Lipohexapeptide HB1345: A novel anti-infective for acne

P100

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Background

Acne is the most common skin disorder of adolescence and early adulthood with a prevalence of approximately 85%. Generally mild to moderate cases are treated with topical anti-infectives and / or anti-inflammatories.

Antimicrobial peptides are the first line defense against microbial attack in almost all living things (Zhang *et al*. 2006). In response to *P.acnes* and inflammation the human antimicrobial peptide LL-37 is expressed in sebocytes and keratinocytes respectively (Lee *et al*, 2008). Due to binding of lipoteichoic acid (LTA) peptides such as LL-37 have the ability not only to kill *P.acnes* but also significantly reduce its inflammatory potential. However, even though expressed, such peptides often fail to exert potent activity due to inhibition by many of the components in the acne pore. Omiganan (Fritsche et al., 2008), a synthetic version of such an innate immunity peptide also suffers from such inhibition. HB1345 is a first in class lipohexapeptide small molecule peptide mimetic of naturally occurring antimicrobial peptides.

Objective

Here we characterize the clinical potential of HB1345, a first in class anti-infective, specifically designed to address infection and inflammation in acne but also with the potential to function in the hostile environment of the acne pore.

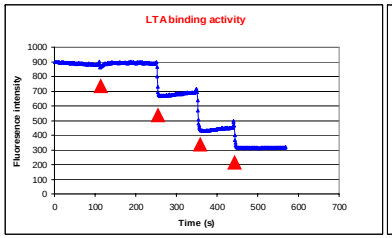
Methods

In vitro antimicrobial activity testing. Minimal inhibitory concentration (MIC) assay was performed by the modified NCCLS microbroth dilution method described by Steinberg *et al*, 1997. Kill kinetics were followed as microbial survival over time in conditions described in the poster.

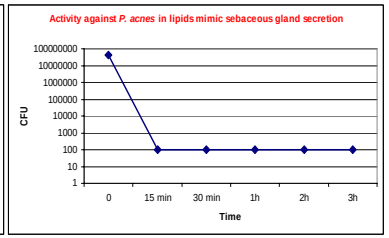
LTA binding assay. The relative binding affinity of peptides for lipotechoic acid (LTA) of *S. aureus* was determined using the modified LPS binding assay described by Scott *et al.(*1999).

S. aureus wound infection – A model fro Gram-positive infection. A standard skin abraded wound model in rat was used to evaluate the efficacy of peptide. Each group consists of 6-12 Sprague-Dawley female rats. On the back of each rat, 1 1x1 inches partial-thickness skin wound was created and contaminated with about 2.5x105 CFU of *S. aureus* per wound followed by application of 0.3ml of aliquot of gel after 30min and 12hrs post infection. The treatment was continued once daily for 3 days. In the end rats were euthanized and the number of bacteria per gram of tissue. Was determined. Statistical analysis was performed using an unpaired student's T-test to determine the significance of the group receiving peptide treatment compare to the control groups.

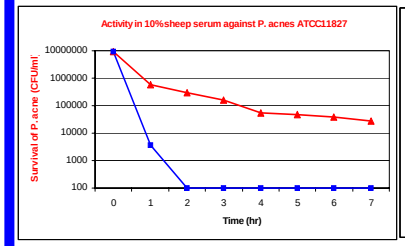
1: Anti-inflammatory



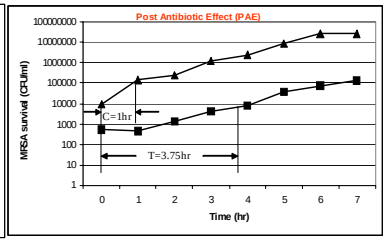
2: Bactericidal



3: Active in serum

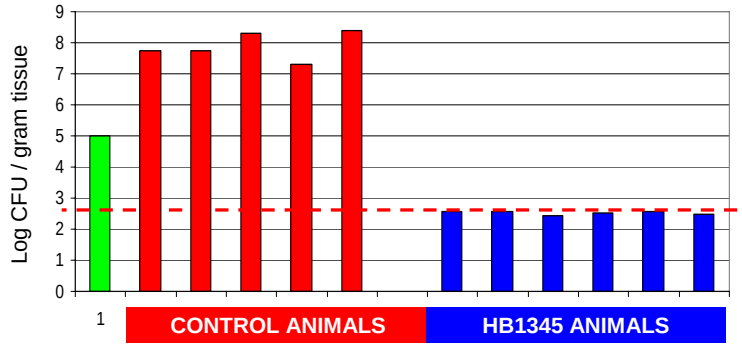


4: Extended PAE



5: Efficacy in skin infection model

Rat abraded skin infection model with animals inoculated with *S.aureus* on day 1 (**green bar**) and the number of bacteria determined on day 3 in control (**red bars**) and treated (**blue bars**) animals.



Mean (Log CFU/g	**7.89**	**2.53**
SD	**0.45**	**0.06**

STATISTICAL SIGNIFICANCE (P<0.001)

Limit of detection

Results

➢ **HB1345 shows potent antimicrobial activity with MICs of 0.5 to 1mg/L against a panel of drug resistant *P. acnes.* In addition serial passaging (40 passages) in sub-MIC concentrations of HB1345 failed to induce resistance (data not shown). In addition the antimicrobial activity is rapidly cidal. FIGURE 2.**

➢ **HB1345 remains highly active under biophysiological environment such as in the presence of serum, cationic ions, and in mixture composed of lipids that mimic the sebaceous gland secretions. FIGURES 2 AND 3.**

➢ **HB1345 neutralizes LTA released by Gram-positive bacteria the source of persistent and long term inflammation. FIGURE 1.**

➢ **HB1345 exhibits an extended post antibiotic effect in the excess of 3hrs. FIGURE 4.**

➢ **HB1345 in a 1% aqueous gel formulation significantly reduced the number of *S. aureus* in an abraded skin infection model. Practically eliminating the pathogen in all animals with once daily dosing for three days. FIGURE 5.**

Conclusion

HB1345 demonstrates great potential as a broad spectrum anti-infective and anti-inflammatory therapeutic for the treatment of dermatological conditions such as acne, acne rosacea and atopic dermatitis. This molecule not only exhibits potent activity but maintains that activity in the presence of biological fluids. The antimicrobial activity is rapidly cidal, does not engender resistance and is not cross resistant with other mechanisms of action. HB1345 has the potential to provide significant clinical benefit.

References

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Commercial support statement

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