Animal health has a great impact on animal productivity, quality, and quantity of given products, as well as on reproduction success and consequently on the economic outcome of animal production. Small ruminant lentiviruses (SRLV) infect animals worldwide causing pain, inevitable death, lower productivity, and consequently significant economic losses. There is no cure or vaccination. Genetic markers associated with host resistance to viral infections and diseases can be applied in animal breeding programs. However, host-pathogen interactions are complex processes, that are mostly understudied not only in animals but also in humans. This substantial lack of knowledge makes viral threat reduction difficult and often not effective in animal breeding.

We hypothesize that: **1/** Small ruminant lentivirus (SRLV) infected and non-infected hosts (here: sheep) show differences in their genomes, epigenomes, transcriptomes, and proteomes. Some of these genetic factors and/or epigenetic marks have an influence on host resistance to infection. **2/** The SRLV genotype modulates the protective effect of the host's genetic variants. The possible mechanism includes the hijacking of the host's epigenetic machinery and the modification of the cell proteome by the pathogen. **3/** Investigating the interplay between genomic, epigenomic, transcriptomic, and proteomic factors of virus-host interactions in SRLV infection has the potential to uncover new possibilities to fight against this group of diseases.

The aims of the project are: **1/** To identify host genetic and epigenetic factors which modulate sheep resistance to SRLV in order to find reliable genetic markers and epigenetic marks associated with SRLV resistance. **2/** To analyze SRLV-induced alternations in host methylome, transcriptome, and proteome to recognize and clarify the potential mechanism of hijacking the host epigenetic machinery and the cell proteome by the virus and the impact of these processes on host-pathogen interactions and host resistance to SRLV infection. **3/** To analyze mechanisms of interplay between genomic, epigenomic, transcriptomic, and proteomic factors involved in host-virus interactions.

The following general research tasks have been planned:

Task 1. Collection and preparation of animal samples and data.

Task 2. Testing sheep samples for SRLV infection status and for *TMEM154* E35K genotype.

Task 3. Multi-omics characterization of sheep with opposite SRLV infection status.

Task 4: Multi-omics data analysis and holistic study on the phenotypic and bioinformatic results.

The results of this project will provide new knowledge on multi-omics factors involved in host-virus interactions influencing a lentiviral infection. Moreover, the outcomes of the project will contribute to the understanding of the phenomenon of hijacking the host epigenome and changing the host transcriptome and proteome by pathogens like lentivirus. The proposed project has the potential to deliver evidence on new genes involved in genetic resistance to SRLV in sheep. On the other hand, results on epigenetic, transcriptomic, and proteomic effects of the virus may indicate new possibilities for cure and prophylaxis. Such results can provide new targets for additional investigation into lentiviral infections that may generalize beyond SRLV to other members of the lentiviral family, e.g., HIV-1 virus in humans. We expect that adopting improved epigenetic and genomic measures for prevention against the virus infections will subsequently pave the way for a more focused and efficient application of marker-assisted selection or genomic selection in animal breeding programs aiming at increasing the resistance to virus infections in the near future.