Propionibacterium acnei is a major contributing factor to acne vulgaris, a common disorder that is estimated to affect 9.4% of the global population. P. acne colonizes and proliferates within the pilosebaceous follicles causing the induction of local inflammatory response. This is mediated through the interaction of P. acne with epidermal keratinocytes leading to activation of toll-like receptors and later resulting in the production and secretion of pro-inflammatory mediators. Lipoprotein particles (LPC) small molecules represent a novel class of topicaly applied non-steroidal anti-inflammatories that can be used in consumer products and more potent derivatives for drug development to treat skin diseases. Here we report IPC derived, SIG1459, downregulates these inflammatory signaling pathways and directly decreases P. acne viability. Keratinocytes exposed to P. acne, peptideglycan and FSL-1 released pro-inflammatory cytokines and were inhibited by SIG1459 with IC50 values in the nanomolar range. In an in vitro growth inhibition assay of cultured P. acne, SIG1459 outperformed anti-acne agents, benzoyl peroxide (BPO) and salicylic acid, exhibiting a strong MIC of 5 μM, MBC of 10 μM, and eradicating P. acne biofilm formation (MBC) at 21 μM. Lastly, 1% SIG1459 formulation in a 5% acriflavine single blind vehicle controlled study was shown to significantly outperform 3% BPO using an investigator global assessment acne score. SIG1459 (n=35) resulted in a ≥2 grade reduction after 8 weeks, while BPO (n=15) resulted in a 1.5 grade reduction. Moreover, SIG1459 was well tolerated with no adverse reactions (stinging, burning, dryness, stinging), which as expected were reported by subjects in BPO arm of the study. These data demonstrate that phyllo-cysteine derived IPCs, SIG1459 represent a novel chemical class that provides a dual modulating benefit to acne by limiting bacterial proliferation and inhibiting inflammation.

Fig. 1. IPCs target both P. acne induced inflammation and growth

Propionibacterium acnes (P. acne) is a major contributing factor to the inflammatory component of acne. The interaction of bacterial cell-wall components including peptidoglycan (PGN) and lipopptides with keratinocytes (NHEK) leads to an innate immune response via activation of toll-like receptors (TLR2, TLR2/TLR6) resulting in the production and secretion of pro-inflammatory mediators. Phyllo-cysteine compound SIG1459 derived from our IPC library platform inhibits both P. acne induced cytokine production and growth.

Fig. 2. SIG1459 demonstrates strong antimicrobial activity versus P. acne

Normal Human Epidermal Keratinocytes (NHEKs) were pre-treated with test compounds for 2 hours and later cultured for 24 hours with P. acne live bacteria (10 μCFU/mL) and co-treated with test compounds. Interleukin-8 (IL-8) levels were measured by ELISA. Data represent average results from 3 independent experiments. IC50 values were determined by non-linear regression analysis using the four-parameter logistic equation.

Fig. 3. SIG1459 eradicates P. acnes biofilm formation

Normal Human Epidermal Keratinocytes (NHEKs) were pre-treated with test compounds for 2 hours and later cultured for 24 hours with TLR2 agonist (PGN, 10 μg/mL) or TLR2/TLR6 agonist (FSL-1, 0.1 μg/mL) and co-treated with test compounds. IL-8 (IL-8) levels were measured by ELISA. Data represent average results from 3 independent experiments. IC50 values were determined by non-linear regression analysis using the four-parameter logistic equation. * p value ≤ 0.05 by Student t test compared to PGN- or FSL1-only treated cells.

Fig. 4. SIG1459 inhibits P. acnes-induced cytokine release

SIG1459: A novel anti-acne isoprenylcysteine compound

José R. Fernández,1 Karl Rouzard,1 Corey Webb,1 Michael Voronkov,2 Jason Healy,1 Masanori Tamura1, Kristen L. Hughey,2 Bryn B. Stock,2 Maxwell Stock,1 Joel S. Gordon,1 Eduardo Pérez1
1Signum Dermalogix, 133 Wall Street, Princeton, NJ; 2Princeton University, Department of Molecular Biology, Princeton, NJ

Abstract

Propionibacterium acnei is a major contributing factor to acne vulgaris, a common disorder that is estimated to affect 9.4% of the global population. P. acne colonize and proliferate within the pilosebaceous follicles causing the induction of local inflammatory response. This is mediated through the interaction of P. acne with epidermal keratinocytes leading to activation of toll-like receptors and later resulting in the production and secretion of pro-inflammatory mediators. Lipoprotein particles (LPC) small molecules represent a novel class of topically applied non-steroidal anti-inflammatories that can be used in consumer products and more potent derivatives for drug development to treat skin diseases. Here we report IPC derived, SIG1459, downregulates these inflammatory signaling pathways and directly decreases P. acne viability. Keratinocytes exposed to P. acne, peptideglycan and FSL-1 released pro-inflammatory cytokines and were inhibited by SIG1459 with IC50 values in the nanomolar range. In an in vitro growth inhibition assay of cultured P. acne, SIG1459 outperformed anti-acne agents, benzoyl peroxide (BPO) and salicylic acid, exhibiting a strong MIC of 5 μM, MBC of 10 μM, and eradicating P. acne biofilm formation (MBC) at 21 μM. Lastly, 1% SIG1459 formulation in an 8-week single blind vehicle controlled study was shown to significantly outperform 3% BPO using an investigator global assessment acne score. SIG1459 (n=35) resulted in a ≥2 grade reduction after 8 weeks, while BPO (n=15) resulted in a 1.5 grade reduction. Moreover, SIG1459 was well tolerated with no adverse reactions (stinging, burning, dryness, stinging), which as expected were reported by subjects in BPO arm of the study. These data demonstrate that phyllo-cysteine derived IPCs, SIG1459 represent a novel chemical class that provides a dual modulating benefit to acne by limiting bacterial proliferation and inhibiting inflammation.

Fig. 5. SIG1459 attenuates TLR2 and TLR2/6-induced IL-8 production

Normal Human Epidermal Keratinocytes (NHEKs) were pre-treated with test compounds for 2 hours and later cultured for 24 hours with P. acne live bacteria (10 μCFU/mL) and co-treated with test compounds. Interleukin-8 (IL-8) levels were measured by ELISA. Data represent average results from 3 independent experiments. IC50 values were determined by non-linear regression analysis using the four-parameter logistic equation.

Fig. 6. SIG1459 (1%) outperforms BPO (3%) in an 8-week acne clinical tolerance study

A multi-site use single-blinded study was conducted in healthy male and female subjects, aged ≥18 years with evaluator assessed mild to moderate acne, to evaluate the potential efficacy of test skincare product by utilizing subjective questionnaires, visual evaluations and digital photography (n=15 per group). Subjects used the assigned product at home for 8 weeks. Subjects returned post baseline at week 2, 4 and 8. At all visit subjects underwent expert clinical grading and test site photography. At Visit 4, subjects also completed a Self-Perception Questionnaire (SPQ). *Values are given as mean ± SEM. ** p value ≤ 0.05, *** p value ≤ 0.01 by Student t test between group differences from baseline scale values from baseline.

Facial Cream (1% SIG1459) was tested in a randomized single-blind vehicle-controlled study (Active, n=35; Vehicle, n=15) to demonstrate the safety and tolerability in subjects with mild to moderate facial acne. The severity of acne signs and symptoms on the faces of ≥ ≥ 20% in each visit subjects were clinically assessed by IGA scale during an 8-week Study period. In addition, UV light mode was utilized to observe porphyrins fluorescence (orange-red dots). Reduction of porphyrins is an indirect measure of P. acne killing. Several subjects using the SIG1459 facial cream demonstrated marked visual improvement in the signs and symptoms of acne as well as reduction in porphyrins during and after weeks 2-8 of application.

Summary/Conclusions

• Lipoprotein particles (LPC) compound SIG1459 dose-dependently inhibits keratinocyte L-8 secretion in response to P. acne, TLR2 and TLR2/6 heterodimeric specific ligands, suggesting the potential for inhibition of the initial neutrophil infiltration on P. acne exposure by modulating keratinocyte TLR2/6 signaling.

• SIG1459 has antimicrobial activity against P. acne: inhibiting its growth, demonstrating bacterial activity and blocking biofilm formation better than current cosmetic anti-acne actives.

• SIG1459 is well tolerated clinically in human subjects with acne prone skin and significantly outperforms Benzoyl Peroxide on the acne IGA clinical scale at week 2 and week 8. Moreover, a reduction in porphyrins on the face, is observed suggesting a reduction in P. acne counts in vivo, supporting in vitro findings.

• IPC compounds represent a novel class of anti-acne molecules derived from our IPC technology platform. SIG1459 and its derivatives provide safe, dual modulating benefits to combat acne