The aim of the project is to determine how IFIT1 and IFIT2 proteins regulate their own expression through mRNA binding. IFIT proteins (interferon-induced proteins with tetratricopeptide repeats) constitute a family of RNA-binding proteins found in vertebrates. These proteins play a key role in the immune response, and their expression is induced by viral infection, stimulation with interferon, or the detection of pathogen-associated molecular patterns (PAMPs). Such patterns include, among others, lipopolysaccharides (LPS), which are components of Gram-negative bacterial cell walls, as well as RNA motifs recognized as "non-self"– including the cap0 motif, present at the 5’ end of some viral RNAs.

In humans, the IFIT family comprises four proteins – IFIT1, IFIT2, IFIT3, and IFIT5 – of which only IFIT5 exists in a monomeric form. The remaining proteins form complexes with each other, and the composition of these complexes significantly affects their function and stability. IFIT proteins are widely recognized as antiviral proteins. Due to their affinity for RNA motifs found in viruses, they can effectively bind viral mRNA and thereby regulate its translation. To date, IFIT1 is the best-characterized member of the family; it binds cap0 RNA and blocks its translation, thereby inhibiting viral replication. In contrast, IFIT2 displays sequence specificity, binding motifs rich in adenine and uracil. Such motifs are not unique to viral RNA—they are also present in host-derived mRNAs. The potential involvement of IFIT2 in binding such mRNAs has not yet been fully described or explained, nor have its functional consequences been elucidated.

In our research, we are particularly interested in IFIT2, whose role in viral infection remains unclear. It has been observed that IFIT2 is utilized by the influenza A virus to support the translation of viral proteins, which contradicts the established view of IFIT proteins as antiviral agents. In our studies, we have observed that IFIT2 binds to its own mRNA and that IFIT3 plays an important role in this process. Additionally, we have noted that IFIT1 is also capable of cellular RNA binding.

As part of this project, we plan a three-step research strategy. First, we will investigate how individual IFIT proteins influence the recognition of IFIT1 and IFIT2 mRNAs. Next, we will apply the iCLIP2 technique – an advanced method that will allow us to identify IFIT binding sites on mRNAs at single-nucleotide resolution. In the final stage, we will examine how the interaction of IFIT proteins with the RNA motifs identified in the previous step affects translation and mRNA stability. This will allow us to determine whether IFIT proteins promote or inhibit protein synthesis from their own mRNAs.

Our research will shed new light on the functions of IFIT proteins in regulating the immune response, going beyond their classical antiviral roles. Demonstrating that they can autoregulate their own expression may reveal a previously unknown feedback mechanism in the immune system. The data generated in this project, including iCLIP2 and Ribo-seq profiles, will also be a valuable resource for other researchers working in the fields of RNA biology and immunology.