Interferons (IFN) represent a family of cytokines which can be divided into three groups: type I, II and III. Type I IFNs consists of IFNβ, κ, ω, ε and 13 IFNα molecules, type II comprises the single IFNγ and type III consists of IFN λ1, λ2, λ3 and recently discovered λ4. IFNs are produced and released by host cells in response to the presence of pathogens (such as viruses, bacteria and parasites) and also tumor cells. In response to the virus interferons are released by infected cells causing nearby cells to enter the so-called anti-viral state in which they are protected against viral invasion. Interferons are part of the innate immunity which is capable of controlling and fighting with virus infections in the absence of adaptive immunity. However, viruses can still replicate and cause disease in vivo, because in the course of evolution they obtained strategies for at least partially circumventing the IFN response. Nevertheless, our immunity never sleeps and is evolving simultaneously with viruses.

By interacting with their specific receptors, IFNs activate signal transducer and activator of transcription (STAT) complexes; STATs are a family of transcription factors that regulate the expression of certain immune system genes. It was thought that only one, so-called "canonical pathway" exists. In this process IFNs induce expression of a group of so-called IFN-stimulated gene (ISG): in response to IFN STAT1 and STAT2 proteins are phosphorylated and together with IRF9 (interferon regulatory factor 9) form the trimeric ISGF3 (IFN-stimulated gene factor 3) complex which recognizes a specific sequence in the ISG promoters called ISRE (interferon stimulated response element). Activation of the type I IFN signaling pathway is induced within minutes after stimulation and leads to the induction of more than 300 ISGs, most having antiviral activity. Thus, this canonical response is robust but with transient profile. For this reason the ISGF3-dependent response pathway for a long time was thought to be the fundamental line of defense against viral infections. However, recent studies provide evidence that a subset of IGS is expressed even at 72h after IFNα stimulation, what excludes the ISGF3 involvement. It appears that together with the classical ISGF3 complex alternative ISGF3 component-based complexes can exist in the cell and depending on the abundance of these components and their phosphorylation status a variety of complexes can be assembled and drive the antiviral gene expression. However, it still requires extensive studies to identify their exact role in ISGs expression regulation in the presence and absence of IFN and how they cooperate in protection against viral infection. This clearly implies that the innate immune response is far more complex as previously anticipated.

For a deeper understanding of the complexity of this system, in this project we propose to perform experiments using contemporary whole-genome approaches of molecular biology such as Next Generation Sequencing (NGS) as well as Chromatin Immunoprecipitation-sequencing (ChIP-Seq). These techniques allow to specify how the various complexes interact with chromatin and how they regulate transcriptional activity of specific ISGs, depending on the time of exposure to interferon. We also determine to identify the existence of genes specifically recognized by the particular complexes. Furthermore, by performing the antiviral assay we will be able to check the effectiveness and cooperativity of canonical and alternative complexes in the fight against viruses. These studies will shed light on so far unclear issues concerning the complexity of the innate immune response, which in the future could give the foundation for origin of new, more effective antiviral drugs, and may also result in the discovery of biomarkers for monitoring the course of viral infection and its treatment.