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

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Vishal Deshmukh, PhD[1], Melinda Pedraza, BS[1], Charlene Barroga, PhD[1], Luis Dellamary, BS[1], Sunil KC, PhD[1], John Seykora, MD, PhD[2], and Yusuf Yazici, MD[1]

[1]*Samumed, LLC, San Diego, CA,* [2]*University of Pennsylvania, Philadelphia, PA*

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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

- Depilated (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.
- Depilated 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/xid nu/nu (BNX nude) mice bearing the Foxn1 mutation[4] (causing a keratinization defect that leads to hair shredding 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

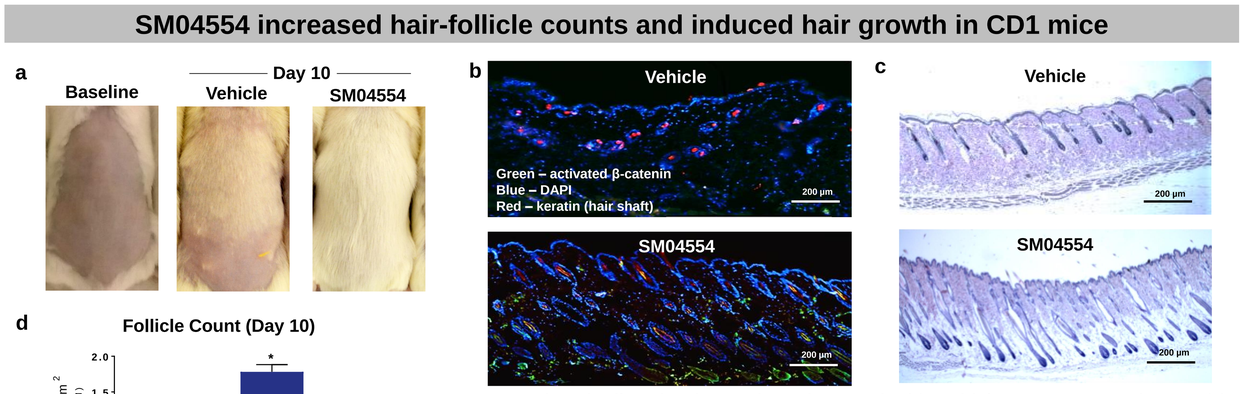

Figure 1. CD1 mice depilated using Nair and treated with vehicle or SM04554 (0.1%w/v). (**a**) Images of mice at Baseline and Day 10. (**b**) IHC images of mouse skin stained for β-catenin and keratin on Day 10. (**c**) Histological images of mouse skin stained with H&E on Day 10. (**d**) Quantification of hair follicles/mm^2 from skin sections in (**c**). 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

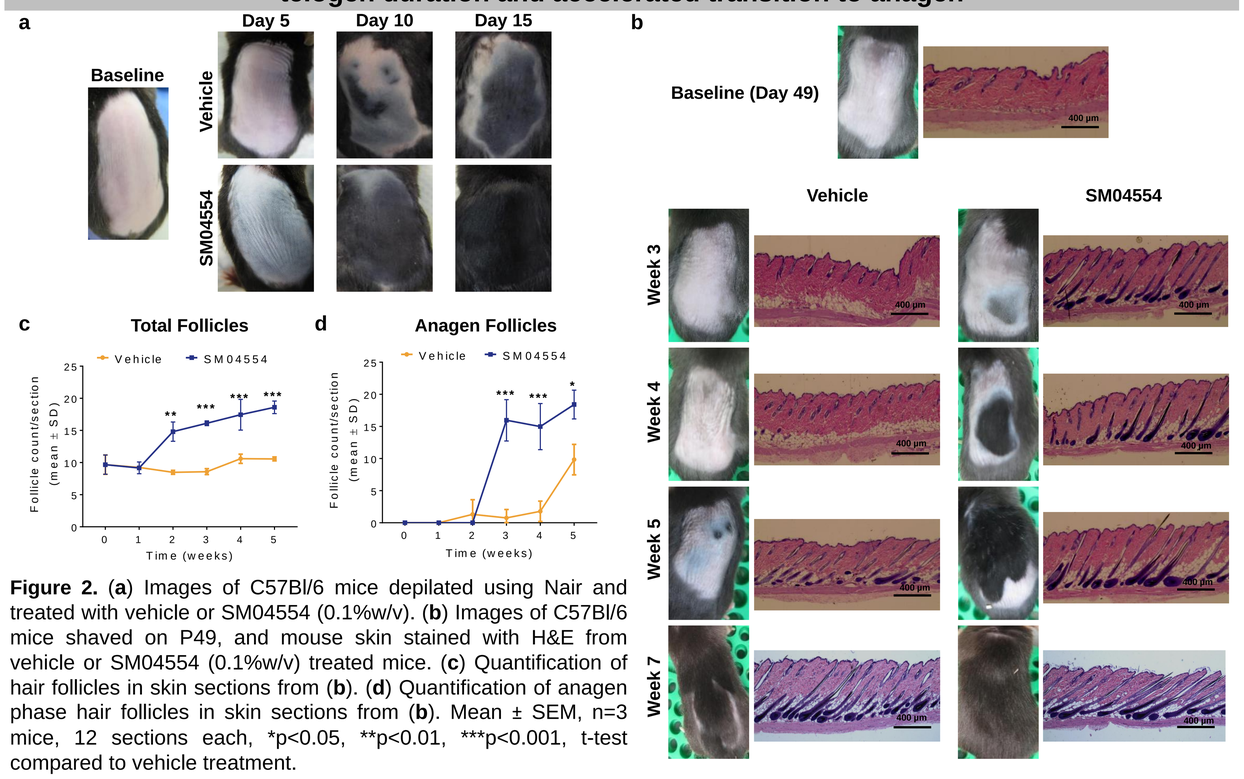

Figure 2. (**a**) Images of C57Bl/6 mice depilated using Nair and treated with vehicle or SM04554 (0.1%w/v). (**b**) Images of C57Bl/6 mice shaved on P49, and mouse skin stained with H&E from vehicle or SM04554 (0.1%w/v) treated mice. (**c**) Quantification of hair follicles in skin sections from (**b**). (**d**) Quantification of anagen phase hair follicles in skin sections from (**b**). Mean ± SEM, n=3 mice, 12 sections each, *p<0.05, **p<0.01, ***p<0.001, t-test compared to vehicle treatment.

Results

SM04554 increased Wnt signaling and proliferation specifically in hair follicles

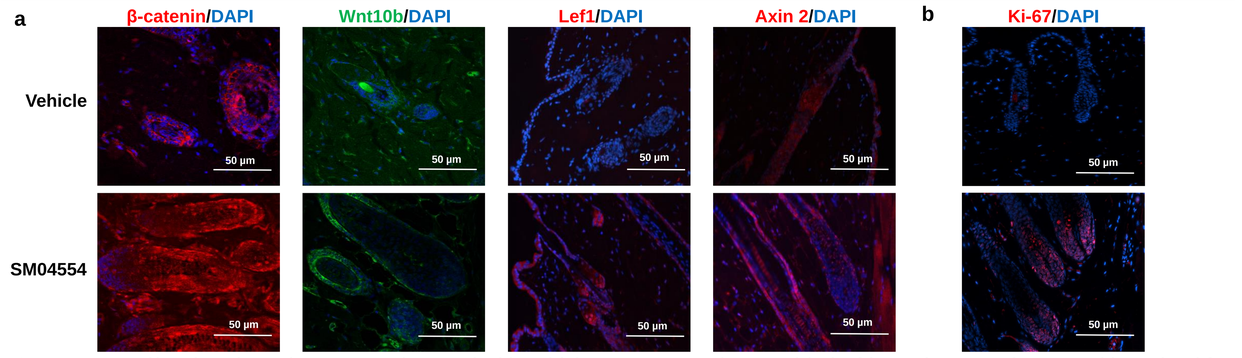

Figure 3. C57Bl/6 mice shaved on P49 and treated with vehicle or SM04554 (0.1% w/v). (**a, b**) IHC images of mouse skin stained for (**a**) Wnt pathway markers β-catenin, Wnt10b, Lef1, and Axin 2 and (**b**) proliferation marker Ki-67 following 4 weeks of treatment. Images are representative of 6 mice/group and 8 sections/mouse.

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

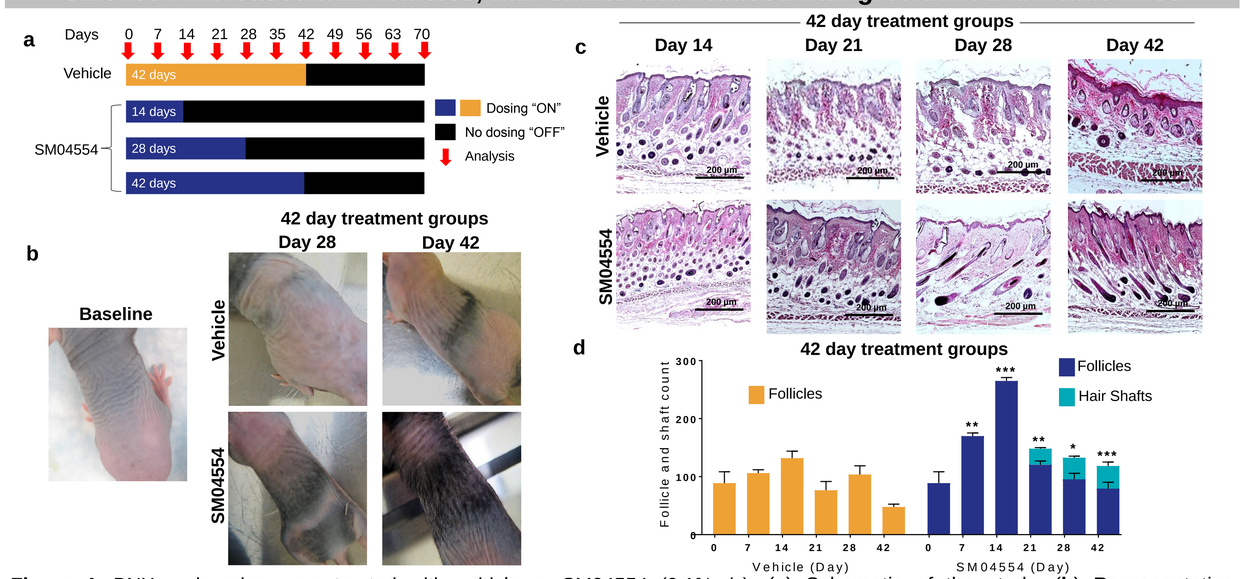

Figure 4. BNX nude mice were treated with vehicle or SM04554 (0.1%w/v). (**a**) Schematic of the study. (**b**) Representative macrophotography of BNX nude mice. (**c**) Histological images of mouse skin stained with H&E. (**d**) Quantification of hair follicles and shafts in skin from (**c**). Mean ± 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

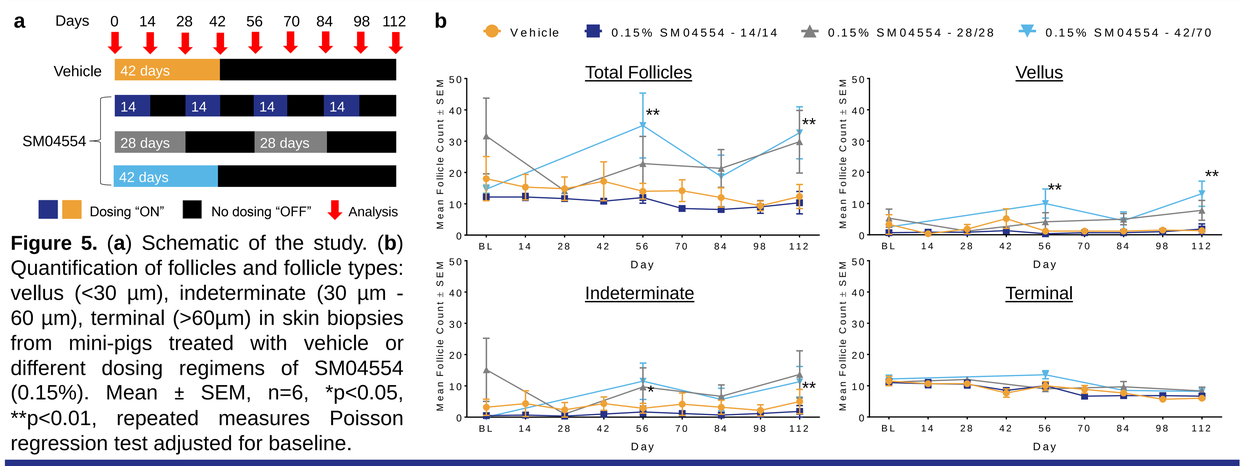

Figure 5. (**a**) Schematic of the study. (**b**) Quantification of follicles and follicle types: vellus (<30 µm), indeterminate (30 µm - 60 µm), terminal (>60µm) in skin biopsies from mini-pigs treated with vehicle or different dosing regimens of SM04554 (0.15%). Mean ± SEM, n=6, *p<0.05, **p<0.01,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

Discussion and Conclusions

- In depilated 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 'ON-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

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9381 Judicial Drive ● San Diego, CA 92121 ● Email: info@samumed.com