A challenge in biomedical research is exploiting new targets for medicine development. RNA directly causes many diseases and yet is believed to be recalcitrant to small molecule targeting. Our focus has been on developing technologies to identify which cellular RNAs are “druggable” targets for small molecules and small molecules to target them. In this talk, I will focus on the development of small molecules that target RNA structures and trigger their elimination or degradation from cells and pre-clinical animal models. For example, structure-binding ligands have been endowed with the ability to affect degradation of repeat expansions to study molecular recognition of small molecules to RNA from cells to mouse models of disease. Mutant alleles that drive disease can be specifically targeted by structure-binding compounds. Small molecules can also facilitate natural decay of repeat expansions in various ways that are mechanistically distinct, that include affecting RNA processing to cause decay and facilitating unnatural interaction of RNAs with ribonucleases. These studies and others suggest that RNAs can be a rich source of small molecule targets and their biology can be programmably manipulated in many ways including targeted degradation.