Hedgehog stimulation and hair growth: can we regrow lost hair with oxysterols?

Abstract:

Although seldom a serious health threat, hair loss, also known as baldness or alopecia, can affect both men and women, often leaving a negative impact on the affected person’s psychological well-being, self-confidence and outlook on life. For example, male pattern baldness, the most common form of hair loss, can be the cause of psychological insecurity, especially for younger men who are just starting out in life. Similarly, hair loss induced by chemotherapy adds unwelcome visible scars to the suffering of cancer patients. Currently available drug treatments for the various forms of hair loss have only moderate success and are often plagued by unpleasant side effects. Finasteride (Propecia), Dutasteride (Avodart) and Minoxidil (Rogaine) are three medications used to treat male pattern baldness; however, they typically work far better to prevent further hair loss than to regrow lost hair. Most hair loss is actually caused by a lack of hair regrowth rather than the increased shedding of hair. Hair growth follows distinct growth cycles and is driven by hair stem cells associated with each hair follicle. In male pattern baldness, hormonal and other factors lead to a shortened growth (anagen) phase of the hair follicle, resulting in deactivated hair stem cells and diminished hair growth. Importantly, these hair stem cells just lie dormant but do not actually die off during male pattern baldness and several other forms of hair loss. To regrow hair, it may be possible to reactivate dormant hair stem cells by stimulating their cellular signaling. The Hedgehog signaling pathway provides a cellular signal that is crucial for hair growth by triggering the hair follicle to reenter the active growth phase. At MAX BioPharma, a startup company based in Santa Monica, California, we have developed drug candidates that can stimulate Hedgehog signaling through a safe mechanism. While we are working on applications of Hedgehog signaling in bone growth and osteoporosis, we believe these drug candidates may also work in alleviating different types of hair loss. Here, we propose to test our most promising drug candidate, Oxy133 (Figure 1), in a simple model of hair growth using shaved mice. We plan to apply Oxy133, dissolved in vitamin E skin oil, to a patch of shaved skin on the mice’s back to document hair regrowth and compare it to untreated mice. If we can document increased hair growth in this proof of principle experiment, it would help validate our approach and lead to other hair growth studies. Once the approach is validated, we plan to seek out partnerships with the pharmaceutical and cosmetic industries to further develop and make this new treatment available to hair loss patients.
The Founder of MAX BioPharma, Dr. Farhad Parhami, worked at UCLA as a biomedical researcher and Professor of Medicine for over 22 years. While at UCLA, Farhad first studied the effects of certain sterols, including cholesterol and oxidation products of cholesterol, so called oxysterols (Figure 1), on the cellular signaling of adult stem cells. Remnants from our prenatal period, adult stem cells can be found in all human tissues and are crucial elements for our body’s normal maintenance as well as repair and recovery from injury or disease. For example, skin injuries, such as cuts or bruises, are repaired with help from skin progenitor cells, so called fibroblasts, which become activated during wound healing. Similarly, broken bones heal by drawing in bone progenitor cells that reside in the bone marrow and turn into mature bone cells, so called osteoblasts, near the site of bone injury. Farhad’s research demonstrated that adult stem cells can be activated by oxysterols without affecting other cells that are not stem cells. That is because oxysterols work by stimulating stem cell specific signals, such as Hedgehog signaling, in a safe manner that does not lead to overstimulation, which can be potentially dangerous. This so called “allosteric” activation amplifies only preexisting Hedgehog signals found in the adult stems cells. About 16 years ago, researchers at Stanford University discovered molecules that can directly activate Hedgehog signaling through a different mechanism in nearly all cells, not just stem cells. Researchers at Curis, a biotech company based in Cambridge, MA, later showed that these molecules do work quite well to stimulate hair growth in shaved mice and other experiments. Unfortunately, their safety profile was unacceptable for use in humans. Oxysterols may offer a second chance to alleviate hair loss by stimulating hair stem cells: due to the allosteric mechanism of the oxysterols, prospects for drug safety and effectiveness are much improved. Preliminary testing of some naturally occurring oxysterols, shown in Figure 2, does suggest that

Figure 1: The chemical structures of Cholesterol, oxysterols 20(S)-Hydroxycholesterol, 22(S)-Hydroxycholesterol and Oxy133.

Context:
they mildly stimulate hair growth in shaved mice. Drug candidate Oxy133 is derived from the naturally occurring oxysterols and has been thoroughly tested for optimal activity and preclinical safety. The Hedgehog activity of Oxy133 exceeds that of the naturally occurring oxysterol by several hundred fold and should stimulate hair growth more strongly. In addition, we believe that Oxy133 is suited for dermatological applications due its high solubility in skin oil.

Naturally occurring oxysterols (1:1 mixture of 20(S)-hydroxycholesterol and 22(S)-hydroxycholesterol) were formulated in vitamin E skin oil and applied topically once daily to a 2cm x 2cm shaved area on the back of C57BL/6 mice (2 per group). Oxysterol was applied at 50 or 100 μg. All photos were taken after 18 days.

White circles represent the areas that were shaved and photographed 18 days after shaving.

F. Parhami et al., unpublished observations.

Figure 2: Preliminary testing of naturally occurring oxysterols, dissolved in vitamin E skin oil and applied topically to the skin of shaved mice, does suggest a mild stimulation of hair regrowth relative to the untreated control.

Goals of the project:

The long term goal of this project is to offer a new, safe and effective treatment option to people suffering from hair loss. The immediate goal of the project is to test for the ability of Oxy133, a sterol based activator of Hedgehog signaling, to enhance hair growth in shaved mice through topical application of the compound, a simple but effective model of hair regrowth. If successful, this pilot study will provide data that can be presented to potential industry partners and government agencies who will help us develop the technology for commercialization.
Timeline description:

The study will take about 2 months from start to finish. Oxy133 is already available and the mice will be purchased from commercial vendors. After shaving the mice's backs, we will apply Oxy133, dissolved in vitamin E skin oil, topically daily at two doses for 3 weeks to observe and document hair growth patterns compared to mice treated with vitamin E skin oil alone (without Oxy133). At the end of the study, if hair regrowth is enhanced with Oxy133 treatment as we anticipate, we will carry out histological examination of the skin and hair follicles.

Milestone deliverable items and dates for expected completion:

Daily assessment of hair growth in mice receiving topical application of Oxy133 and documenting the changes photographically.

References:

