A Small Molecule Modulator of the Wnt Pathway (SM04554) as a Potential Topical Treatment for Androgenetic Alopecia (AGA)

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Background

- Androgenetic alopecia (AGA) is a common form of hair loss in both men and women.1
- Current treatments focus on antagonizing the effect of dihydrotestosterone (DHT), prolonging the hair cycle, or hair transplants.2 Treatment of AGA using a safe and effective topical agent that induces hair growth remains an unmet medical need.
- Wnt signaling, which is inhibited in AGA, plays a critical role in growth and maintenance of hair follicles and hair.3
- SM04554, a novel, topical, small molecule Wnt pathway modulator, was evaluated in a series of preclinical animal studies to determine its potential to induce hair follicle proliferation and hair growth.

Hypothesis: Modulation of Wnt signaling using SM04554 would result in increased hair follicle proliferation and hair growth.

Methods

- Depleted (follicles synchronized in anagen) male CD1 mice were treated with vehicle or SM04554 (0.1% w/v) for 10 days to evaluate the effects of SM04554 during anagen. Hair growth was assessed visually and follicle counts were evaluated by histological Hematoxylin and Eosin (H&E) staining.
- Depleted male C57Bl/6 mice were treated with vehicle or SM04554 (0.1% w/v) for 15 days and hair growth was assessed visually to evaluate the effects of SM04554 during anagen in a second mouse strain.
- Effects during telogen (models AGA follicle stage) were measured using C57Bl/6 mice, shaved then treated for 7 weeks, starting on post-natal day (P) 49. Hair growth was assessed visually and follicle counts were evaluated by histological H&E staining.
- Levels of Wnt signaling and hair growth markers were measured by immunohistochemistry (IHC) staining for β-catenin, Lef1, Wnt10b, and Axin2, and proliferation using Ki-67, and qualitatively compared to vehicle treatment.
- Effects of dosing regimens (treatment durations and ON-OFF cycles) were evaluated in beige/nude/xd nu/nu (BNX nude) mice bearing the Foxn1 mutation4 (causing a keratinization defect that leads to hair shedding in the follicle), and in Hanford mini-pigs. Visual hair growth and histological follicle counts were assessed at multiple timepoints in both studies, with classification of follicle types (vellus, indeterminate and terminal) in the mini-pig study.

Results

SM04554 increased hair-follicle counts and induced hair growth in CD1 mice

Figure 1. CD1 mice depleted using Nair and treated with vehicle or SM04554 (0.1% w/v). (a) Images of mice at Baseline and Day 10. (b) IHC images of mouse skin stained for β-catenin and keratin on Day 10. (c) Histological images of mouse skin stained with H&E on Day 10. (d) Quantification of hair follicles/mm² from skin sections in (e). Mean ± SEM, n=6 mice/group, 6 sections/mouse, *p<0.05, t-test compared to vehicle treatment.

SM04554 increased hair-follicle counts and induced hair growth in C57Bl/6 mice with shortened telogen duration and accelerated transition to anagen

Figure 2. (a) Images of C57Bl/6 mice depleted using Nair and treated with vehicle or SM04554 (0.1% w/v). (b) Images of C57Bl/6 mice shaved on P49, and mouse skin stained with H&E from vehicle or SM04554 (0.1% w/v) treated mice. (c) Quantification of hair follicles in skin sections from (b), (d) Quantification of anagen phase hair follicles in skin sections from (b). Mean ± SEM, n=6 mice, 12 sections each, *p<0.05, **p<0.01, ***p<0.001, t-test compared to vehicle treatment.

SM04554 increased Wnt signaling and proliferation specifically in hair follicles

Figure 3. C57Bl/6 mice shaved on P49 and treated with vehicle or SM04554 (0.1% w/v). (a) IHC images of mouse skin stained for (a) Wnt pathway markers β-catenin, Wnt10b, Lef1, and Axin2 and (b) proliferation marker Ki-67 following 4 weeks of treatment. Images are representative of 6 mice/group and 8 sections/mouse.

SM04554 increased hair-follicles, hair-shafts and induced hair growth in BNX nude mice

Figure 4. BNX nude mice were treated with vehicle or SM04554 (0.1% w/v). (a) Schematic of the study. (b) Representative macrophotography of BNX nude mice. (c) Histological images of mouse skin stained with H&E. (d) Quantification of hair follicles and shafts in skin from (c). Mean ± SEM, n=6 mice, 6 sections/mouse, *p<0.05, **p<0.01, ***p<0.001, t-test compared to vehicle.

SM04554 increased hair-follicle counts and induced hair growth in Hanford mini-pigs

Figure 5. (a) Schematic of the study. (b) Quantification of follicles and follicle types: vellus (<30 μm), indeterminate (30 μm - 60 μm), terminal (>60 μm) in skin biopsies from mini-pigs treated with vehicle or different dosing regimens of SM04554 (0.15%). Mean ± SEM, n=6, *p<0.05, **p<0.01, repeated measures Poisson regression test adjusted for baseline.

Discussion and Conclusions

- In depleted CD1 and C57Bl/6 mice, SM04554 increased follicle counts and hair growth compared to vehicle, with increased expression of Wnt pathway markers and proliferation marker Ki-67 specifically in the hair follicles.
- In C57Bl/6 mice shaved and treated from P49, SM04554 increased follicle counts during telogen, shortened telogen duration, accelerated the onset of anagen and induced hair growth as compared to vehicle.
- In BNX nude mice, SM04554 treatment increased follicle counts and induced hair growth, overcoming the Foxn1 mutation-driven keratinization defect. Continuous dosing was superior to ‘ON-OFF’ regimens.
- In mini-pigs, continuous SM04554 treatment for 42 days was superior to shorter or ‘OFF’ dosing regimens, and increased vellus and indeterminate follicle counts compared to vehicle, with effects sustained for 70 days post-treatment.
- SM04554 has potential as a topical therapy for AGA and is being evaluated in clinical trials.

References