



# ALTANT RESUPLYS

INTRODUCTION

In the current high density animal production systems, vast amounts of antimicrobials are used to combat bacterial diseases. This results in an alarming increase in resistance levels of bacteria that cause problems in animals and humans. Alternative strategies to prevent and treat bacterial infections are urgently needed particularly for pathogens causing serious animal infections, such as those caused by *Streptococcus suis* in pigs. Besides clinical infections, the additional more serious problem of multiresistant microorganisms in husbandry (e.g. MRSA, ESBLs) and their potential transmission to humans also exists. In this project two non-antibiotic therapies have been developed and used to decolonize pathogenic bacteria from colonized animals. These treatments are based on lysin therapy (using phage lytic enzymes to kill bacteria) and phage therapy (using viruses to kill bacteria). Lysins are proteins that have a very strong, rapid and specific bactericidal effect. Bacteriophages are highly specific and self-replicating. Lysins and phages are safe for vertebrates and show no adverse effects.

TARGET

The target pathogens are *Streptococcus suis*, one of the most important bacterial infections in pig production worldwide, and Methicillin Resistant *Staphylococcus aureus* (MRSA), a zoonotic pathogen widely spread in production animals worldwide. For *S. suis* the aim was to identify, isolate and produce lysins and bacteriophages and evaluate their ability to decolonize these organisms and thus prevent infection in animal experiments. For MRSA an existing lysin was tested for efficacy in colonized pigs.

One *S.suis* specific phage was obtained which demonstrated (strain-specific) efficacy *in vitro* only. The most promising results for decolonizing *S. suis* from contaminated pigs were obtained using lysins. Two novel *S. suis*-specific lysins have been identified, cloned and produced as bio-active recombinant molecules. Importantly these lysins demonstrated a broad range of activity against the most prevalent *S. suis* serotypes, as in contrast to the phage. As expected, their lytic activity *in vitro* was rapid for all of these strains. The clinical efficacy was tested in a pig infection/transmission *S. suis* (serotype 9) model. Read-out parameters were: the effect on the transmission ratio between pigs, the prevention of clinical signs (arthritis, meningitis, fever), the effect on total bacterial counts, the *in vitro* effect on colonized tonsils, and adverse effects. Infected animals received a series of treatments with lysins orally (treatment of the tonsils) and intra-nasally.

Clear differences were demonstrated between the lysin-treated and control groups for most of the read-out parameters with a positive effect in the lysin-treated group. There were no adverse effects observed in these experiments.

Patent protection is in progress for the two novel lysins.

For MRSA, a lysin has been produced and is currently being used in two types of MRSA colonization models in pigs (natural infection and an experimental infection). The read-out parameters are reduction of total bacterial counts in nasal swabs.

In *in vitro* experiments designed to identify organisms resistant to lysins, no resistance could be observed even after repeated incubation of the target bacterial species with the lysins.

RESULTS

PROPOSITION

In these studies a clear proof of potential of the application of both phages and lysins has been demonstrated. The application of bacteriophages is however limited to the strain of bacteria and therefore their practical use is restricted. The use of lysins to control clinical disease in *S. suis* models of infection is very promising. These positive results need to be confirmed with other highly prevalent and clinically relevant *S. suis* serotypes (e.g. serotype 2). The effects measured can and should be optimised by improving the formulation and the effective dose.

The attractiveness of using lysins to control pathogenic infections may result in a broadly applicable platform technology as will be demonstrated by the effects of the MRSA lysin.

The consortium therefore seeks partners that are interested in the basic technology of applying lysins and or phages to decolonize infected animals or prevent excessive colonization with clinical or public health consequences. Proprietary technology on the production and formulation of such applications is an additional value that will enhance the potential of such products.

Project is open for participation