RNA is extensively modified in all organisms, with more than 100 chemically distinct nucleotides identified to date, primarily in abundant tRNAs. Human RNA modifying enzymes are implicated in diverse diseases including many cancers, but the disease-relevant RNA targets are currently unknown. We have developed new sequencing based methods that reveal widespread and regulated modification of mRNAs with pseudouridine and 2′-O-methylribose. I will present our recent progress towards understanding the distribution, regulation and function of these novel mRNA modifications.