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New window-Insighting a potential solution of anti-MRDs from AMPs

Plectasin, a cationic antimicrobial peptides from the saprophytic fungus *Pseudoplectania nigrella*, exhibits strong bactericidal activity toward the key gram-positive pathogens--*Staphylococcus aureus* and *Streptococcus pneumoniae*. Arenicin-3, a member of the arenicin family from the marine lugworm *Arenicola marina*, has high activity against gram-negative bacteria. Recently, our team has focused the innovation of above AMPs and their uses in control of animal diseases: (1) molecular design made antimicrobial activity against MRSA of NZ2114/MP1102 over 15 times higher than its parent peptide plectasin; (2) the platforms of high expression (expression level of 2.3 g/L by *Pichia pastoris*) and purification (purity over 93%) were built for low-cost production and industrial application; (3) *in vitro* dual antibacterial mechanisms of plectasin derived peptides involved interfering with the cell membrane and intracellular DNA of derived peptides towards methicillin-resistant *S. aureus* (MRSA), *Streptococcus suis*, *Clostridium perfringens* were revealed, as well as in mechanisms of arenicin-3 derived peptides against *Escherichia coli* and *Salmonella typhimurium*, whose multi-target mode of action indicated the low resistance mechanisms differed from antibiotics; (4) MP1102/NZ2114 internalized into the cells via clathrin-mediated endocytosis and macropinocytosis and distributed in the cytoplasm and exhibited intracellular bacteriostatic efficiency in professional phagocyte (RAW264.7) and non-professional phagocyte (MAC-T). In addition, conjugating with cell-penetrating peptides improved the intracellular antibacterial activity of marine peptide N2 against the *S. typhimurium*; (5) *in vivo* study showed that NZ2114 and arenicin-3 derived peptides effectively increased the survival of mice, decreased the bacterial translocation in lung and liver, inhibited the release of TNF- α and IL-1 β , and relieved the lung, liver, and spleen from acute injury induced by *S. aureus*, *S. suis*, *E. coli*, and *S. typhimurium*. The above results indicate a potential of plectasin and its derived peptides and arenicin-3 derived peptides as new ATA agents against gram positive and negative pathogens infections in animal.

Recent Publications

1. Wang X, Wang XM, Teng D, Mao RY, Hao Y, Yang N, Li ZZ, Wang JH (2018) Increased intracellular activity of MP1102 and NZ2114 against *Staphylococcus aureus* *in vitro* and *in vivo*. *Scientific Reports* 8(1):4204.
2. Li Z, Wang X, Teng D, Mao RY, Hao Y, Yang N, Chen HX, Wang XM, Wang JH (2017) Improved antibacterial activity of a marine peptide-N2 against intracellular *Salmonella typhimurium*, by conjugating with cell-penetrating peptides-bLFCin 6 Tat 11. *European Journal of Medicinal Chemistry* 145:263.
3. Yang N, Liu XH, Teng D, Li ZZ, Wang XM, Mao RY, Wang X, Hao Y, Wang JH (2017) Antibacterial and detoxifying activity of NZ17074 analogues with multi-layers of selective antimicrobial actions against *Escherichia coli* and *Salmonella enteritidis*. *Scientific Reports* 7: 3392.
4. Zheng XL, Wang XM, Teng D, Mao RY, Hao Y, Yang N, Zong LF, Wang JH (2017) Mode of action of plectasin-derived peptides against gas gangrene-associated *Clostridium perfringens* type A. *PLoS ONE* 12(9): e0185215.
5. Hao Y, Yang N, Wang XM, Teng D, Mao RY, Wang X, Li ZZ, Wang JH (2017) Proposed title: Killing of *Staphylococcus aureus* and *Salmonella enteritidis* and neutralization of lipopolysaccharide by 17-residue bovine lactoferricins: improved activity of Trp/Ala-containing molecules. *Scientific Reports* 7,4427.

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6. Wang XM, Teng D, Mao RY, Yang N, Hao Y, Wang JH (2017) Combined systems approaches reveal a multistage mode of action of a marine antimicrobial peptide against pathogenic *Escherichia coli* and its protective effect against endotoxemia. *Antimicrobial Agents and Chemotherapy* 61(1): e01056-16.
7. Jiao J, Mao RY, Teng D, Wang XM, Hao Y, Yang N, Wang X, Feng XJ, Wang JH (2017). *In vitro* and *in vivo* antibacterial effect of NZ2114 against *Streptococcus suis* type 2 infection in mice peritonitis models. *AMB Express* 7:44.

Biography

IFR, CAAS. He is mainly engaged in the research and development of antimicrobial peptide (AMP) and alternatives to antibiotics (ATA) for over twenty years, and has run over 20 national research projects/funds with over 180 publications in the academic journals since 1988. He is a winner of Beijing S & T Award, 1st class (R01, 2017) and China State S & T Progress Award, 2nd class (R03, 2001). His other titles includes a chief scientist of AMP & ATA direction of National Innovation Program of Agricultural Science & Technology in CAAS, vice director of Key Laboratory of Feed Biotechnology, MOA, and chairman of the 9th International Lactoferrin Conference (2009) and member of its Scientific Committee (2008-), distinguished expert of MOA and national talent of the Ministry of Human Resource in New Century.

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