PROJECT SUMMARY

African swine fever (ASF) is one of the most complex viral diseases affecting livestock and has tremendous socio-economic impact. Over the last decade, the disease has conquered several new areas and keeps spreading. The causative agent is an enveloped DNA virus of the *Asfarviridae* virus family that is generally rather stable. The disease has its roots in sub-Saharan Africa where it is transmitted in an ancient sylvatic cycle among warthogs and soft ticks of genus *Ornithodoros*. This cycle is not accompanied by overt disease or mortality in warthogs. However, any introduction of the disease into the domestic pig sector or into Eurasian wild boar populations leads to a severe multi-systemic disease that can resemble a viral hemorrhagic fever with exceptionally high lethality (over 90% of the infected animals die). To date, neither treatment nor a licensed vaccine exist and detailed knowledge about correlates of protection but also severe outcomes and pathogenesis are lacking. To address gaps in understanding ASF disease, this consortium aims to identify factors at the level of the pathogen, the host species and their immune cells that will define host/cellular susceptibility and protection. Moreover, we will try to explain phenomena such as the observation of higher seroprevalence rates or resistance in the field.

Specifically, we will coordinately evaluate correlates of protection and basic host-virus interactions in multiple hosts including susceptible domestic pigs (SPF and conventional farm-raised) and European wild boar and resistant red river hogs. Responses of relevant ASFV strains with moderate and high virulence will be compared in these hosts. For part of this work, we will employ a systems immunology approach that will use computational biology tools to process all collected data from the consortium including virological, clinical and immunological readouts and immune cell transcriptomics. This will identify immunological processes and mechanism of both the innate and adaptive arms that are relevant in controlling ASFV or on the contrary that relate to disease severity. Among the studies addressing the long-term fate of animals and drivers of disease dynamics, we will experimentally address the impact of maternal immunity on disease outcome using a sow-suckling piglet model. Moreover, we will also address the possibility of ASFV reactivation following survival from ASFV infection. To this end, classical swine fever superinfection and chemical immunosuppression will be used. Addressing dose responses as an explanation or means for outcome variability, we will also use repeated low dose infection followed by highly virulent challenge of those pre-triggered animals. Finally, the presence of the virus in semen and possibility of vertical transmission will be formally investigated. Evolutionary pressure on the viral genome by host immune responses will be examined for the different isolates using deep sequencing. Aspects of cellular susceptibility will be investigated in macrophage subpopulations by combining complementary approaches in vivo and in vitro.

The project will combine knowledge, expertise, and reagents of six teams with high international reputations in ASFV research and porcine immunology to improve basic knowledge on ASFV host interactions and mechanisms of protective immunity. The multipronged and combinatorial approach of this consortium will reveal virus-host interactions at the animal and cellular level, which will reveal mechanisms of higher resistance, immunity and alternative transmission pathways.