Prot-RAN: What drives the RAN translation?

The short tandem repeats, usually three to eight base pairs long, are common in human genome. They are also genetically unstable and their uncontrolled expansion may lead to inherited disorders. For example, in the **5'UTR of fragile X mental retardation 1 (*FMR1*) gene**, healthy individuals possess typically between 5 and 54 CGG trinucleotide repeats, while premutation expansions (**55-200 CGG repeats**) causes **fragile X-associated tremor/ataxia syndrome (FXTAS)**, and a full mutation (above 200 repeats) leads to fragile X syndrome (FXS). To date, more than 40 human inherited disorders were linked to the expansions of simple repeat sequences, mostly trinucleotide repeats. Among those typically multisystem diseases are Huntington's disease (HD), myotonic dystrophy and mentioned above FXS and FXTAS.

In Prot-RAN project, we will focus on the expansion of trinucleotide CGG repeats (CGG^{exp}) in the 5'UTR of *FMR1* gene, which causes common neurodegenerative disease, FXTAS. The pathogenesis of FXTAS remains unclear, and to date, various pathogenesis models have been proposed. One of the possible mechanism is the **repeat associated non-AUG initiated (RAN) translation**. This phenomenon is based on the observation that the expanded short tandem repeats can trigger the production of mutant proteins, without the canonical AUG initiation codon, which is usually used for protein translation. Resulting aberrant proteins accumulate in nuclear inclusions in the brain of FXTAS patients, leading to neuronal death.

Despite emerging reports about the possible mechanisms driving RAN translation, still little is known about this process. The main goal of the Prot-RAN project is to **identify proteins regulating RAN translation**, which will help to understand the disease mechanisms and find potential drug targets for neurodegenerative diseases- FXTAS, HD and other short tandem repeat expansion disorders.

To achieve this goal, we will bridge cutting-edge proteomics with RNA biology techniques. Briefly, we will employ the CGG^{exp} RNA-targeting pull-down approaches combined with proteomic profiling, RNA mutagenesis, protein expression analysis and RNA/protein interaction studies. The role of identified proteins will be then verified in other expansion disorders, e.g. HD, giving insight into more global context of the RAN translation. As a result, the discovered factors driving RAN translation could be used as potential new targets for therapeutic strategies of microsatellite expansion disorders.