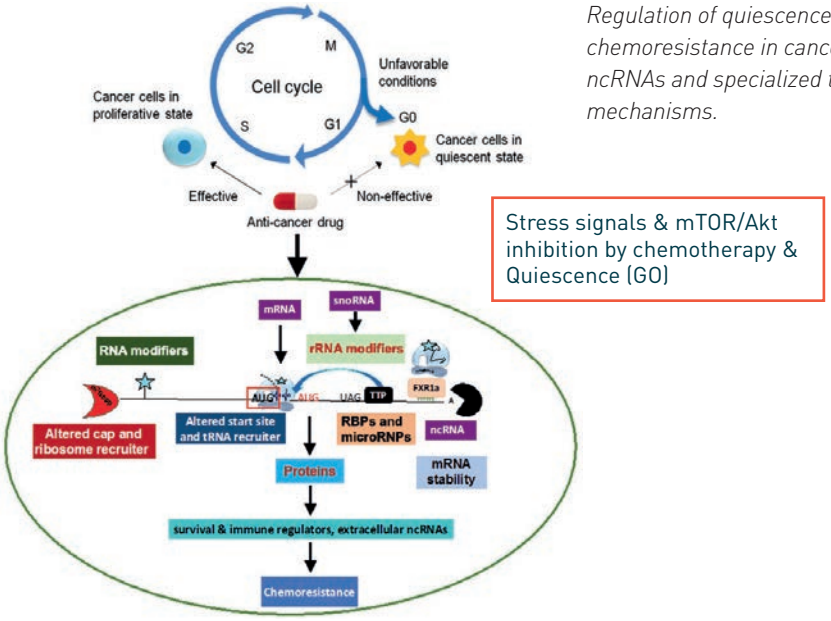
The Vasudevan laboratory focuses on the role of post-transcriptional mechanisms in clinically resistant quiescent cancer cells. Tumors demonstrate heterogeneity, harboring a small subpopulation that switch from rapid proliferation to a specialized, reversibly arrested state of quiescence that decreases their susceptibility to chemotherapy. Quiescent cancer cells resist conventional therapeutics and lead to tumor persistence, resuming cancerous growth upon chemotherapy removal. Our data revealed that post-transcriptional mechanisms are altered, with modification of noncoding RNAs, associated complexes and ribosomes—molecules that control vital genes in cancer—which are important for the persistence of quiescent cancer cells. The primary goal of our research is to characterize the specialized gene expression and their post-transcriptional regulators that underlie persistence of resistant cancer cells. A complementary focus is to investigate the modification of post-transcriptional regulators and their mechanisms in response to quiescent conditions and chemotherapy-induced signaling. Our goal is to develop a comprehensive understanding of the versatile roles of regulatory RNAs in cancer as a basis for early detection of refractory cancers and for designing new therapies.

Quiescent (G0) cells are observed as a clinically relevant population in leukemias and other tumors associated with poor survival. G0 is a unique, nonproliferative phase that provides an advantageous escape from harsh situations like chemotherapy, allowing cells to evade permanent outcomes of senescence, differentiation, and apoptosis in such tumor-negative environments. Instead, the cell is suspended reversibly in an assortment of transition phases that retain the ability to return to proliferation and contribute to tumor persistence. G0 demonstrates a switch to a distinct gene expression program, upregulating the expression of mRNAs and regulatory non-coding RNAs required for survival. Quiescence regulators that maintain the quiescent, chemoresistant state remain largely undiscovered.

Our studies revealed that specific post-transcriptional regulators, including AU-rich elements (AREs), microRNAs, RNA-protein complexes (RNPs), ribosome factors and RNA modifiers, are directed by G0- and chemotherapy-induced signaling to alter expression of clinically important genes. AU-rich elements (AREs) are conserved mRNA 3'-untranslated region (UTR) elements. MicroRNAs are small noncoding RNAs that target distinct 3'UTR sites. These associate with RNPs, ribosome associated factors and their modifiers to control post-transcriptional expression of cytokines and growth modulators. Their deregulation leads to a wide range of diseases, including tumor growth, immune and developmental disorders.

We identified post-transcriptional effectors associated with mRNAs and noncoding RNAs by developing in vivo crosslinking-coupled RNA affinity purification methods to purify endogenous RNPs. Our recent studies revealed mechanistic changes in



Regulation of quiescence & chemoresistance in cancer by ncRNAs and specialized translation mechanisms.

Stress signals & mTOR/Akt inhibition by chemotherapy & Quiescence (G0)

G0: uncovering inhibition of conventional translation and its replacement by non-canonical mechanisms that enable specific gene expression in G0 to elicit chemoresistance. These specialized mechanisms are driven by modifications of mRNAs, associated regulator RNAs and proteins, and ribosomes, which are induced in G0- and chemotherapy-induced signaling. These investigations reveal gene expression control by RNA regulators and non-canonical translation mechanisms that cause tumor persistence. Based on our data demonstrating altered RNPs, modifications, and specific translation in G0, we propose that transiently quiescent, chemoresistant subpopulations in cancers are maintained by specialized post-transcriptional mechanisms that permit selective gene expression, necessary for chemotherapy survival and tumor persistence.

The primary goal of our research is to characterize the specialized gene expression program in quiescent, chemoresistant cancers, and its underlying post-transcriptional and translational regulators that contribute to G0 and tumor persistence. A concurrent focus is to investigate RNA modifications and mechanisms of noncoding RNAs, RNPs, and ribosomes in G0 that contribute to chemoresistance, using cancer cell lines, in vivo models, patient samples, and stem cells. An important direction is to identify unique G0-specific RNA markers and develop novel therapeutic approaches to block selective translation in G0, of targets that encode for critical immune and tumor survival regulators—and thereby curtail chemoresistance.

The lab has four core directions:

1. To characterize microRNAs and noncoding RNAs, and their cofactors that control the expression of tumor survival regulators, using in vivo biochemical purification methods.
2. To investigate the mechanisms of post-transcriptional and translational regulation by noncoding RNAs, RNPs, and ribosome regulators.
3. To elucidate the modification and regulation of key mRNAs and ribosomes, by G0- and chemotherapy-induced signaling.
4. To develop therapeutic approaches that interfere with selective translation, and manipulate interactions of noncoding RNAs with targets that encode for critical tumor survival regulators. These studies should lead to a greater understanding of the versatile role of post-transcriptional mechanisms in cancer persistence and to novel approaches in RNA-based therapeutics.

Selected Publications:

Chery J, Petri A, Wagschal A, Lim S-Y, Cunningham J, **Vasudevan S**, Kauppinen S, Naar AM. Development of Locked Nucleic Acid antisense oligonucleotides targeting viral proteins and host factor NPC1. *Nucleic Acid Therapeutics*. 2018; 28(5):273-284.

Bukhari SI, Truesdell SS, and **Vasudevan S**. Analysis of microRNA mediated translation of in vitro transcribed reporters in G0 THP1 cells. *Methods in Molecular Biology*. 2018; 1686:251-264.

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Liu M, Roth A, Yu M, Morris R, Bersani F, Rivera MN, Lu J, Shioda T, **Vasudevan S**, Ramaswamy S, Maheswaran S, Diederichs S, Haber DA. The IGF2 intronic miR-483 selectively enhances transcription from IGF2 fetal promoters and enhances tumorigenesis. *Genes & Dev*. 2013; 27(23):2543-8.