



ALTANT ASIA

Host Defence Peptides (HDPs) are small peptides with broad-spectrum antimicrobial activity against a variety of Gram-negative and Gram-positive bacteria, fungi, protozoa and some enveloped viruses. In contrast to 'classic' antibiotics, HDPs use multiple mechanisms to kill bacteria such as cell wall permeabilisation, inhibition of DNA replication and protein synthesis. In addition, HDPs exert multiple immunomodulatory functions, such as LPS neutralisation and orchestration of the cytokine production of immune cells. More importantly: these multiple actions of HDPs have *prevented the development of antimicrobial resistance*, despite the fact that these peptides are part of the natural host defence of animals for millions of years. Therefore, these peptides are an excellent paradigm for development of new antimicrobials for use in live stock.

The primary aim is to develop novel 'peptide antibiotics' for veterinary prophylactic and/or therapeutic use. On laboratory scale, antibacterial and/or immunomodulatory sequence requirements of host defence peptides of pig and chicken have been determined but their activity may be improved through specific structural changes.

- 1) *In vitro* analysis indicated that the 27 amino acid HDP chicken Cathelicidin 2:
 - possesses a strong and broad spectrum antibacterial activity
 - inhibits LPS-induced immune response of macrophages
 - stimulates cytokine production of macrophages directly
- 2) The antibacterial activity is located in a relatively short segment of the N-terminus of the peptide, while the immunomodulatory activity is located in the central area (Fig.1).
- 3) Point mutations which induced slight changes in hydrophobicity and amphipathicity of the shortened peptides increase antibacterial and/or immunomodulatory activity.
- 4) Contrary to the mature peptide, shortened peptides are non-haemolytic or cytotoxic.
- 5) *In vivo* testing of these peptides is currently ongoing.
- 6) Similar experiments have been performed with porcine HDPs. These peptides also contain short core elements that possess the antibacterial activity. Immunomodulatory elements of these peptides are less clearly defined yet.
- 7) Patent application has been filed

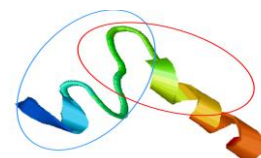


Fig.1 Structure of chicken Cathelicidin 2. Ellipse represent core elements required for antibacterial (blue) and immunomodulatory activity (orange).

Animal-specific host defense peptides may be used as a paradigm to develop new anti-infectives. Proof of principle has been demonstrated for chicken peptides and good progress is made to achieve a similar proof for porcine peptides.

The consortium invites industrial partners that are interested in the development of these antibiotics to cooperate in two main areas: 1) cost-effective large scale production of these peptides, and 2) development of an efficient carrier system that protects the peptides from proteolysis in, for example, the upper digestive tract.

Other areas of interest of our consortium are:

- The use of specific feed additives to improve wellness and productivity of live stock by enhancing intrinsic HDP levels.
- The use of HDPs derived peptides as adjuvant in vaccine formulations.

Companies interested in development of peptide antibiotics are invited to discuss ideas and Opportunities to combine efforts.

Project is open for participation