# PROJECT SUMMARY

Infectious diseases of livestock continue to cause a major financial impact globally, threatening food security and public health. Disease control measures comprise a combination of biosecurity with both preventative and therapeutic treatments. However, vaccination remains the most cost-effective tool by far to prevent, manage and even eradicate diseases.

Maternally derived antibodies (MDA) play a critical role in protecting neonatal livestock against infectious diseases during their early life. However, MDA can dampen immune responses of neonates to vaccination through a number of distinct mechanisms, including the neutralisation of live attenuated vaccines and the inhibition of neonatal B cell responses. Thus, as MDA wanes immunised animals remain vulnerable to pathogen challenge.  In this project, we will test vaccine strategies designed to enhance immune responses in neonatal animals with MDA. Our state-of-the-art approaches to this challenge span improved immunogen design, antigen delivery configuration and immunopotentiators.

We will focus on two major endemic viral diseases: bovine respiratory syncytial virus (BRSV) in cattle and porcine reproductive and respiratory syndrome virus (PRRSV) in pigs, for which the consortium has developed preliminary tools and knowledge of strategies to counteract different mechanisms of MDA interference. BRSV is estimated to cause 14-71% of bovine respiratory disease outbreaks globally and PRRSV is considered the most economically important disease affecting the global pig industry with estimated losses in Europe exceeding €1.5 billion *p.a*. In both these infections, MDA interfere with neonatal vaccination leading to high vulnerability at the time of weaning or feedlot/fattening where MDA are low and active immunity is not yet in place.

The project is structured with three complementary work-packages (WP):

WP1: Designing BSRV immunogens to exploit differences in antibody repertoires between adult and neonatal cattle. We will identify epitopes on the pre-fusion (preF) protein that are differentially targeted by neonatal and adult antibody repertoires. Epitope-scaffold antigens preferentially recognised by neonates will be anchored on N-nanorings, that are immunogenic carriers easy to produce in bacteria at low cost. These will be evaluated in $MDA^{+}$ calves for protection against experimental BRSV challenge.

WP2: A DNA vaccine-based approach against PRRSV to counteract MDA interference. We will generate DNA vaccines where PRRSV antigens are fused to XCL1 or anti-MHC-II scFv, as dendritic cell (DC) targeting moieties that we have shown enhance immunogenicity. We will then test if a targeted DNA prime/modified live vaccine (MLV) boost vaccine strategy enhances cell mediated and antibody responses and increase vaccine efficacy in MDA+ piglets. Complementary in vitro experiments will be conducted using DC targeted antigens to understand how they counteract the MDA-negative effect on B-cell responses.

WP3: Engineering immune checkpoint inhibitors (ICIs) to enhance neonatal responses to vaccination. Immune checkpoints are natural regulators of the immune system, crucial for maintaining self-tolerance and reducing immunopathological responses. Immune checkpoint inhibitors are highly effective cancer immunotherapeutics and are emerging as a novel class of adjuvants for prophylactic immunization. We will evaluate whether genetically engineering PRRS MLV to express peptide-based ICIs will potentiate vaccine responses of MDA+ piglets resulting in enhanced protection.

The outputs from this project will directly benefit the development of improved vaccines against these two key diseases but also as a concept since the approaches may be exploited in the context of other pathogens, livestock species and humans.