Study identifies 'chink in the armor' of Schmallenberg virus

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A key building block in the Schmallenberg virus could be targeted by anti-viral drugs, according to a new study led from the University of Leeds.

The disease, which causes birth defects and stillbirths in sheep, goats and cattle, was first discovered in Germany in late 2011 and has already spread to more than 5,000 farms across Europe, and 1,500 farms in the UK alone.

There is currently no way of treating infected animals, but a study published in *Nucleic Acids Research* reports that the Schmallenberg virus nucleocapsid protein, which protects its genetic material, could be its Achilles' heel.

A University of Leeds-led team of virologists and structural biologists used X-ray crystallography and electron microscopy to decipher the three-dimensional shape of the nucleocapsid protein and also show how it builds the inner workings of the virus itself.

Dr John Barr, of the University of Leeds' Faculty of Biological Sciences and co-leader of the study, said: "The protein forms a chain a bit like a necklace that wraps around and protects the RNA, the genetic material of the virus. This chain also recruits other proteins that are vital to the virus' ability to multiply and cause disease. We have developed a very finely detailed picture of the shape of the protein and all the nooks and crannies that it needs to present to other molecules to be able to

function."

The nucleocapsid proteins bind together in a ring-like structure of four identical protein units, and the ring is held together by contacts between the protein units, a bit like people holding hands in a circle.

Co-lead Dr Tom Edwards, also from Leeds' Faculty of Biological Sciences, said: "The shape of the nucleocapsid protein has shown us important details of how the individual proteins in these rings are interacting. This not only tells us how the virus works, but importantly we think we can block that interaction and disrupt the process of making the ring. That could be the chink in its armour. It would stop the protein wrapping up the RNA, and would essentially kill the virus. We are now designing small molecules that could block ring formation and could therefore be an effective antiviral drug."

The Schmallenberg virus appears to be spread by midges. It causes a relatively mild illness in adult animals but is responsible for stillbirths and birth defects in cattle, sheep and goats.

The Department for Environment, Food and Rural Affairs (DEFRA) believes the disease was probably brought into the UK from infected midges blown across the Channel. It has since spread rapidly, causing severe losses on many holdings across the entire UK. There is new evidence that the Schmallenberg virus can also spread to wild animal populations such as deer and wild boar, raising the possibility that a reservoir of the disease could develop outside the control of farmers and cause problems for many years to come.

Developing a vaccine for the Schmallenberg virus is a possibility. One already exists for the similar Akabane virus, but the discovery by the Leeds-led team is the first step toward developing a treatment that could be used after an animal is infected.

The research was funded by The Wellcome Trust and involved researchers from The University of Leeds, The University of Alabama at Birmingham, The University of St Andrews, The Veterinary Laboratories Agency, and the University of Liverpool.

More information: The paper, "Nucleocapsid protein structures from orthobunyaviruses reveal insight into ribonucleoprotein architecture and RNA polymerization," is published in *Nucleic Acids Research*.

Provided by University of Leeds