Presentation Abstract Submission

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Research Title	Long Non-Coding RNA Biology of Cancer and Diabetes in the Post-Genomic Century

Abstract:

Two-thirds of human genes do not encode proteins. Long non-coding RNA (lncRNA) genes are the most abundant, but least understood, class of non-protein-coding human genes. Their lack of protein-coding capacity had earlier been computationally defined, but lacked experimental validation. In the ENCODE (Encyclopedia of DNA Elements) Consortium, we were the first to empirically test for lncRNA translation in human cells using mass spectrometry, finding that nearly all lncRNAs are not translated. We subsequently discovered, and functionally confirmed, primate-specific estrogen-induced oncogenic (and estrogen-repressed tumor-suppressor) lncRNAs in human estrogen receptor positive breast cancer cells. By combining ribosome profiling with mass spectrometry, we now pinpoint rare estrogen-regulated translation of several short open reading frames in these lncRNAs. These hormone-regulated translational events take place even when transcription of the corresponding lncRNAs is not estrogen-responsive. One of these lncRNAs exhibits systematic in-frame mis-translation of multiple stop codons into amino acids, an apparent gene-specific violation of the human genetic code. Our precision-medicine work encompasses the identification and lab-based validation of direct disease causative candidate lncRNAs that we discovered and annotated from Genome-Wide Association Studies of type 2 diabetes, obesity, and the metabolic syndrome. In a current industry collaboration, we focus on liver-specific targets that we validated in primary human hepatocytes and that are amenable to sequence-specific injectable RNAi-based drugs.