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CAPIXYL™

HAIR FERTILIZER

in-cosmetics ASIA Innovation Zone Best Ingredient Award 2011 BRONZE CAPIXYL™

CHINA COMPLIANT · PRESERVATIVE FREE · ECO FRIENDLY

Hair Loss Generalities

- Humans have **+/- 100 000 hairs** on scalp.

  -A daily loss of 40 to 100 hairs is normal (up to 175 during season changes - automn and spring)

  -Alopecia = daily loss >100 hairs during a long period (app. 2 months).

- **Main Cause of hair loss**:

  -Genetics
  -Hormonal change or imbalance (childbirth, menopause);
  -Improper nutrition (deficiency in certain vitamins and minerals);
  -Stress;
  -Diseases like diabetes or lupus;
  -Medications (drugs or chemotherapy);
  -Seasonal changes;
  -Aging & Photo-aging.

- Hair loss can be **permanent** or **temporary.**

- Affects **both men and women** although men experience a much higher degree of hair loss (notably around the temples and the vertex) than women, but following menopause it may affect 75% of women older than 65 years old.

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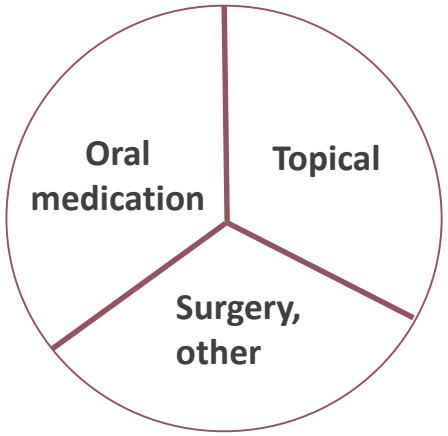
Market Info

Global anti-hair loss market 2015 = 7.2 billions USD
expected to exceed USD 10 billions by 2024 => +4%/year



Global cosmetic hair market 2015 = 81 billions USD

Global cosmetic anti-hair market 2015 = 2 billions USD

Common ingredients:
-Caffeine
-Niacin
-Vitamin B6
-Keratin
-etc

Well-known ingredients

- **Vasodilation**
Minoxidil (Regain®/Rogain®) an OTC vasodilator medication known for its ability to slow or stop hair loss and promote hair regrowth

5% Minoxidil for men
2% Minoxidil for women

- **Hormonal (DHT transformation)**
Finasteride (Propecia®) is a drug that acts by inhibiting the enzyme that converts testosterone to dihydrotestosterone (DHT) in androgenic alopecia

- **Collagen rigidification & hair anchoring**
Aminexil® is a patented molecule by L'Oréal. Fights against the stiffening of hair roots, and thus preserves the tissue surrounding the hair bulb.

MARKET OPPORTUNITY?

- Minoxidil was first used in medicine for patients suffering from cardio-vascular diseases. The activity on alopecia was later observed as an adverse effect.

- Minoxidil is the n°1 reference in the topical market but:
  -Minoxidil works on 1 person out of 2 & on younger people (18 to 40)
  -Side effects: burning, irritation, redness, chest pain

- Market is looking for alternatives to replace Minoxidil or combine to it in order to:
  - Decrease its concentration and thus side effects
  - Act on complementary targets to improve efficacy

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Hair Science

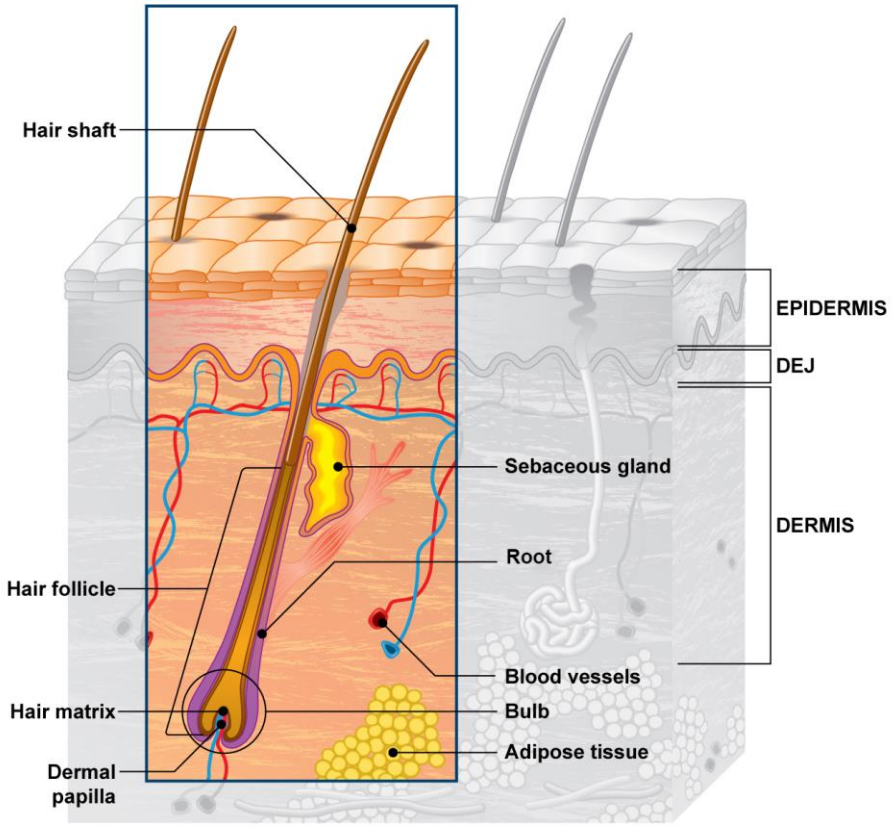
Hair structure consists of:

- **Hair shaft**: dead part above skin consisted of an accumulation of keratin (hard protein) produced by the keratinocytes of hair follicle.

- **Hair follicle**: small cavity made up of keratinocytes that extend in dermis. From this organ, an alive root develops as a progressive accumulation of keratinocytes continuously dividing in the hair matrix.

  At the base of the follicle is the dermal papilla, a vasculary part which brings nutriments and oxygen to grow the attached hair in formation

The hair follicle's healthy condition and size are major criteria for an optimized hair growth.



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Hair Science

Each follicle has the capacity to self-regenerate allowing to grow many hairs over a lifetime (±20 to 30 hair growth cycles).

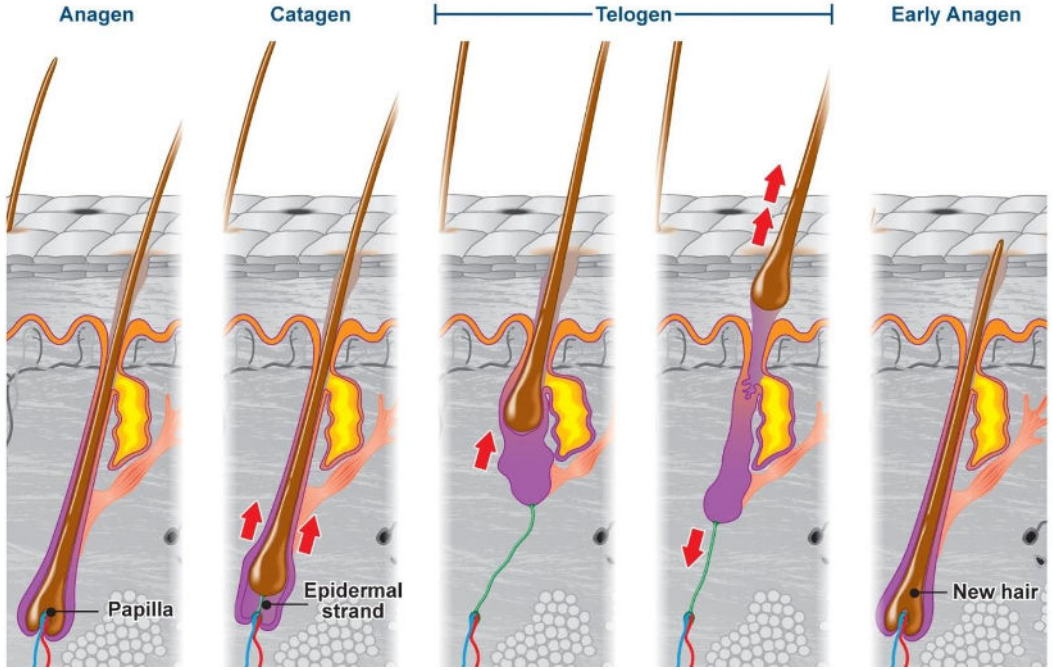
The hair follicle / hair growth cycle has 3 distinct phases:

- **Anagen**: (70-85% hair is in **growth phase**). Hair roots grow for 2-6 years due to a progressive and continuous proliferation of keratinocytes in the hair matrix . **Hair follicle is complete (mature) and its activity is optimal.**

- **Catagen**: (1-2% hair is in **regression phase**). The root detaches from the dermal papilla, **the hair follicle shrinks** and migrates toward the scalp and remains in this phase for 2-3 weeks.

- **Telogen**: (15-30% hair is in **resting phase**). Hairs stay attached to the scalp for about 3 months and then fall out. **The degenerated hair follicle starts to regenerate** and migrates downward the bottom of epidermis.

Next hair growth cycle starts when dermal papilla & regenerated follicle join together again & new hair begins to form.



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HAIR FOLLICLE : THE KEY PLAYER OF THE HAIR GROWTH CYCLE

2 key elements control the hair follicle cycle:

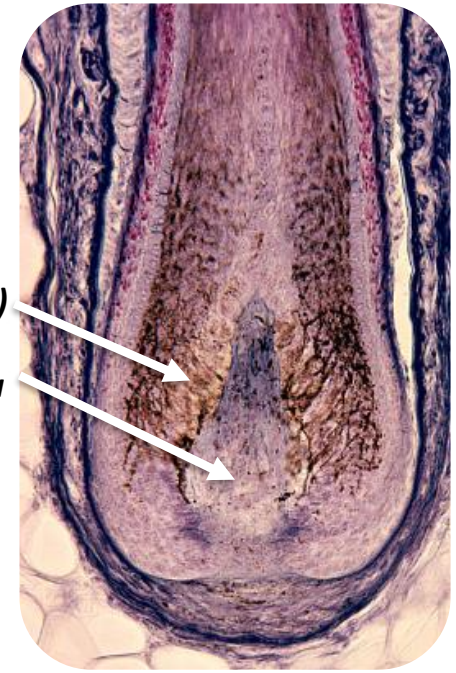
DERMAL PAPILLA

-sends signals to rythm cycle phases;

-its size have a great influence on the quality and size of hair follicle, and then on the quality of the hair in formation;

-composed of fibroblasts and collagen matrix. Produces anchoring proteins to attach hair.

=> Need to maintain matrix integrity for an optimal size and activity



HAIR FOLLICLE STEM CELLS (HFSC)

- are responsible to generate, maintain and renew the hair follicle;

- provide keratinocytes for hair follicle and hair

=> Need to activate HFSC

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FOCUS ON HAIR FOLLICLE STEM CELLS (HFSC)

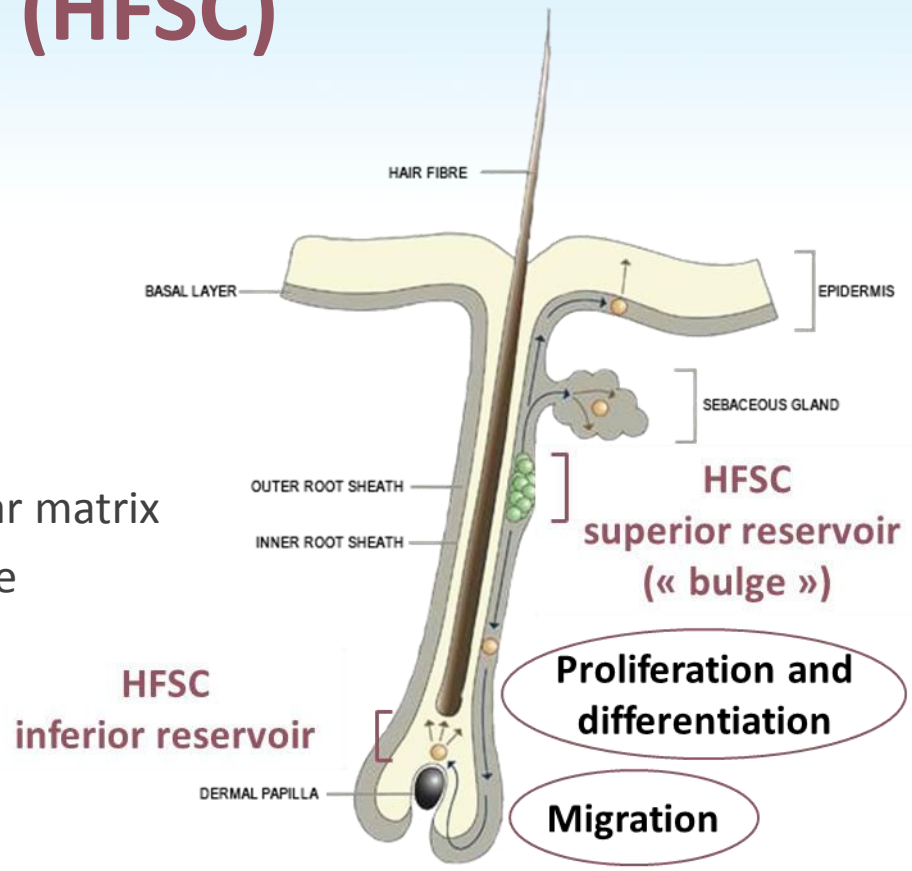
- HFSC reside in 2 specific zones:
  -under sebaceous glands (superior reservoir -“bulge”)
  -above the bulb (inferior reservoir)

- HFSC are in a dormant state during telogen phase

=> Reactivated to regenerate hair follicle during anagen phase

=> They proliferate (cell division), differentiate into follicular matrix keratinocytes and migrates to the bottom of the hair follicle

=> Keratinocytes continue to divide and accumulate to form the hair



The activation of HFSC by Capixyl™:

- On existing hair:

-prolongs growth phase (anagen) of existing hair by maintaining hair follicle => prevention of hair loss

-improves hair formation by providing higher number of keratinocytes => longer/stronger hair

- On fallen hair:

-Improves hair regrowth du to a better hair follicle regeneration

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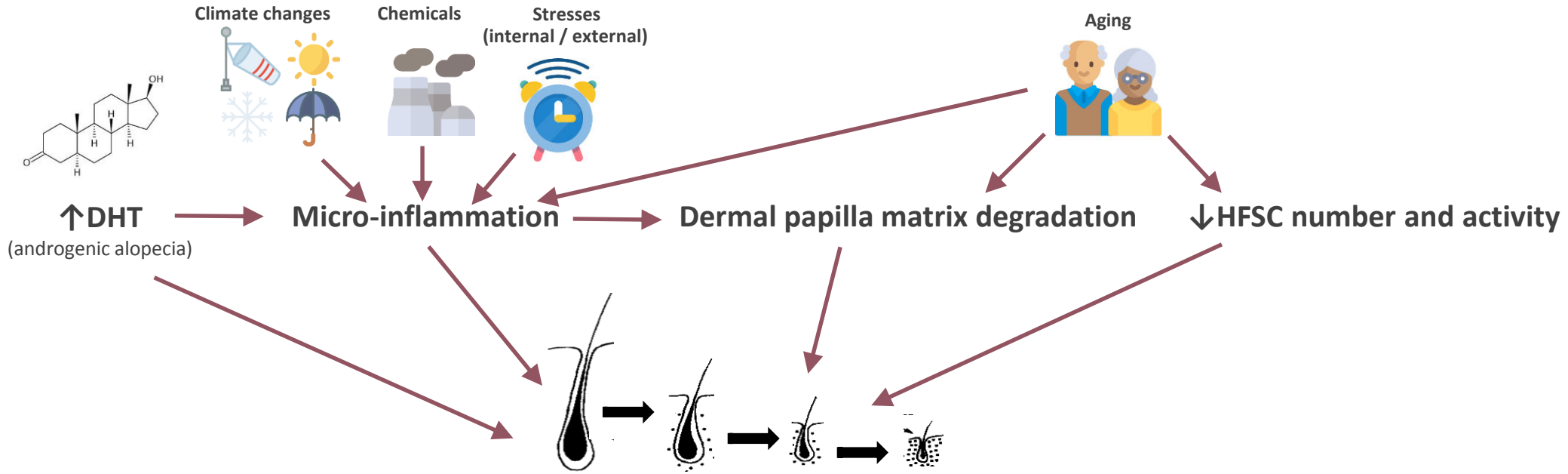
How Is the Hair Cycle Is Disrupted?

Both **hair thinning and hair loss** are due to a progressive **miniaturization of hair follicle,** associated with a **shorter anagen phase**. Smaller, hair follicle produces thinner hair until it can't produce hair anymore (baldness is the last step).

Several factors are responsible for hair follicle miniaturization (men and women):



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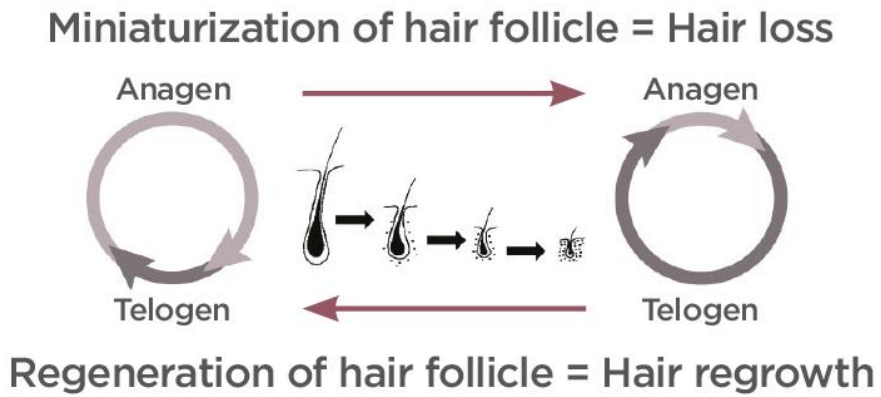
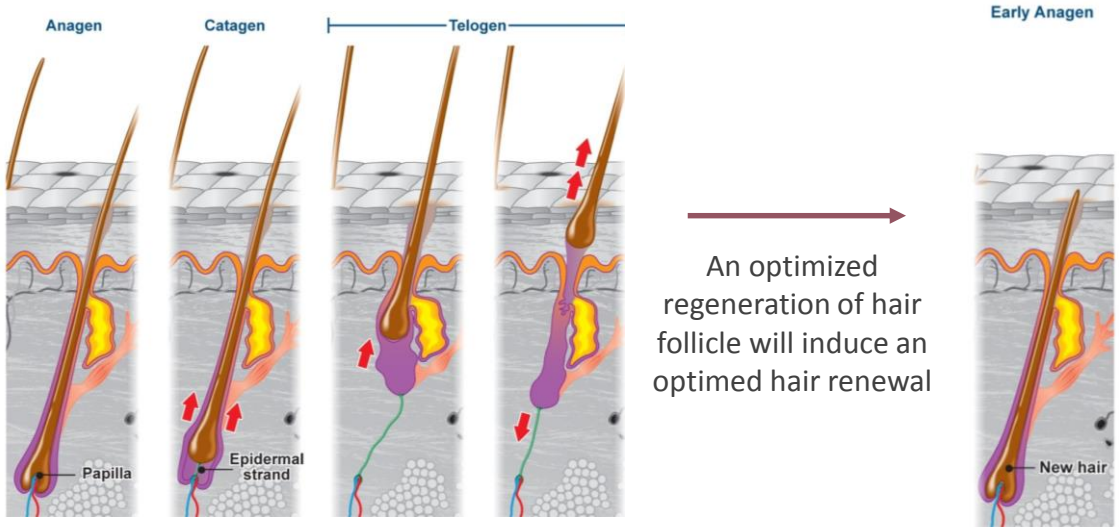
How to grow stronger Hair?

Optimized hair follicle size and health are the key to decrease/prevent hair thinning and loss and to stimulate hair growth.





Maintaining of hair follicle inegrity

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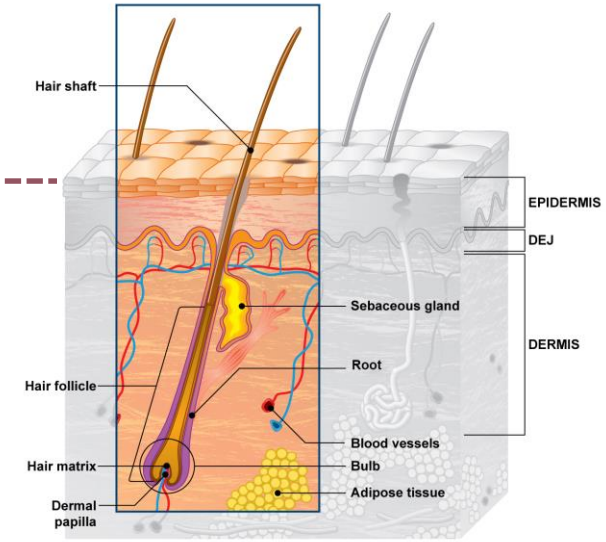
How to grow stronger Hair?

Healthy and dense grass

- Good soil quality and quantity
- Good nutrition
- Good anchorage

Healthy and dense hair



- Good hair follicle quality and size
- Good nutrition from dermal papilla
- Good anchorage

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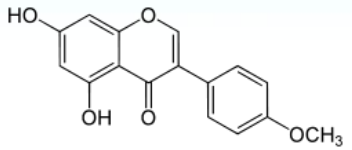
CAPIXYL™: UNIQUE ANTI-HAIR LOSS COMBINATION

Biochanin A extracted from Red Clover *(Trifolium pretense)*



Biochanin A is a powerful flavonoid.

Biochanin A is an **effective inhibitor of 5-α-reductase (type I & II)** activity, thus modulating the conversion of testosterone to **DHT** in androgenic alopecia.

+

Acetyl tetrapeptide-3

4 amino acids biomimetic peptide derived from a signal peptide which stimulates tissue remodeling.

The peptide has a direct effect on hair follicle. The remodeling signal will increase the size of hair follicle for **better hair anchoring** and vitality.

=

Capixyl™

A clinically proven anti-hair loss active!!!

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Ex vivo & *In vitro* TESTS

- Effect on hair follicle stem cells
- Effect on hair cell activity
- DHT Modulation (5-α reductase inhibition)
- ECM integrity and anchoring proteins
- Anti-Inflammation effect

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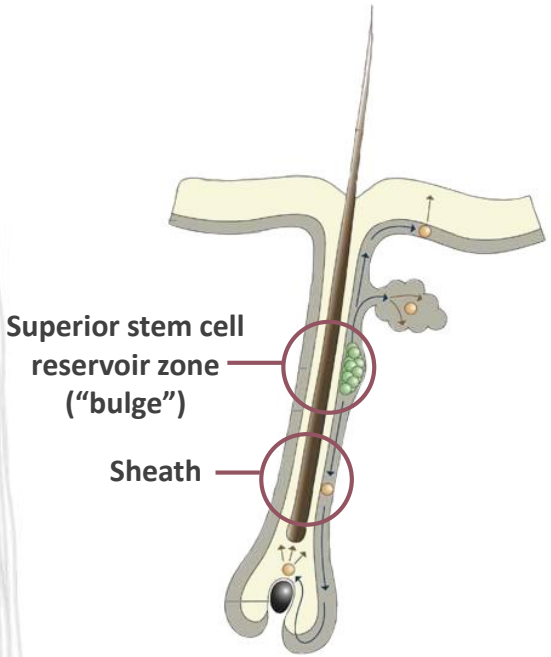
STIMULATION OF HFSC ACTIVITY

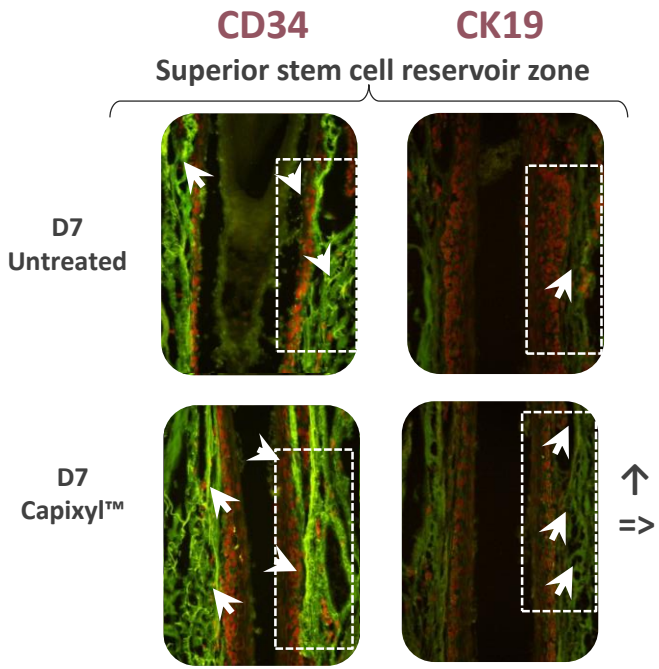
NEW RESULTS

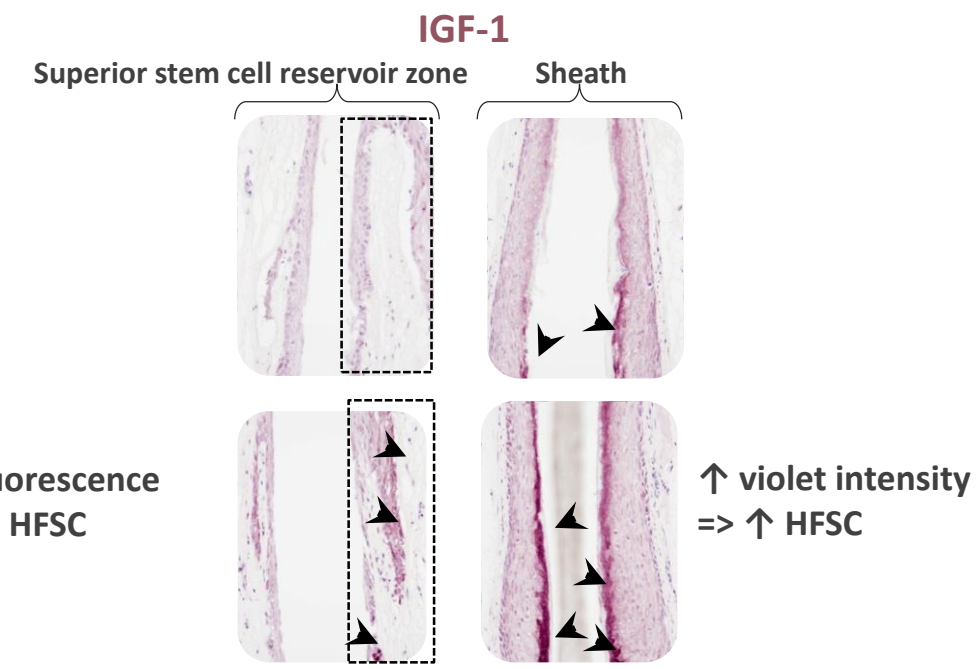
Ex vivo test protocol

- Hair follicles in anagen phase (from a 49 years old woman) were isolated and treated or not with 1% Capixyl™ during 7 days (Philpott method)
- Staining and cross sections to observe:

CD34, CK19 = specific markers of stem cells (fluorescence) & **IGF-1** = growth factor involved in follicle regeneration (can induce HFSC maturation/differentiation)







Capixyl™ improves HFSC proliferation and migration for a better hair follicle regeneration

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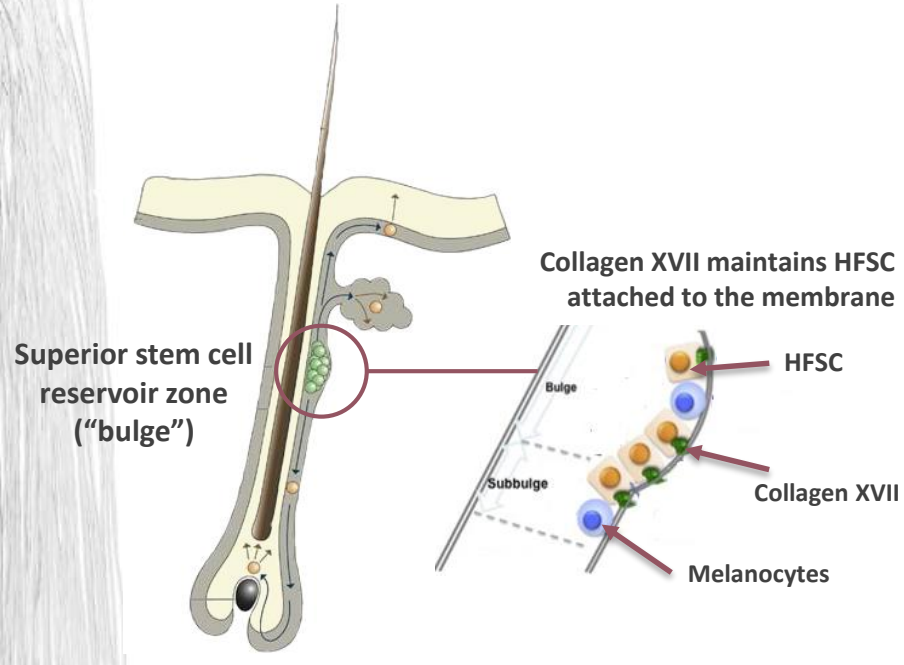
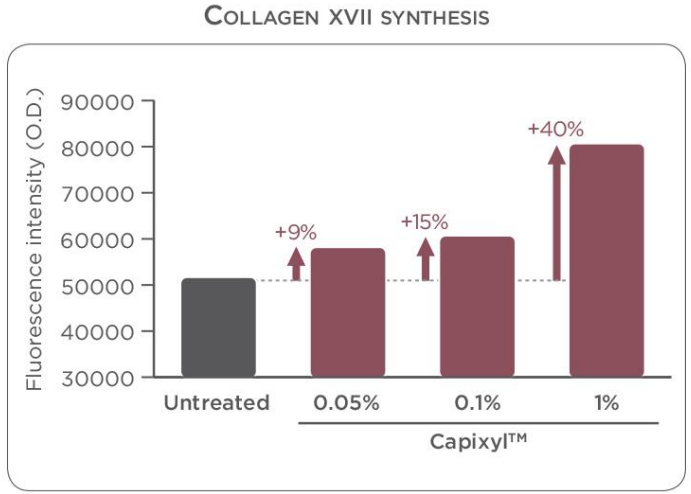
STIMULATION OF COLLAGEN XVII SYNTHESIS

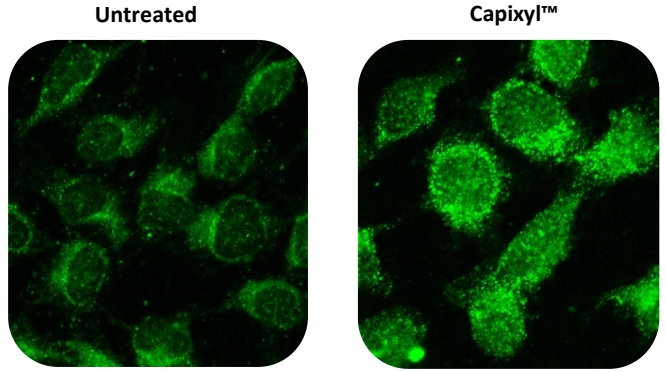
NEW RESULTS

In vitro test protocol

- Keratinocytes treated with Capixyl™ 0.05%, 0.1% and 1% for 24h
- Immunofluorescence labelling of collagen XVII (anchoring proteins)







Capixyl™ stimulates collagen XVII synthesis thus maintaining the high quantity of HFSCs in the reservoir

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STIMULATION OF CELL ACTIVITY

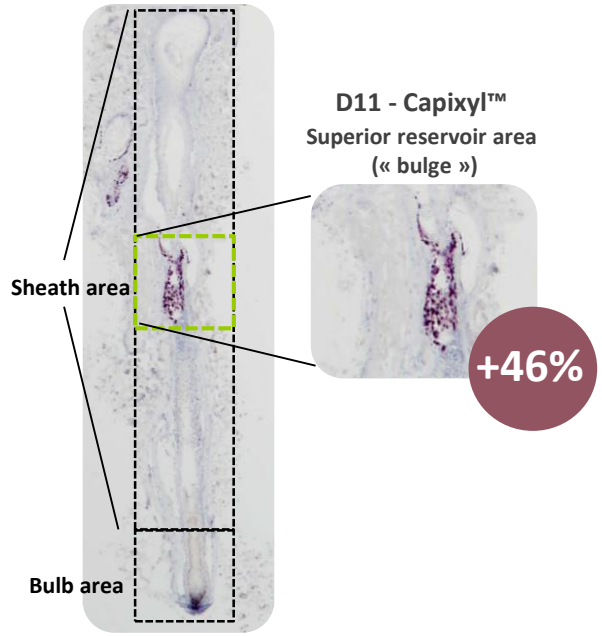
NEW RESULTS

Ex vivo test protocol

- Hair follicles in anagen phase (from a 49 years old woman) were treated or not with 1% Capixyl™ during 11 days (Philpott method)
- Cells in division were identified by immunolabelling of Ki67 (in violet) and quantified in the **bulb** and in the **sheath** areas (including bulge)

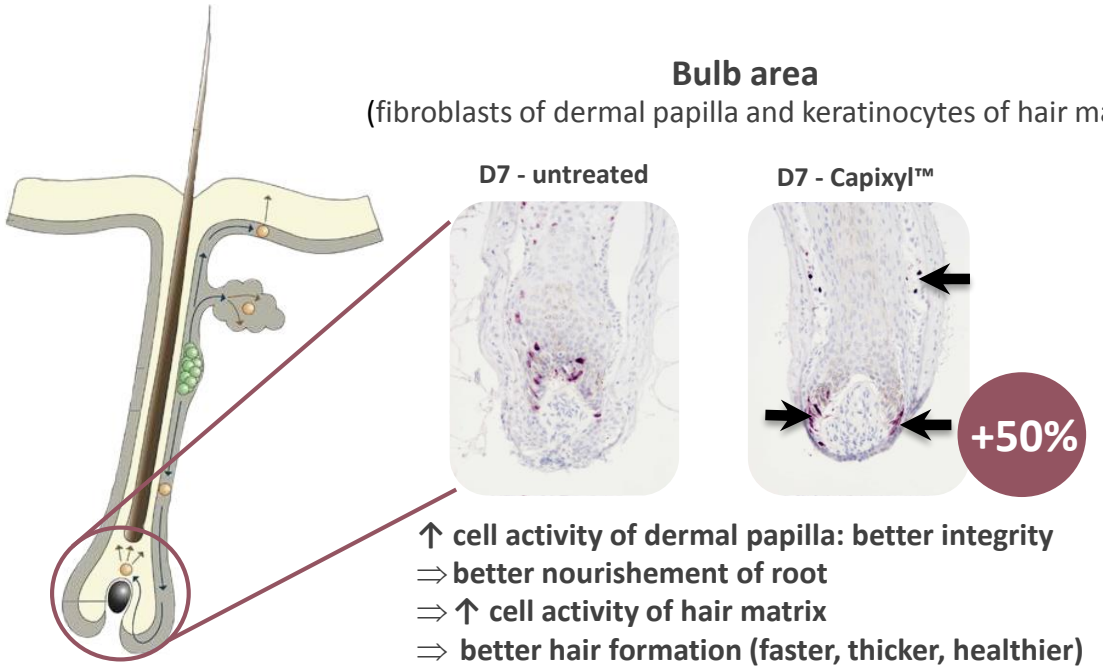
Sheath area

(keratinocyte of hair follicle and HFSC in the bulge)



Bulb area

(fibroblasts of dermal papilla and keratinocytes of hair matrix)



↑ cell activity of dermal papilla: better integrity
⇒ better nourishement of root
⇒ ↑ cell activity of hair matrix
⇒ better hair formation (faster, thicker, healthier)

Capixyl™ stimulates cell division favoring optimal hair follicle structure and hair formation

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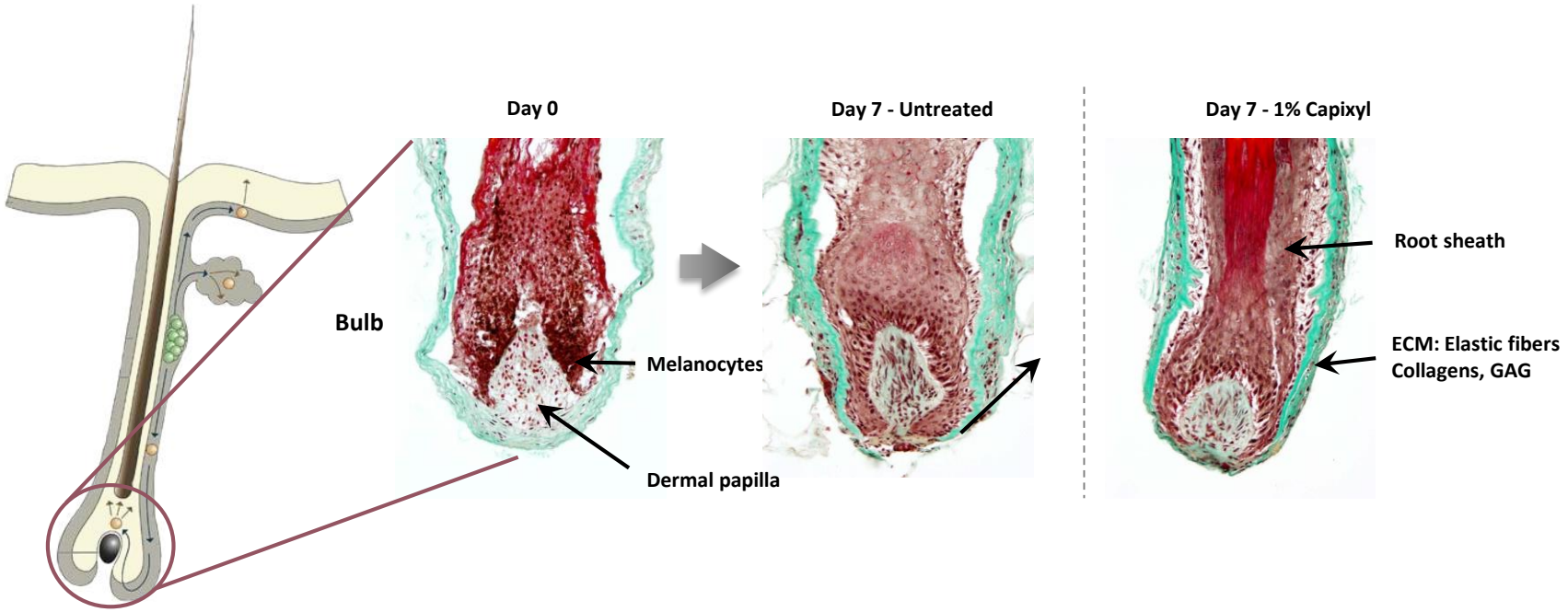
IMPROVEMENT OF HAIR MATRIX MORPHOLOGY

NEW RESULTS

Ex vivo test protocol

- Hair follicles in anagen phase (from a 49 years old woman) were treated or not with 1% Capixyl™ during 7 days (Philpot method)
- Observation of the general morphology by microscopy



Capixyl™ clearly improves the cohesion of the hair follicle to the ECM, offering optimal environment for higher activity

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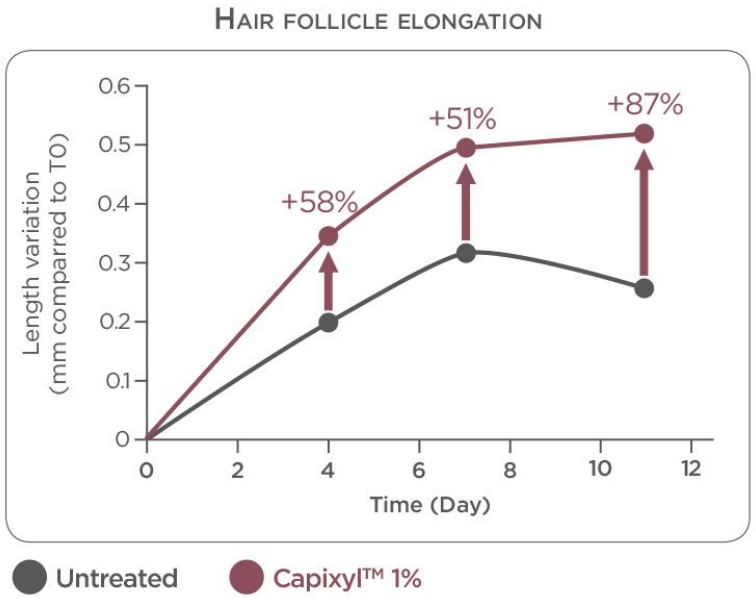
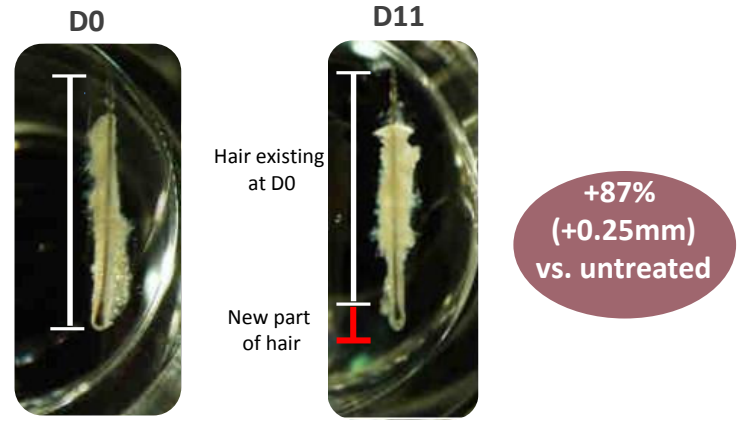
STIMULATION OF HAIR GROWTH

NEW RESULTS

Ex vivo test protocol

- 2 lots of 17 hair follicles in anagen phase (from a 49 years old woman) treated or not with 1% Capixyl™ during 11 days (Philpot method)
- Hair length variation (=elongation) was measured at D0, D4, D7 and D11 with a micrometer by optical microscope.





Capixyl™ clearly stimulates hair growth!

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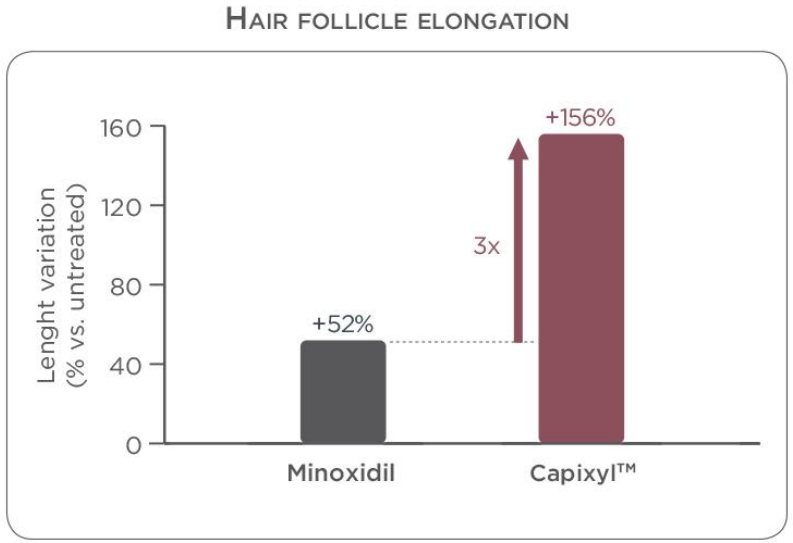
STIMULATION OF HAIR GROWTH VS. MARKET REFERENCE

***Ex vivo* test protocol**

- Human hair follicles in anagen phase were cultured with Acetyl Tetrapeptide-3 at 10^{-7}M (≈ 0.016% Capixyl™ solution) or Minoxidil at 120 X 10^{-7}M during 7 days (Philpot method)
- Hair length variation (=elongation) was measured with a micrometer incorporated in a optical microscope



Capixyl™ stimulates hair growth with higher activity than the market reference product, Minoxidil

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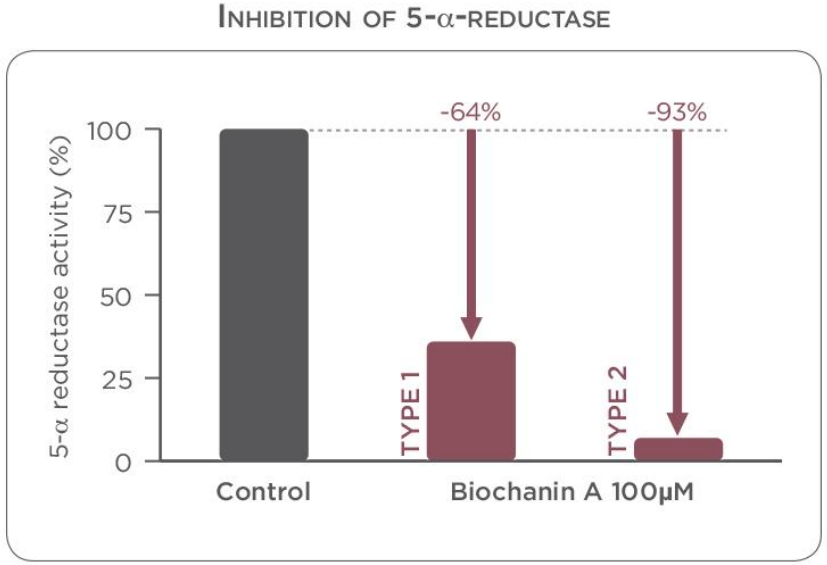
Modulation of Dihydrotetosterone (DHT)

***In vitro* test protocol**

- Cells were incubated with Biochanin A and radioactive Testosterone
- The amount of labelled of DHT and Testosterone was determined by TLC (thin layer chromatography) and scanning.
- Calculation of 5-α reductase activity



Capixyl™ inhibits 5-α reductase activity, thus confirming the decrease in DHT production to reduce androgenic alopecia

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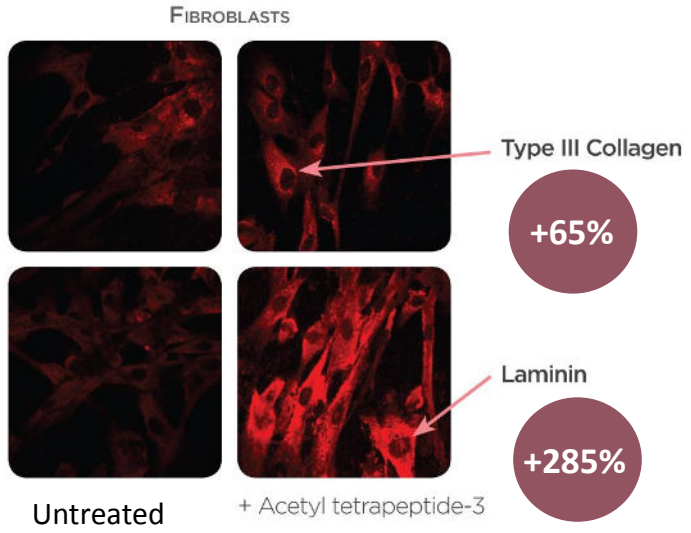
INCREASE IN MATRIX STRUCTURE AND ANCHORING PROTEINS

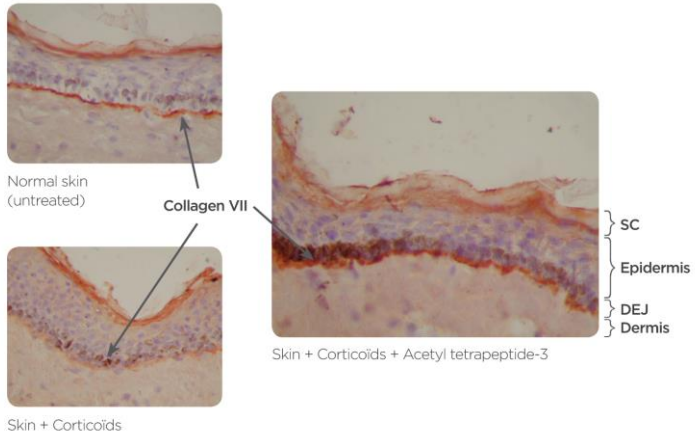
***In vitro* test protocol** (Laminin and Collagen III)

- Human fibroblasts were treated during 3 days acetyl tetrapeptide-3 10^{-7}M
- **Laminin** and **Collagen III** were labelled by immunofluorescence and quantified by image analysis



***Ex vivo* test protocol** (Collagen VII synthesis)

- Human skin explants were pre-treated with dermocorticoïds in order to reproduce natural aging pattern.
- Skin explants were then treated with 10^{-3}M Acetyl tetrapeptide-3 during 2 days
- **Collagen VII was** stained and quantified by image analysis



Capixyl™ improves collagens and laminin synthesis favoring dermal papilla structure and hair anchoring

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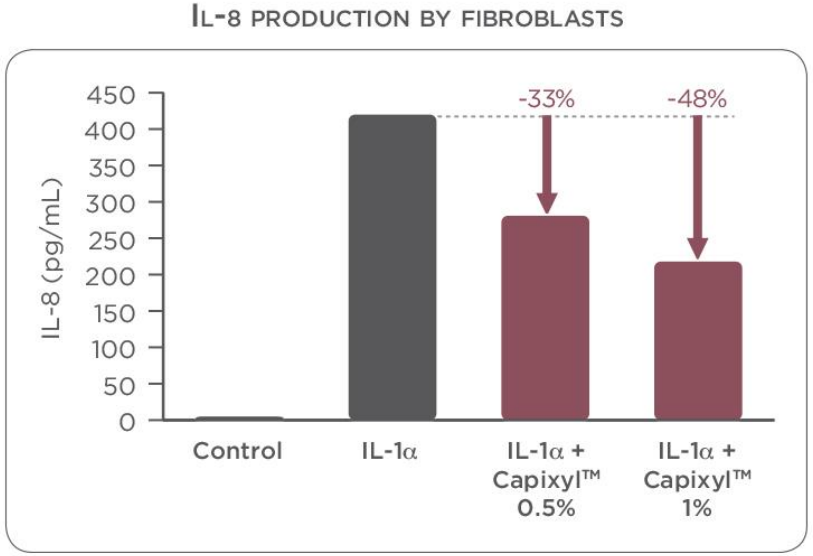
DECREASE IN MICRO-INFLAMMATION

***In vitro* test protocol**

- Inflammation was induced in human fibroblasts with IL-1α
- Fibroblasts were incubated with Capixyl™ 0.5% and 1% for 24h
- IL-8 quantification using an Enzyme Immunoassay Kit



Capixyl™ decreases pro-inflammatory cytokines production with a dose dependent effect thus limiting hair follicle micro-inflammation

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CAPIXYL™ MULTI-TARGET EFFICACY SUMMARY

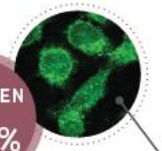
Activation of Growth

Stimulates the hair follicle regeneration process

NEW RESULTS

Preserves Hair Follicle Stem Cell (HFSC) quantity by maintaining them attached to the membrane

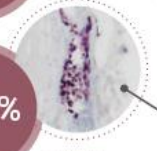
COLLAGEN XVII +40%



NEW RESULTS

Activates HFSC by stimulating their proliferation (↑ Ki67, ↑ CD34, ↑ CK19, ↑ IGF-1)

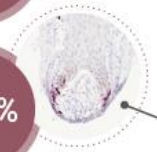
+46%



NEW RESULTS

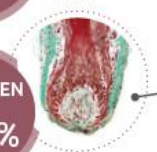
Accerelates hair formation by improving bulb cells activity (↑ Ki67)

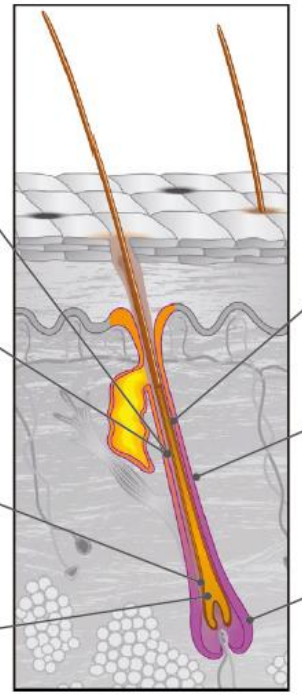
+50%



Increases dermal papilla activity by improving its morphology

COLLAGEN III +65%





Limitation of Loss

Reduces the hair follicle miniaturization process

-93%

Modulates DHT by inhibiting 5-α reductase activity

IL-8 -48%

Reduces local micro-inflammation by decreasing cytokine production

COLLAGEN VII X3

LAMININ X4

Improves hair anchorage to dermal papilla by increasing anchoring protein production

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Clinical Study on Hair Loss

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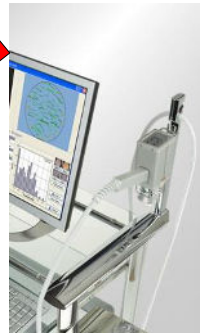
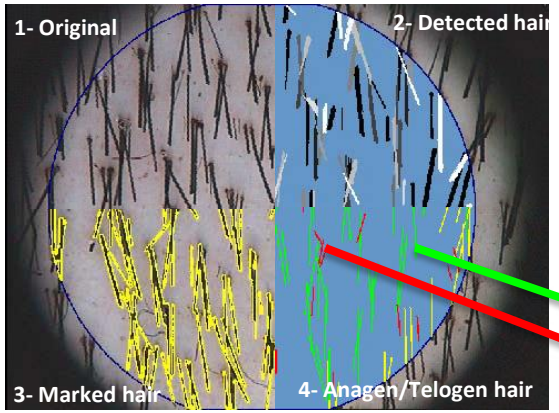
TRICHOGRAM METHODOLOGY

1. Hair **shaving** (~1.8 cm^2 areas)

2. **Picture** of the area zones taken with as TricoScan 3 days after shaving to evaluate the number of hair in anagen and telogen phases according their hair growth speed.
Anagen phase was determined as a growth rate of 0.3 mm/day.



3. Image taken by microscopy & automatic digital image analysis



Green : Anagen
Red : Telogen

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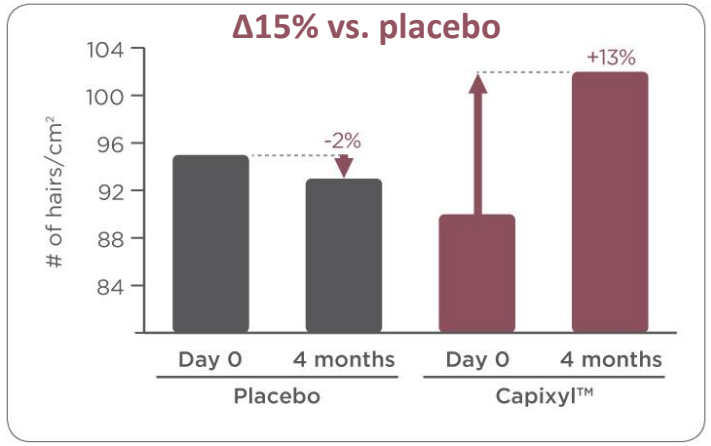
Improvement of Hair Growth Cycle

***In vivo* study protocol**

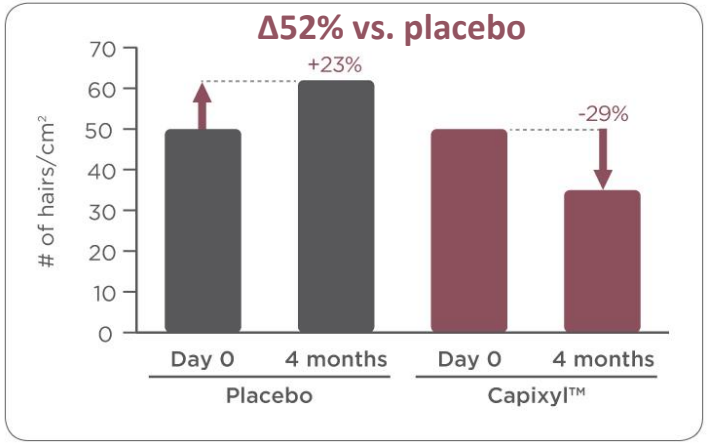
- 30 men with androgenetic alopecia (average age 46) with maximum 200 hair on the treated zone including less than 70% in anagen phase
- 2 groups: 15 treated with a 5% Capixyl™ lotion and 15 treated with a placebo
- 1X/D application at night time of 20 drops of products for a 4 month period
- Quantification of the number of hair per cm^2 (density) by analysis of digital trichogram (by TrichoScan)

Average anagen hair density



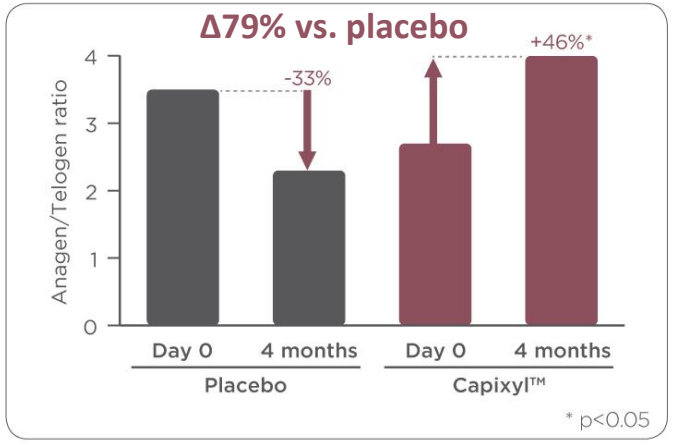
Clear increase in the anagen hair density = HAIR GROWTH

Average telogen hair density



Strong reduction in the telogen hair density = STOPS HAIR LOSS

Anagen/telogen ratio



More than 70% of the volunteers saw an improvement in their condition

Capixyl™ improves the hair growth cycle and reverses alopecia conditions with outstanding results!

Tested formulas: Capixyl 5%, Water 75%, Alcohol 20% - Placebo: Water 75%, Alcohol 20%

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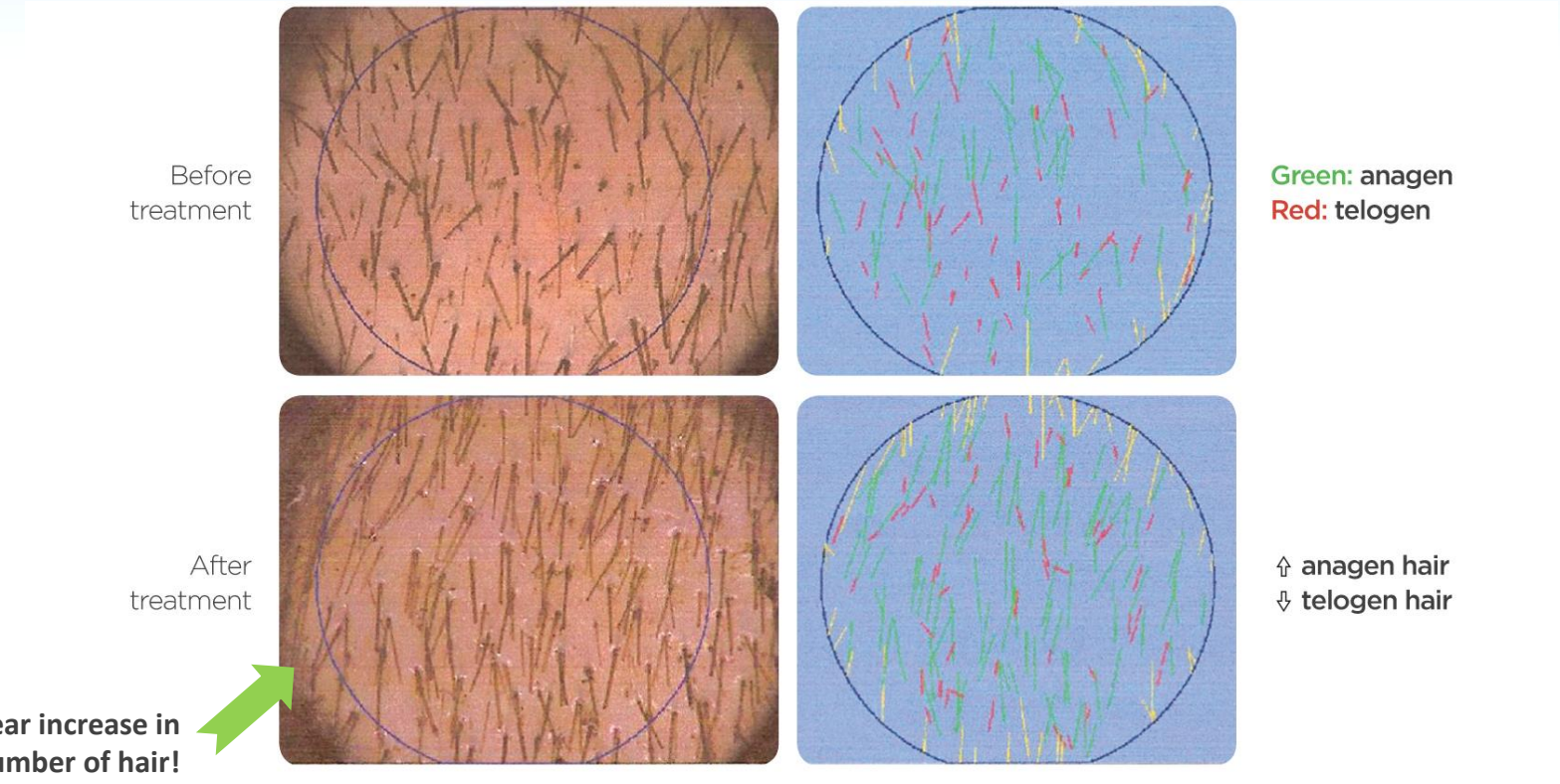
IMPROVEMENT OF HAIR DENSITY



Capixyl™ is an efficient solution to visibly decrease alopecia

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CAPIXYL™ EFFECT ON EYELASHES

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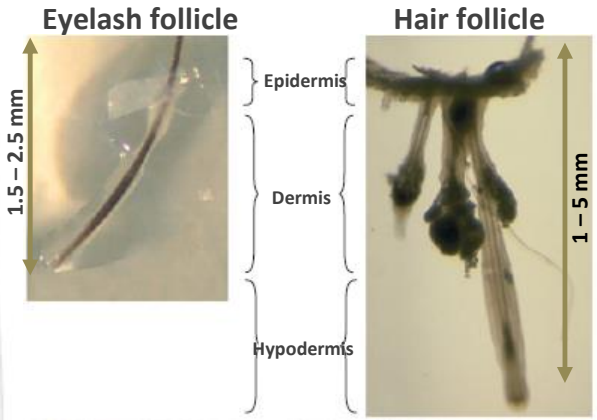
Hair and Lash similarities

Upper lid: 100-200 lashes; length: 8-12 mm

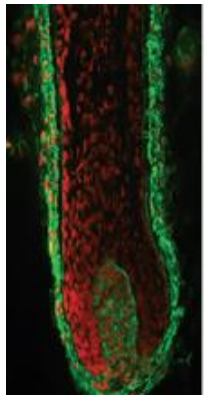
Lower lid: 75-100 lashes; length: 6 to 8 mm

After 40 years old, the number of eyelashes decreases and they become thinner

Eyelash follicle has the same overall structure as scalp hair follicles, but much shorter (due to a shorter hair cycle).



Specific labeling with ECM proteins antibodies revealed a similar morphology to that observed in the scalp hair follicle



Hair Growth Cycle: Hair vs. Eyelash

	Anagen Growth phase	**Catagen** Regression phase	**Telogen** Resting phase	**Growth rate**
Hair	**2 - 6 years** 70 - 85% hair	**100 days** 15 - 30% hair		**0.3 - 0.6 mm daily**
Eyelash	**1 - 3 m** *(ref.1)* **22 - 55 d** *(ref.2)* 15 - 40%	**4 - 9 m** *(ref.1)* **~2 m** *(ref.2)* 60 - 85% lashes		**0.12 mm daily**

ref.1: Ethnic characteristics of eyelashes. Br J. Dermatol. 2006. Na et al. Amorepacific
ref 2: Human eyelashes characteriz
ation. Br J. Dermatol. 2010. Thibaut et al. L'OREAL

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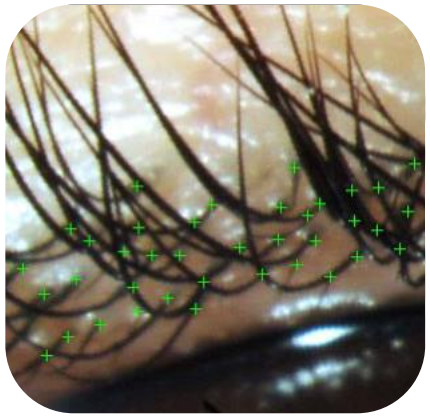
METHOD

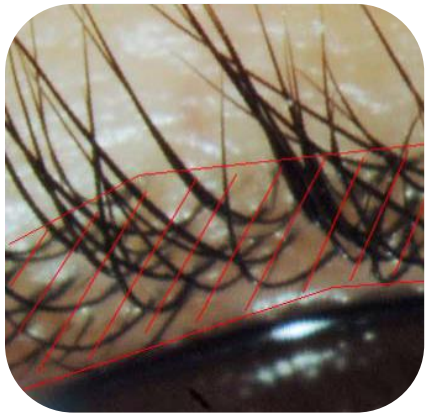
1 - At D0, 4 weeks and 8 weeks, photographs of the upper lashes were taken with a camera fixed on a biomicroscope

Lash density
(number of roots per unit of surface)

2 - Counting the number of lashes in the specific area to be analyzed



3 - Measurement of the surface where the lashes growth



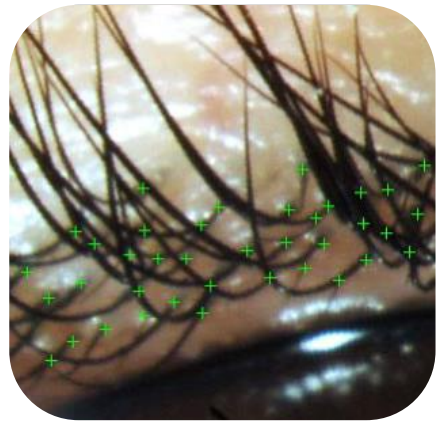
4 - Determination of the lash density

Number of young lashes

2bis - Counting the number of new lashes according the morphology and characteristics of young lashes (in comparison with adult lashes):

- less coloring
- thinner
- shorter

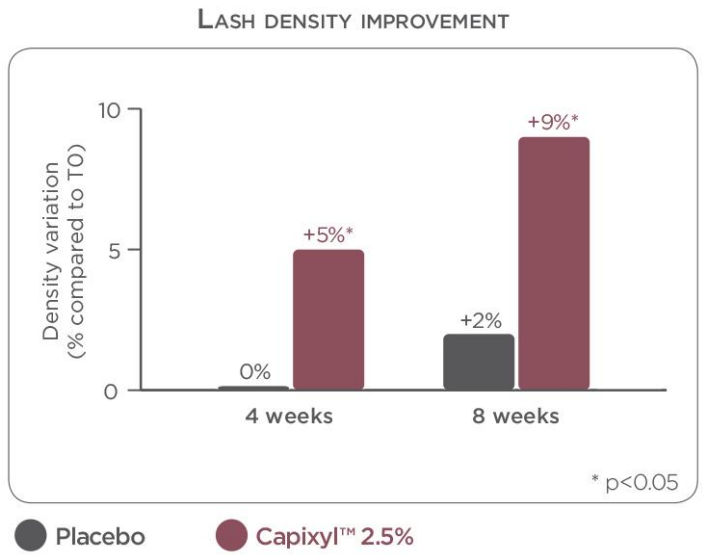
.

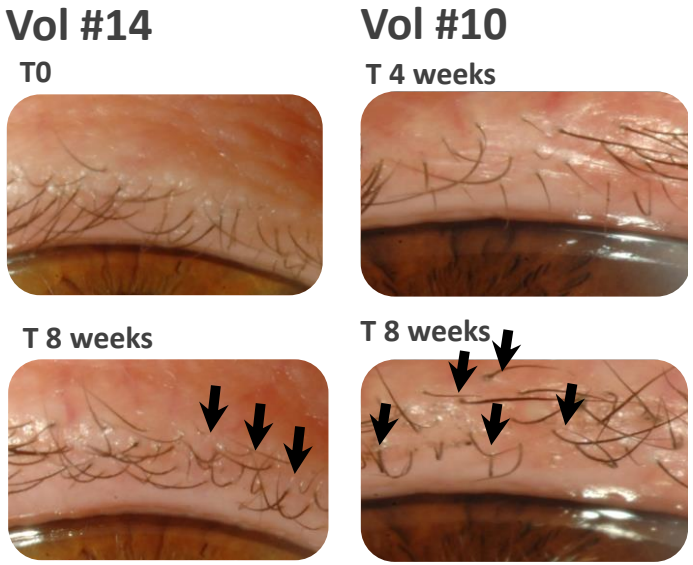


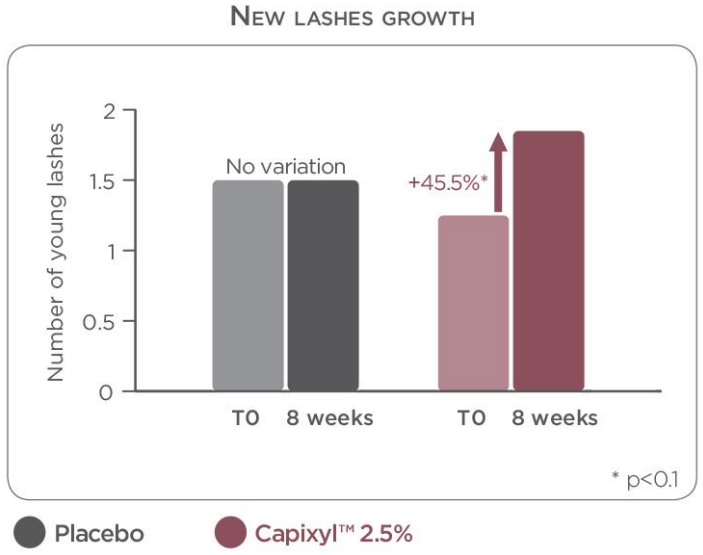
EVALUATION OF THE LASH DENSITY

***In vivo* study protocol**

- 17 women (25-68 years old)
- Application of a 2.5% Capixyl™ gel or a placebo gel on the upper and lower lashes of the eye in the morning and in the evening during 8 weeks
- Evaluation of lash density and number of new lashes at 4 weeks and 8 weeks on image taken with a biomicroscope







After 4 weeks 73% of the subjects improved in lash density and 93% had an effect after 8 weeks

Capixyl™ induces a clear and significant increase in the lash density (increase in new lashes & decrease in falling lashes)

Tested formula: Capixyl™ 2.5%, Water 88.1%, Glycerin 3%, VP/VA Copolymer 2%, Carbomer 1%, Preservatives, Ph adjuster

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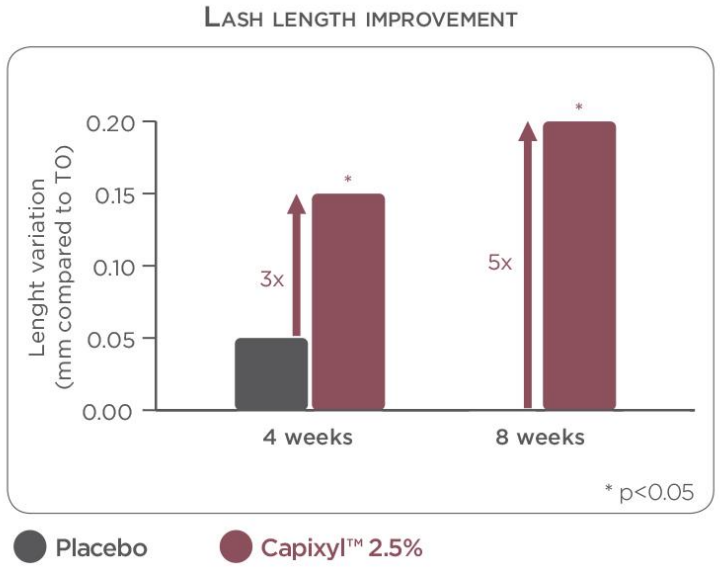
Evaluation of the lash length

***In vivo* study protocol**

- 17 women (25-68 years old)
- Application of a 2.5% Capixyl™ gel or a placebo gel on the upper and lower lashes of the eye in the morning and in the evening during 8 weeks
- Assessment of the mean length of the upper ciliary fringe (for each eye) on photography taken with a digital camera at D0, 4 weeks and 8 weeks



The evolution of lash length is 3 and 5 times better after Capixyl™ application (4 and 8 weeks respectively) in comparison with placebo

Up to 0.70 mm after 4 weeks!

After 8 weeks 73% of the subjects saw an improvement in the length of their lashes

Capixyl™ significantly limproves lash growth after only 4 weeks

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EVALUATION OF THE LASH LENGTH

Vol #3

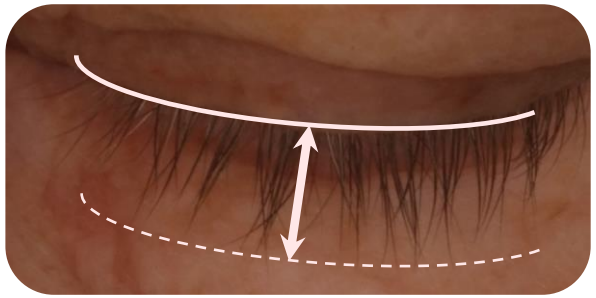
T0

T 4 weeks

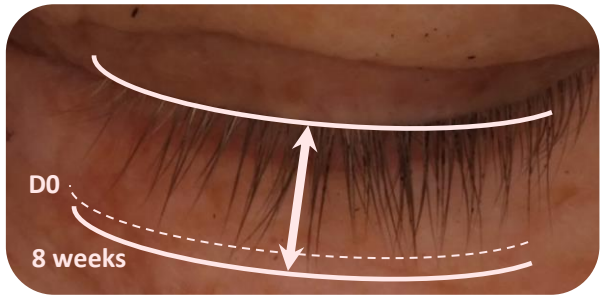
Up to 0.70 mm after 4 weeks!

Vol #2

T0

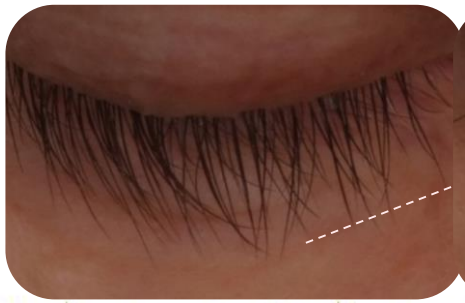


T 8 weeks



Vol #16

T0



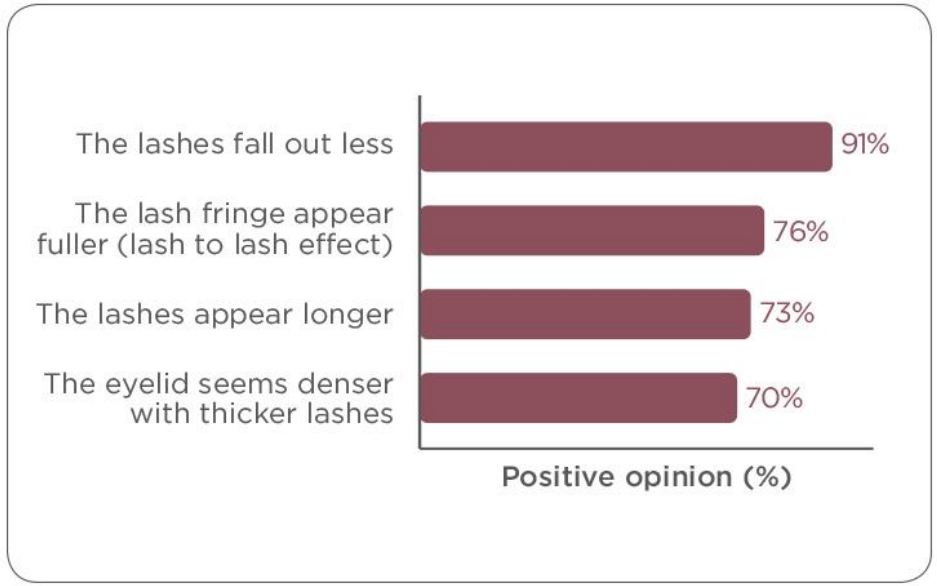
T 4 weeks

T 8 weeks

Consumer Test

Protocol

- 17 women (25-68 years old)
- Application of a 2.5% Capixyl™ gel or a placebo gel on the upper and lower lashes of the eye in the morning and in the evening during 8 weeks
- Assessment of the mean length of the upper ciliary fringe (for each eye) on photography taken with a digital camera at D0, 4 weeks and 8 weeks



Consumers noticed a real improvement when they used Capixyl™ in an eyelash treatment

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TOXICOLOGY

- Skin tolerance (48h single patch test) (tested concentration: 25%)
- Eye tolerance (HET-CAM) (tested concentration: 15%)
- Sensitization (HRIPT on 100 volunteers) (tested concentration: 15%)
- Mutagenicity (AMES) (tested concentration: 25%)
- Phototoxicity (*In vitro* 3T3) (tested concentration: 15%)

ECOTOXICITY

- Biodegradability (OECD 301D)
- Aquatic toxicity on daphnies (OECD 202)

Excellent safety profile

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CAPIXYL™
HAIR FERTILIZER

IMPROVES HAIR GROWTH CYCLE
- Stimulates hair follicle regeneration/decreases hair follicle miniaturization
- Improves growth phase (anagen) and reduces loss phase (telogen)
- Provides faster results than market reference

MULTI-TARGET ACTION
- Preserves hair follicle stem cells (HFSC) NEW RESULTS
- Modulates DHT (↓ 5-α reductase)
- Stimulates dermal papilla matrix and anchoring proteins synthesis (collagen III, collagen VII and laminin)
- Decreases microinflammation (↓IL-8)

CONSUMER BENEFITS
- Helps provide stronger, thicker, healthier and fuller hair, lashes and eyebrows
- Anti-thinning effect
- Visible results without adverse event

SYNERGISTIC COMPLEX
- Biomimetic peptide
- Red clover flower extract rich in biochanin A

MANUFACTURER BENEFITS
- Efficient cosmetic alternative to Minoxidil
- Complements Minoxidil mechanism of action for more efficient results
- Easy-to-formulate in all types of formulas for hair and eyelashes

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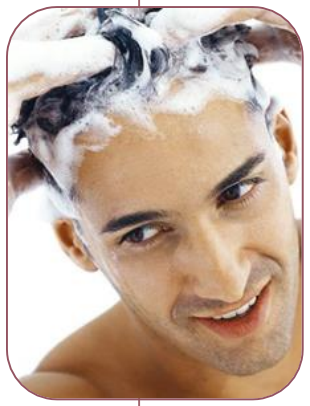
CAPIXYL™ PRODUCT INFORMATION

INCI NAME	Water (and) Butylene Glycol (and) Dextran (and) Acetyl tetrapeptide-3 (and) Trifolium Pratense (Clover) Flower Extract
ADDITIVE	None
APPEARANCE	Transparent liquid
FORMULATION	Should be incorporated at the end of the formulation at a temperature below 40°C
DOSAGE	0.5-2.5%: preventive care 2.5-5 %: intensive treatment
OPTIMUM PH	4.0 - 8.0
APPLICATIONS	**HAIR (leave on & rince off)** •Anti-hair loss products •Hair regrowth products •Anti-aging hair care products •Hair treatment for menopaused women •Treatment for seasonal hair loss **EYELASH/EYEBROW** •Serum •Mascara •Pencil •Make up remover



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HEALTHY SCALP SERUM

	INGREDIENTS	INCI NAME	%
A	Deionized Water	Water	93.60
	Dissolvine® Na	Tetrasodium EDTA	0.10
	Chlorphenesin	Chlorphenesin	0.30
	Phenoxyethanol	Phenoxyethanol	0.80
B	Lecigel™	Sodium Acrylates Copolymer (and) Lecithin	1.50
C	Vitapherole® E1000	Tocopherol (and) Helianthus Annuus (Sunflower) Seed Oil	0.20
D	Defenscalp™	Water (and) Epilobium Angustifolium Flower/Leaf/Stem Extract	1.50
	Capixyl™	Butylene Glycol (and) Water (and) Dextran (and) Acetyl Tetrapeptide-3 (and) Trifolium Pratense (Clover) Flower Extract	2.00

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Features & Benefits

FEATURES	BENEFITS
Unique combinaison: Peptide with botanical active	Stable, easy to work with and performant
Synergistic mechanism of action	Acts on all parameters influencing hair loss
High efficacy	Low dosage (starting at 0.5%)
Better efficacy than the reference molecule	Provides faster results
Clinically proven	Helps provide thicker and fuller hair

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THANK YOU!