Transfer RNAs (tRNAs) are indispensable for decoding genetic information from messenger RNA into protein. Specific environmental insults induce the fragmentation of cellular RNAs, including tRNAs, which normally act as adaptor molecules during protein synthesis. tRNA fragmentation results in so-called tRNA fragments, which appear to be functional small RNAs and impact cells through mostly unknown molecular mechanisms. Various tRNA fragments have been repeatedly detected during cellular responses to stress such as starvation, oxidation, hypoxia and hypothermia as well as heat shock or irradiation. Importantly, specific tRNA fragments have been implicated in biological processes including proliferation, differentiation and translation, control of transposon activity, intercellular communication and transfer of extra-chromosomal information between generations.

It is generally assumed that tRNA fragments are produced by the activity of enzymes, which introduce “breaks” into tRNAs. A single “break” in a tRNA should result in two tRNA fragments, which are often called tRNA halves. Interestingly though, cells recovering from stress only maintain one tRNA half, which indicates the presence of cellular activities that degrade the other tRNA half.

This project will identify the enzymatic activities, which act on tRNAs that were “broken” during the stress response of human cells. Specifically, the project aims at identifying enzymes, which degrade only one tRNA half in “broken” tRNAs while leaving the other intact. To do so, the project will employ biochemical fractionation of protein complexes induced by experimental stress conditions in human cell culture systems. Once identified, the molecular details defining these activities will be determined by measuring enzymatic reaction parameters on “broken” tRNAs using recombinant protein and RNA approaches.

Given the widespread detection of tRNA fragments in many species, their functional association with specific cellular processes and potential to serve as biomarkers for particular human diseases, identifying the complete molecular machinery that produces tRNA fragments is likely to have a major impact on our understanding as to how these small RNAs exert biological impact. Furthermore, identifying the enzymes whose function impacts the production and thereby likely the function of tRNA fragments will provide molecular insights that could inform diagnostic and even therapeutic avenues connected to utilizing these small RNAs.