**The *NORAD*-stress granule axis and its role in the hyperthermia-induced radio-/chemosensitization of cancer cells.**

Starting with the discovery of tRNAs and rRNAs in the 1950s, the central dogma of molecular biology in which the genes were thought to primarily produce transcripts coding for functional proteins has been irreversibly challenged. While the structure and function of tRNAs and rRNAs were unveiled and well established in the 1970s, other types of identified **noncoding RNAs** at that time were a matter of debate and largely considered to be contamination or remains originated from the interrupted transcriptional process. The question whether they do really exist and possess any actual biological meaning has been long unanswered. In the twenty-first century, with the emergence of high-throughput RNA sequencing technology providing a revolutionary approach for the systematic discovery of new transcripts, we have learned that **more than 90% of human genome is transcribed, yet only a small fraction of less than 3% of nuclear DNA have potential to code for proteins**. **Our knowledge of noncoding transcripts remains limited.** Their emerging functions in disease and development have attracted attention but specific biological functions and biochemical mechanisms have been discovered for only a few of them.

***NORAD* is a newly identified noncoding RNA** activated by DNA damage and required for maintaining genomic stability and DNA repair in human cells. *NORAD* is highly conserved, abundantly expressed in many cell types and tissues, deregulated in numerous human cancers and may act as an important regulator of tumor progression. **These intriguing features make *NORAD* unique among other known noncoding RNAs.** Recent reports suggest that *NORAD* may utilize a novel mechanism to regulate function of proteins. Normally *NORAD* localizes both in the nucleus and cytoplasm but is nearly completely redistributed to the nuclear compartment when cells are treated with DNA damaging agents. This distinct and compelling behaviour is not understood.

***NORAD* caught our attention when we were investigating radio- and chemosensitizing effects of hyperthermia (HT) on cancer cells.** HT – elevation of the tumor temperature above physiological levels (usually to 41-43 °C) is a promising, clinically applied modality in combined anticancer therapies that, via unclear mechanisms, interferes with multiple pathways of DNA repair. Our incomplete understanding of underlying biological processes limits the widespread application of HT in clinics. We discovered that the most effective HT-combined treatment scheme requires one hour exposure of the cancer cells to 42 °C right after irradiation or application of the chemotherapeutic. Our results indicate that one hour of HT used in this therapeutic regime leads to nearly complete re-localization of *NORAD* to structures called stress granules, non-membrane-bound assemblies of RNA and protein that form when cells are exposed to adverse conditions. **In this project we will investigate the role of *NORAD*-stress granule axis in HT-induced radio- and chemosensitization of cancer cells.**

Understanding the intricacies of *NORAD* will not only enrich our knowledge about this specific long noncoding RNA but also shed light on the poorly understood biological functions and underlying biochemical mechanisms of lncRNAs in general. Furthermore, we hope that investigation of the previously unexplored *NORAD*-stress granule axis may enable us to identify potential new targets for the development of innovative anti-cancer therapeutic strategies.