Artificial Intelligence Investigative Small Molecule Enhanced Hair Growth In Ex Vivo Human Hair Follicle

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Introduction

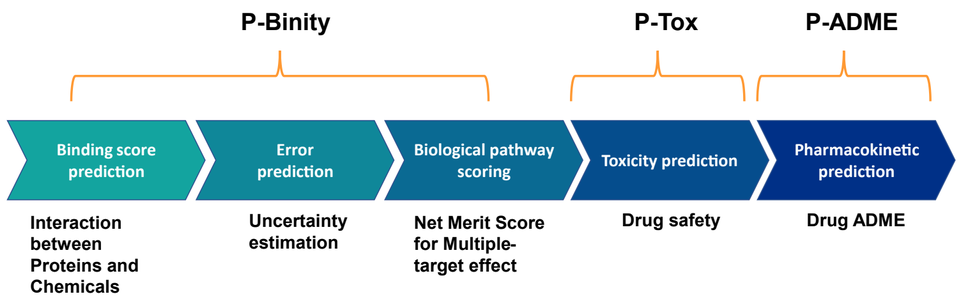
Alopecia is hair loss disorder, caused by aging, hormonal and immunological imbalance. Currently the drugs available for alopecia are limited and often have varying degrees of effectiveness and side effects. This drives the medical community to crave new cure.

The aim of this project is to identify novel drug candidates that can treat hair loss more efficiently and safely than the traditional medications, especially those targeting multiple proteins via our self-developed AI-driven drug discovery system, ***PetaPoly***^{TM}. This system is composed of Graph Neural Network (GNN) and Transformer models, featured by protein-structure-free prediction of ligand-protein interaction binding score.

We identified a promising compound, namely LCH34, that was scored highly in various *in silico* drug property assessments and showed great potency to enhance hair growth in *ex vivo* human hair follicle cells and mouse model. The enhancement might be attributed to regulation of Wnt pathway.

Methods

Chemicals library (10 million small molecules) were evaluated *in silico* using machine learning models to select the top scoring hits in potency and selectivity to multiple on-target proteins involving hair growth associated pathways such as Wnt, androgen, TGF-beta and Jak pathways, and then filtered out the molecules scoring below threshold in toxicity and ADME predictions (Figure 1).

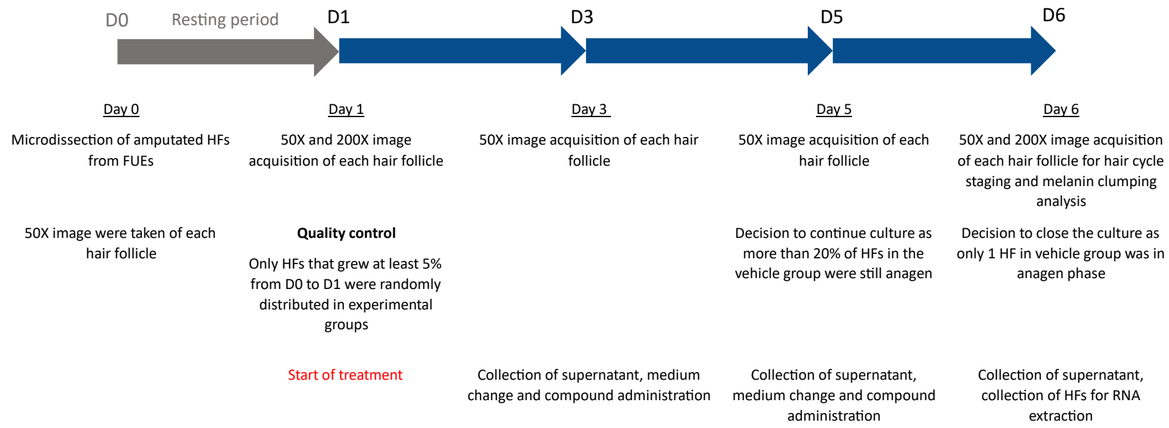


Flowchart of prediction of hits using ***PetaPoly***^{TM} system

The high-ranking candidates were then assessed by protein expression of alkaline phosphatase (ALP) and versican in immortalized human hair follicle dermal papilla cells (HFDPC). The optimal small molecule, **LCH34** was subjected to further biological validation via Western blotting, RT-PCR, *ex vivo* hair follicle growth and *in vivo* anagen prolongation mouse model.

Ex vivo human hair follicle growth assay

Experimental Design



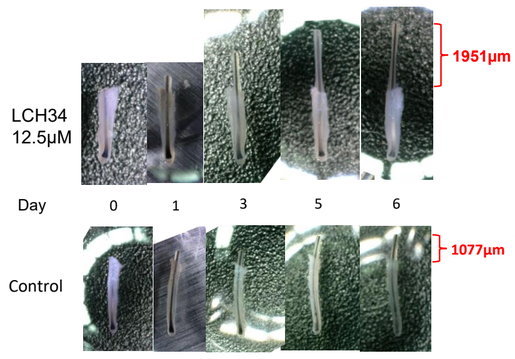
Experimental groups (n = 4HFs/group)

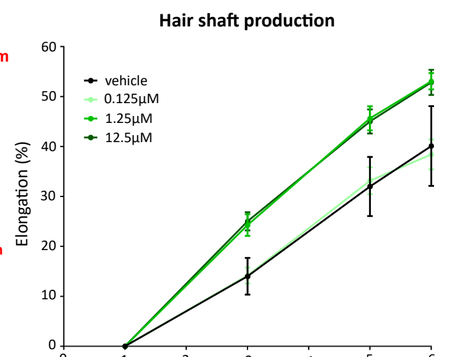
Group	Treatment	Concentration
#1	Vehicle(+ DMSO) – no treatment	-
#2	LCH34	0.125μM
#3	LCH34	1.25μM
#4	LCH34	12.5μM
#5	Max release – Triton X-100	1%

Donor information

Donor	Donor information	Number of HFs at Day 0	Number of HFs at Day 1
Donor 1 HF-MLB-22-139	Caucasian 38 years old male donor, follicular units (occipital)	28 anagen VI HFs	20 anagen VI HFs

LCH34 increased hair shaft production at high concentration

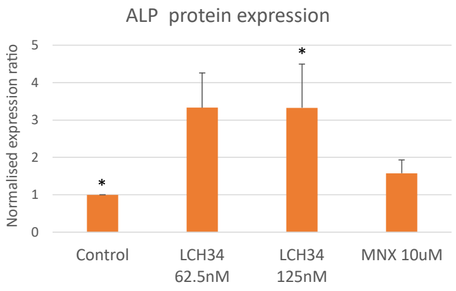


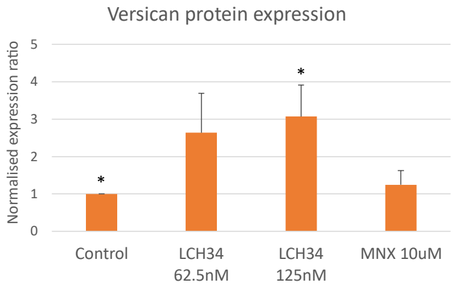


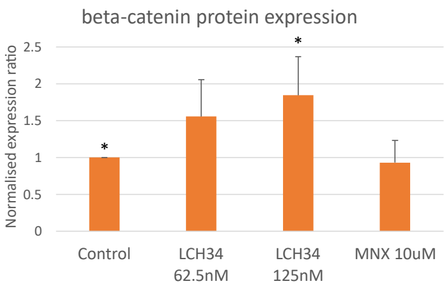
LCH34 on human hair follicle growth (Male, 38yr age)

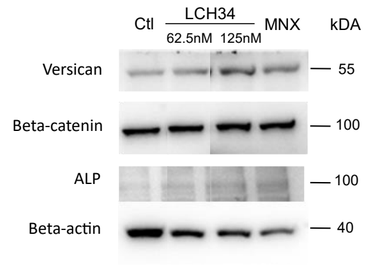
Western blotting and RT-PCR

LCH34 increased ALP, Versican and β-catenin protein expression of HFDPC in dose dependent manner

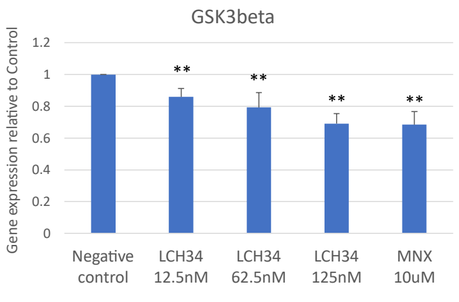


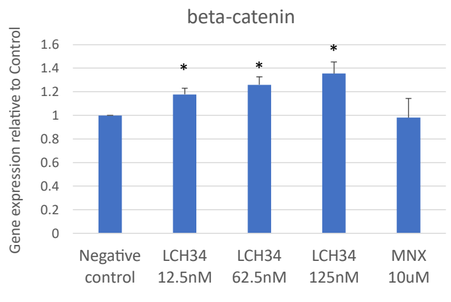




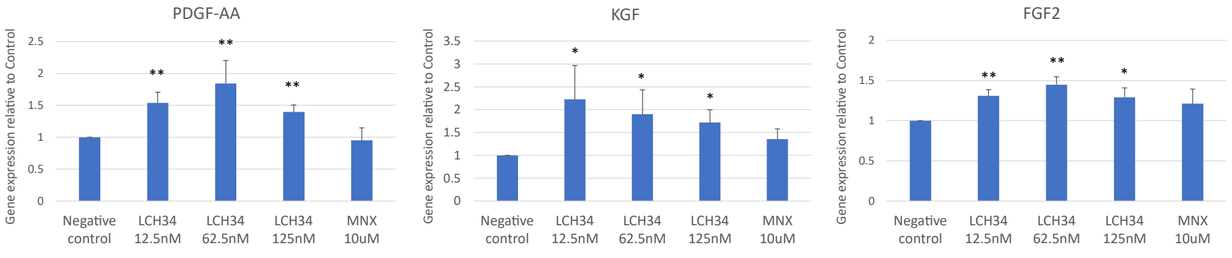


LCH34 activated Wnt signal pathway via downregulation of GSK3beta and upregulation of β-catenin gene expression



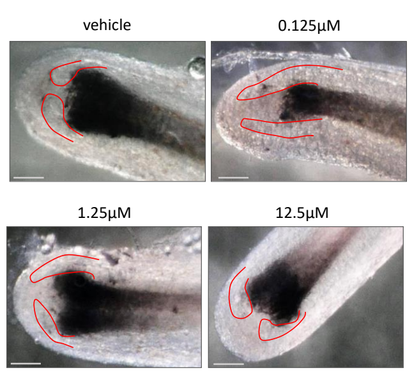


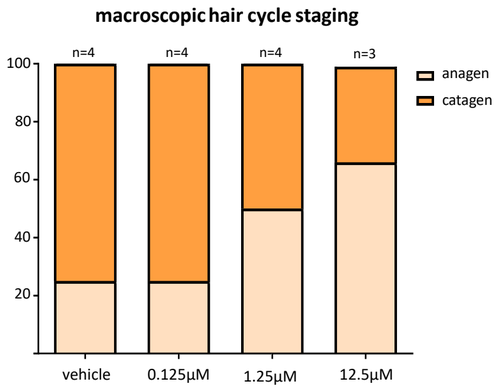
LCH34 enhanced gene expression of three hair growth promoting growth factors: PDGF-AA, KGF, and FGF2



MNX=minoxidil n=4 Mean ± SEM *p<0.05 **p<0.01

LCH34 supported anagen prolongation dose-dependently

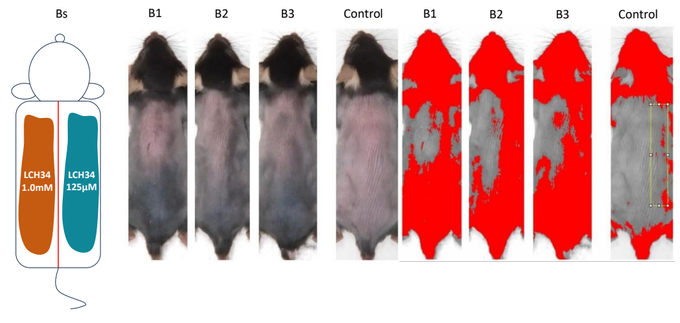


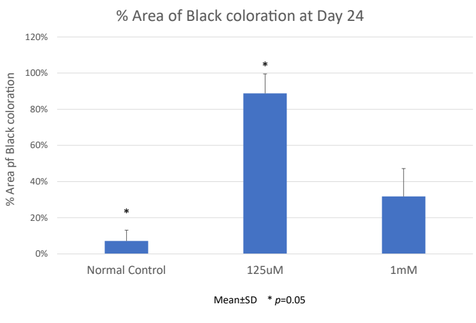


n=3-4 HFs/group from one healthy donor,Mean±SEM, GraphPad Prism 9; D'Agostino Et Pearson omnibus normality test, n too small to determine Gaussian distribution, therefore a non-parametric analysis was applied, Kruskal-Wallis test n.s, Dunn's multiple comparison test - fixed vehicle n.s., Mann Whitney test versus vehicle n.s.; scale bar 100 μm.

Late-breaking result: LCH34 prolonged anagen phase of hair growth in mouse model

LCH34 was applied topically on daily basis for 24 days on mouse skin (8 weeks old) after hair removal. The project was conducted by Prof. Chih-Chiang CHEN's team, National Yang Ming Chiao Tung University





Summary

- Utilizing our AI-driven drug discovery system, ***PetaPoly***^{TM} , we have successfully identified a top-scoring molecule, LCH34, with potency to target multiple proteins for treating alopecia.
- LCH34 enhanced hair shaft elongation and prolonged anagen phase in human ex vivo hair growth assay and potentially extended hair growth in mouse model.
- LCH34 activated Wnt pathway via downregulation of GSK3beta and upregulation of beta-catenin. It enhanced gene expression of hair growth promoting growth factor PDGF-AA, KGF and FGF2.
- Small molecule LCH34 will be developed as a hair growth promoting drug for targeting alopecia, especially with shortened anagen phase.

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