**Title: RNA-binding domain disorder modulates the RNA destabilizing activity in the TTP family of proteins.**

Abstract: Despite the importance of RNA-binding proteins to gene regulation, our understanding of how their structure and dynamics contribute to their biological activity is limited. In this study, we focus on two related RNA-binding proteins—TTP and TIS11d—that regulate the stability of mRNA transcripts encoding key cancer-related proteins, such as tumor necrosis factor-alpha and vascular endothelial growth factor. These two proteins display differential folding propensity in the absence of RNA, despite sharing a high sequence identity. We have identified three residues that determine the folding propensity of the RNA-binding domain in the apo state and have determined the mechanism through which they control folding. We have also showed that increased disorder of the RNA-binding domain is associated with differences in RNA-binding activity in vitro and decreased RNA-destabilizing activity in the cell. Phylogenetic analysis indicates that this family of proteins has only recently evolved to be able to modulate its biological activity through its dynamic structure.

Francesca Massi PhD

Associate Professor

University of Massachusetts Medical School

Biochemistry and Molecular Pharmacology

University of Massachusetts Medical School

364 Plantation Street, LRB

Worcester MA 01605

Phone -508-856-4501

Email - Francesca Massi <francesca.massi@umassmed.edu>