SELECTED OPPORTUNITIES IN DERMATOLOGY

METHODS AND TOPICAL PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF SKIN MICROVASCULAR DYSFUNCTION (BIO 17360)
Target:
- Soluble epoxide hydrolase (sEH)

Product:
- Tested: t-AUCB and GSK2256294 reformulated for topical administration

Application:
- Skin complications especially in diabetic patients
- Systemic Sclerosis

Rational:
- Microvascular dysfunction remains a major contributor to the development of skin complications
- The inventors assessed the impact of the local inhibition of soluble epoxide hydrolase (sEH), which metabolizes vasodilator and anti-inflammatory epoxyeicosanoids, on the diabetic skin microvascular dysfunction

POC:
- The inventors have therefore developed some formulations of sEH inhibitors (GSK2256294 and t-AUCB) for topical administration
- An aqueous gel containing 400 mg/L t-AUCB dissolved in 50% dimethylsulfoxide (DMSO) allowed a stable and continuous diffusion of t-AUCB from 2 hours after application on skin pig ears to over a period of 24h
- The gel with t-AUCB did not significantly modify the basal skin blood flow but improved the altered hyperemic response of db/db mice 2 hours after application

Patent and publication:
Proof of concept

Influence of the solvent on the percutaneous absorption of t-AUCB or GSK2256294 on pigskin

Influence of the solvent on the percutaneous absorption of t-AUCB using Franz’s cells during 24 hours on pigskin (n=3)

Percutaneous passage of t-AUCB using in Franz’s cells during 24 hours on pigskin with solutions DMSO/water (n=3)

Influence of the solvent on the percutaneous absorption of GSK2256294 using Franz’s cells during 24 hours on pigskin (n=3)

Percutaneous passage of t-AUCB using Franz’s cells during 24 hours on pigskin with hydroalcoholic solutions (n=3)
Proof of concept

Impact of the local inhibition of soluble epoxide hydrolase on diabetic skin microcirculatory dysfunction

Evolution of basal skin blood flow (top) and thermal hyperemia (bottom) measured by laser Doppler imaging after a 2-hour topical application of the t-AUCB-containing gel and the vehicle control gel on the dorsal skin of db/db mice (n=13). *P<0.05 vs. before topical application, †P<0.05 vs. vehicle control gel. A.P.U.: arbitrary perfusion unit.

Top, Skin levels of t-AUCB, quantified by liquid chromatography coupled to tandem mass spectrometry, 2 and 24 hours after the topical application of the t-AUCB-containing gel on the dorsal skin of db/db mice (n=6 per time point). Bottom, Thermal hyperemia measured by laser Doppler imaging before, 2 and 24 hours after the topical application of the t-AUCB-containing gel on the dorsal skin of db/db mice (n=6-26 per time point).
Proof of concept

t-AUCB or GSK2256294 levels in the receptor compartment of Franz cells from 0 to 24 hours after topical application on pig ear skin

Evolution of t-AUCB level, quantified by liquid chromatography coupled to tandem mass spectrometry, in the receptor compartment of Franz cells from 0 to 24 hours after gel application on pig ear skin (n=3 per time point).

Evolution of GSK2256294 level, quantified by liquid chromatography coupled to tandem mass spectrometry, in the receptor compartment of Franz cells from 0 to 24 hours after topical application on pig ear skin (triplicate).
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