Preclinical Anti-inflammatory Activity and Safety Assessment of SIG990, a Novel Topical Small Molecule for the Treatment of Rosacea

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Abstract

Isoprenylcysteine (IPC) analogs are structural mimics of the lipidated C-termini of the G subunit of all heterotrimeric G-proteins and small G-proteins, which elicit many inflammatory responses such as the release of pro-inflammatory mediators, and the migration and activation of inflammatory cells. We have previously shown that a novel IPC analog SIG990, could inhibit TPA-induced erythema, edema, neutrophil infiltration and induction of several cytokines (TNF-α, IL-6, IL-8) in vivo (SID 2010 poster # 115) and that IPC analogs reduce toll-like receptor (TLR) inflammatory signaling in vitro (SID 2010 poster #761). Patients with rosacea over-express TLR-2, activating the cutaneous innate immune response thus acting as a key element in disease pathogenesis. Furthermore, activation of G-protein coupled receptor, formyl peptide receptor-like 1 (FPRL1) and reactive oxygen species (ROS) release have also been proposed to be involved in the pathogenesis of rosacea. Utilizing human keratinocytes, endothelial cells and differentiated neutrophils we show SIG990 inhibits both TLR2-induced cytokine production and FPRL1-induced ROS and cytokine release. In vivo experiments demonstrate SIG990 when applied topically inhibits LL-37 induced cutaneous inflammation and neutrophil infiltration. Our results demonstrate SIG990 is a potential therapeutic agent targeting a novel multi-effector anti-inflammatory activity towards TLR and GPCR signaling. Moreover, SIG990 has undergone a comprehensive preclinical safety evaluation and was found to have an excellent topical and systemic safety profile. This new chemical entity will be the subject of an Investigational New Drug application targeting rosacea.

Fig 3. SIG990 Inhibits LL-37-GPCR Induced Cytokine Release in Endothelial Cells

Fig 4. SIG990 Inhibits TLR2-Induced Cytokine Release in Keratinocytes

Fig 5. SIG990 inhibits LL-37 Induced Inflammation in a Murine Model of Rosacea

Fig 6. Summary of SIG990 Toxicity Studies

Summary/Conclusions

SIG990 inhibits key sensors and effectors that contribute to the molecular pathogenesis of rosacea:
- inhibits TLR-NHEK induced cytokine production
- inhibits fMLP-FPRL1 induced ROS production in neutrophils
- inhibits LL-37 activation of FPRL1 induced pro-inflammatory cytokine production in vitro
- Topically applied SIG990 inhibits LL-37 induced neutrophil infiltration and erythema in a mouse model, suggesting a potential effect in LL-37 mediated inflammation in rosacea
- SIG990 is a safe and novel^ topical small molecule in development for the treatment of rosacea with a target IND filing date of Q2/Q3 2011

^ Patent pending
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