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LABORATORIES

Spectral.DNC-N®

Multilateral approach to topical therapy
of hair loss - addressing the complex biology
of the hair follicle.

- Successful therapy involves a multilateral approach to target various pathways of the disease process

- Monophasic therapies have a limited potential for full recovery

- Existing proven monophasic therapies are Finasteride (oral) and Minoxidil (topical)

- A multilateral approach involves studying and testing the properties of various molecules and refining the properties of these molecules by either potentiating desirable effects or minimizing certain undesirable effects.
- A significant number of auxiliary agents are used to fine tune this process.
- Inactive compounds such as solvents also need to be evaluated

- Effectiveness of active molecules also need to be evaluated beyond the 12 month time horizon to establish long term effectiveness that does not drop off with time.

- An example of this is prolonged consumption of sulfotransferase which can reduce efficacy of minoxidil therapy over time.

The major pathways in hair growth have been identified as:

A. Opening Ion channels within cells

B. Stem cell stimulation

C. DHT suppression

D. Perifollicular fiborsis management

E. Autoimmune processes (possible T-Cell involvement)

F. Anti-oxidant effects

G. Prolonging and managing the anagen phase (shortening telogen)

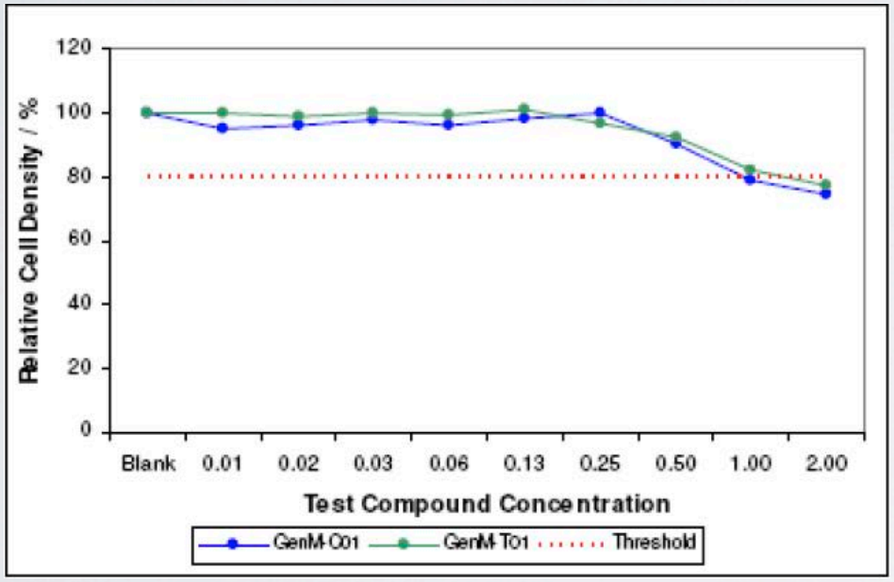
H. Increasing expression of Vascular Endothelial Growth Factor (VEGF)

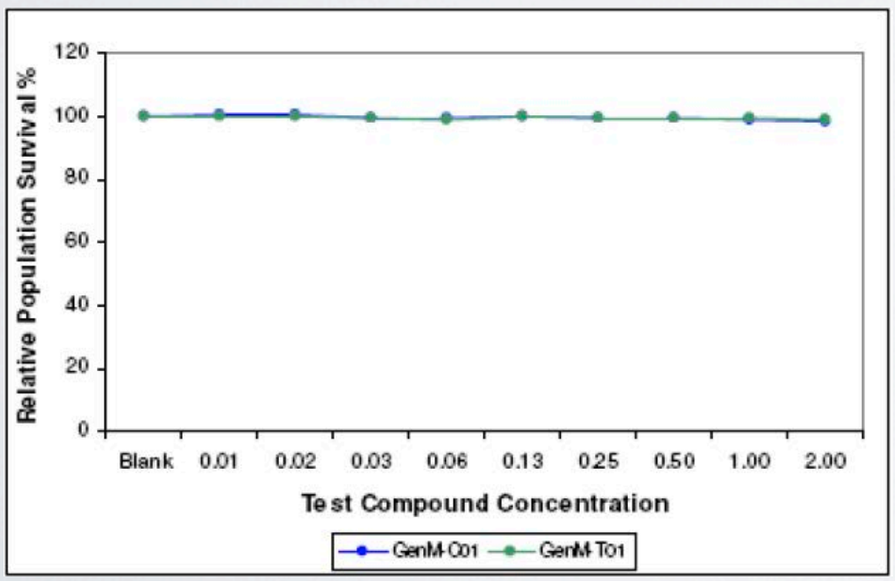
I. Selective suppression of Protein Kinase C isozymes

J. Boosting KI67 expression, a cellular marker for cell proliferation

K. Blocking chronic inflammation of the hair follicle

Example of maximizing efficacy of molecules in multilateral therapy:





- Minoxidil is the most well known agent for topical use (not necessarily the most effective)
- While minoxidil is a hair growth promoter it also has an inherent cytotoxicity which is counterproductive for cell proliferation and stimulation
- Therefore a strategy with auxiliary agents is to mediate this effect by boosting KI67 expression and increasing cell proliferation and using other ion channel opening compounds.

- For minoxidil to work it must be converted to its active metabolite, minoxidil sulfate. The conversion of minoxidil to minoxidil sulfate is catalyzed by sulphotransferase enzymes.

- In a clinical setting, scalp sulphotransferase activity was higher in men who responded to minoxidil compared with those who did not respond.

- Scalp sulphotransferase activity is key in achieving a successful outcome with various compounds and it is best to minimize over consumption of sulphotransferase enzymes to maintain both short term and long term treatment efficacy.

- Sulfotransferases might also be involved in bioinactivation of estrogens and androgens within skin. Therefore it is perhaps not a good idea to distract the sulfotransferases from their normal useful jobs by keeping them busy with the conversion of minoxidil to minoxidil sulfate.

- A significant challenge of using minoxidil sulfate it its inherent instability in aqueous systems.

- In summary, significantly greater effectiveness can be achieved from hair loss therapy if we reverse cytotoxicity, lower the sulphotransferase burden, and mitigate certain 5α-reductase effects.

- While the exact mechanism of action of minoxidil is not known, minoxidil has shown to have no effect on the duration of anagen, however, it shortens telogen. Minoxidil also increases the follicle size.

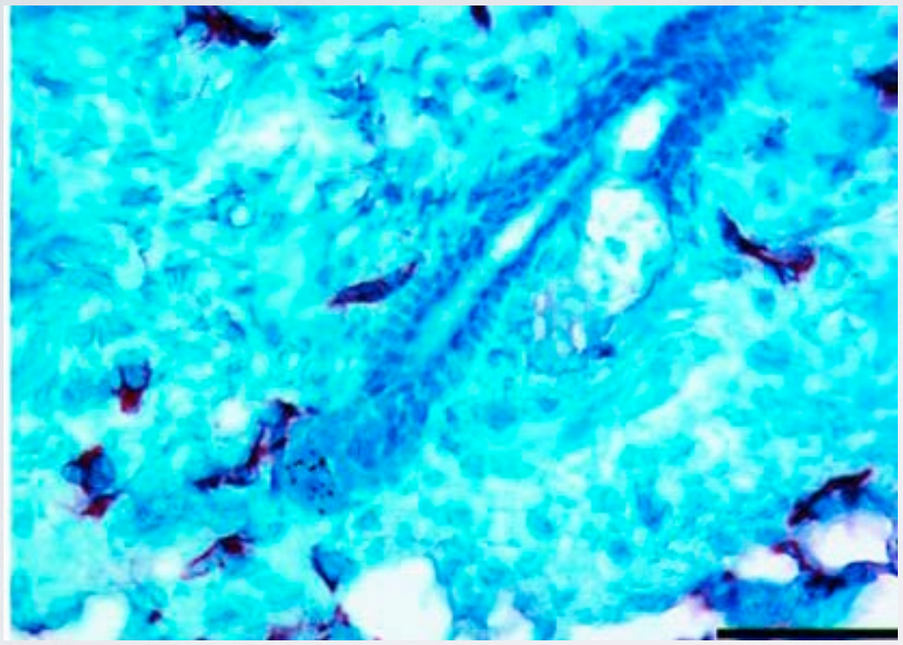
- Since hair growth with minoxidil occurs rather rapidly, it is unlikely that it is caused by reversal of follicular miniaturization, but rather by triggering a shift from telogen into anagen.

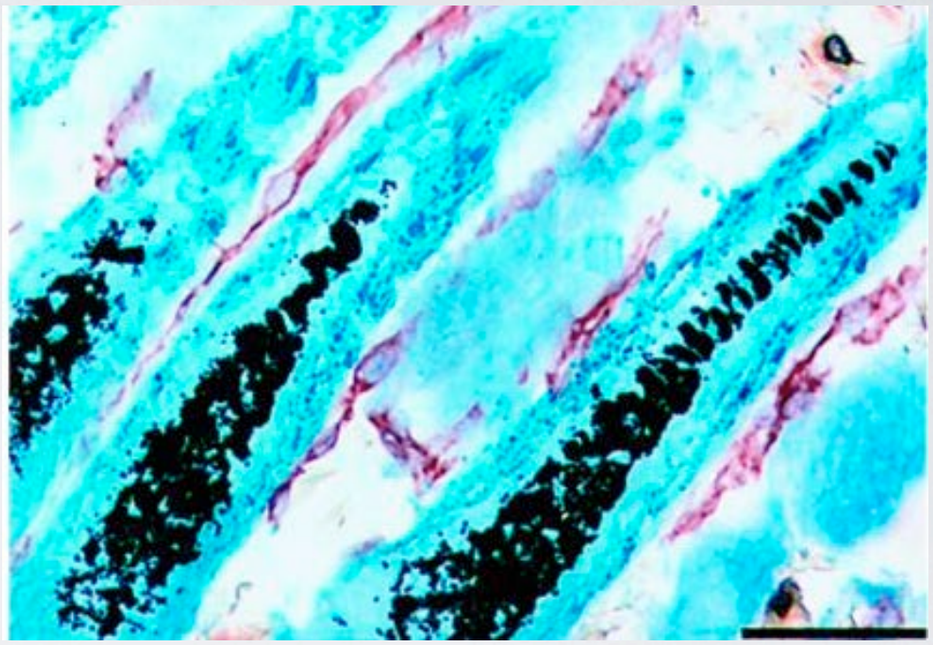
- Therefore conventional therapy with agents like minoxidil or finasteride have significant limitations and do not fully address the complex biology of the hair follicle.

- Protein Kinase C isozymes appear in follicle cells in telogen but are not present in anagen.

- Therefore PKC suppression is an important pathway in treatment.

- The most potent substance for PKC suppression is Procyanidin B2. As a result of PKC suppression the result is a dramatic increase in epithelial cell growth.





- Several compounds work together to significantly promote VEGF expression.

- Capillary proliferation increases during the anagen stage and is directly proportional to VEGF expression.

- Adenosine is a significant hair growth promoter and increases expression of the Fiborblast Growth Factor 7. This is also part of the strategy to counteract cytotoxic effects.

- FGF proteins possess broad mitogenic and cell survival activities, and are involved in a variety of biological processes, including cell growth and tissue repair. This protein is a potent epithelial cell-specific growth factor, whose mitogenic activity is predominantly exhibited in keratinocytes.

- Minoxidil and finasteride have no effect on FGF7.

- Perifollicular fibrosis is premature hair root aging that occurs due to moisture loss, scarring, and collagen overproduction near the hair shaft.

- Whatever the underlying cause, hair loss is linked to the accelerated aging of the roots, characterized by fibrosis. The fibrosis causes the roots to become rigid and compresses the blood vessels that nourish and stimulate them. The roots weaken and hair falls out prematurely. Decreased elasticity is also observed.

- Aminexil, is a highly effective anti-fibrosis molecule, acts on the accelerated aging of the roots by combatting the process of fibrosis.

- The final event in the sequence of degenerative changes that produce involuted non-functional hair follicles are tissue-damaging auto-immune inflammatory and free radical reactions around the follicle.

- Copper Peptides reduce such effects since they block both the inflammatory actions of both interleukin 1and TGF-beta-1 actions in inflammation.

- Copper Peptides used alone have a clinically significant hair growth effect.

Effect of Solvents

- Solvent systems themselves can cause further cytotoxic effects as well as irritation and inflammation of the scalp.

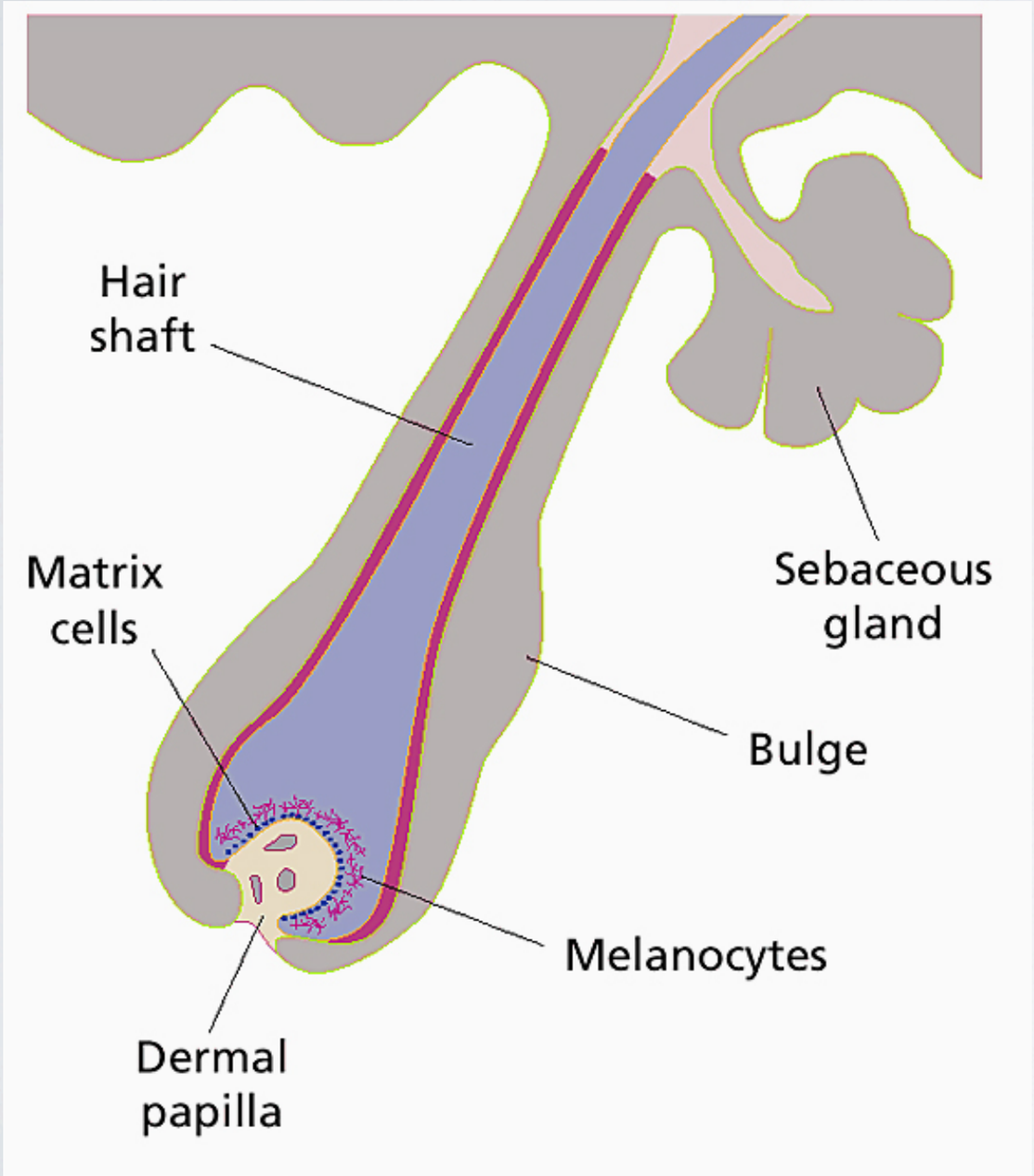
- The most common ingredients found in conventional products are propylene glycol and ethanol at high concentrations.

- These harsh chemicals are needed to dilute minoxidil oil soluble materials.

- A better approach is to use sulphated materials and to encapsulate other oil soluble materials in liposomal vehicle.

- Eliminating propylene glycol and high ethanol levels dramatically improves patient tolerability and comfort

- Hair is not greasy or sticky



- Absorption and delivery play a crucial role
- Histological studies have shown that hair growth molecules tend to concentrate around melanocytes and epithelial cells in the dermal papilla region. (This can probably explain why some people using minoxidil can experience a change in hair color.)

- It is therefore rational to explore ways to increase delivery of compounds like nanoxidil into this region.

- This can happen with delivery systems that utilize submircon spheres with a solid core, an improvement over liposomes

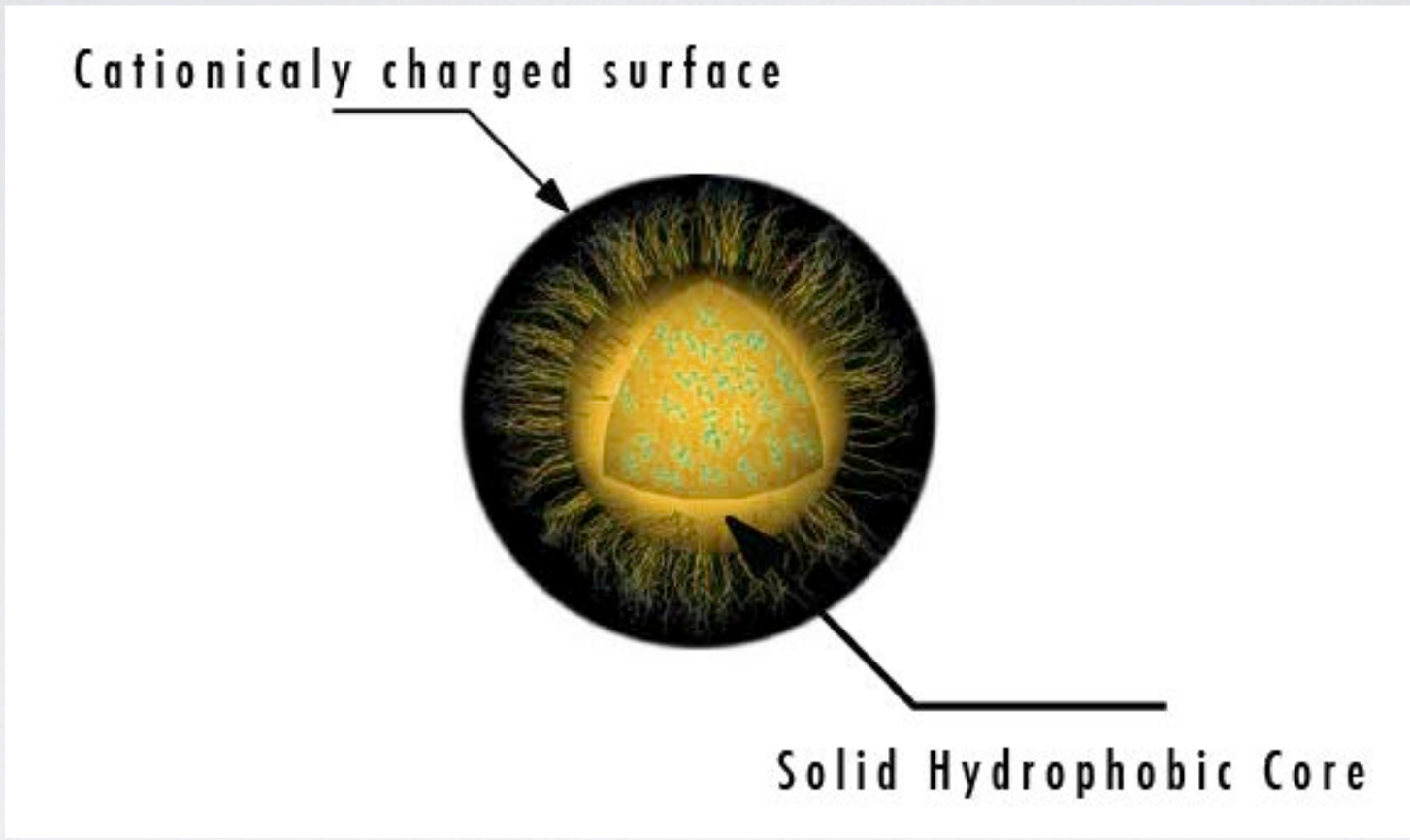
- These submicron spheres that we call nanosomes have the following properties:

A. Hydrophobic

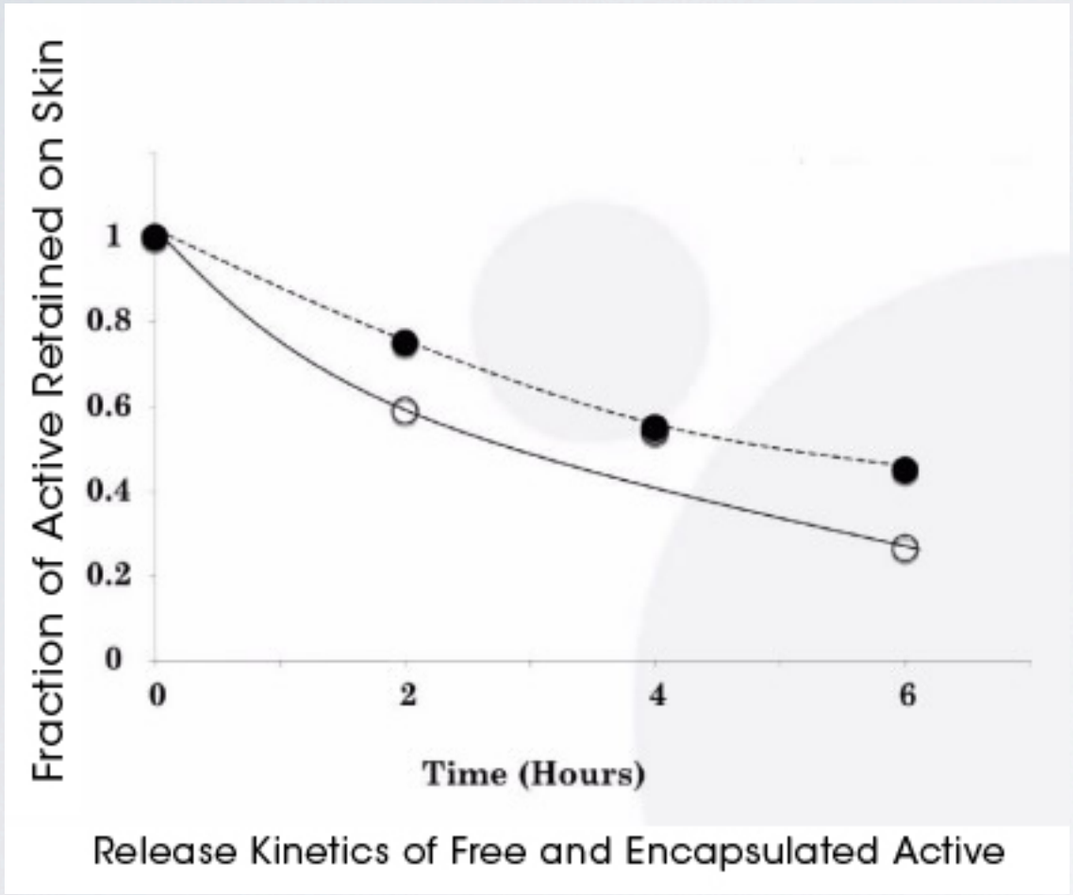
B. Highly Cationic

C. Does not use emulsion based encapsulation

D. Very high stability compared with liposomes



- Due to the cationic and hydrophobic properties of these microspheres, they exhibit bio-adhesive properties.



Release Kinetics of Free and Encapsulated Active

- Ingredients applied normally experience an immediate, short burst in concentration followed by a rapid decline

- Whereas actives released from a controlled release delivery system experience a prolonged concentration at the effective level.

LABORATORIES

FINAL REPORT

PERCEIVED EFFICACY EVALUATION UNDER REAL CONDITIONS OF USE

SPECTRAL.DNC-N®

DS LABORATORIES

Per-E-EP-28257-02-10-11

PERCEPTION Pesquisa em Análise Sensorial Ltda.
Av. Dr. Romeu Tórtima, 739. Barão Geraldo.
Tel: +55 19 3749 8300
CEP 13084-520. Campinas. São Paulo. Brazil

TABLE OF CONTENTS

1.IDENTIFICATION

Research Sponsor

DS LABORATORIES

Address: Rua Visconde de Inhaúma, 64 sala 404

Centro – RJ - Brazil

Telephone: (21) 3546 2943

Institution / Execution

PERCEPTION PESQUISA EM ANÁLISE SENSORIAL LTDA.

Address: Avenida Dr. Romeu Tórtima, 739

Campinas - SP - Brazil

Telephone: (19) 3749 8300

In Charge of Study

In charge of Study Vivian Pessoto Rosa

Product Tested

Official Name	Perception Code
SPECTRAL.DNC-N®	11-28257-02

A sample of the product under study was stored at the research institute as a retention sample for 1 year after the issuance of the final report.

2. OBJECTIVE

The objective of this study was to verify the efficacy of a hair cosmetic product through the subject's subjective perception using Perceived Efficacy evaluations under real conditions of use of **SPECTRAL.DNC-N®** based upon guidelines described in the "Guidelines for the Evaluation of the Efficacy of Cosmetic Products" (COLIPA, 2008) under real conditions of use [sic].

3. LENGTH OF STUDY

This report presents the results obtained after using the product 56 +/- 2 days:
Study start date: 18/Oct/2011
Study end date: 13/Dec/2011

4. STUDY CONDITIONS

The subjects were given explanations and instructed concerning the research objectives and methods. They also received instructions about the study and signed a Free and Clear Consent Form.

After the explanations were given, evaluations of perceived efficacy were made by the subjects using the questionnaires at the beginning of the study and at the end of the study, after using the product fifty-six days (T56).

The approved subjects were instructed to use the product for 56 +/- 2 days, based upon the instructions provided by the company. During this period of time, they were instructed to immediately seek out the person in charge of the study if any sign and/or symptom appeared.

Directions for use

Connect the display lid on the bottle. Spray the scalp where hair loss is most intense, 10 times (10 sprays), taking care to spray the scalp as directly as possible (avoiding product loss by spraying the strands). After product application, massage the entire area. This process should be done in the morning and before going to bed at night.

Application time

56 +/- 2 days

Application site

Scalp

Amount of Product Applied

Apply the amount deemed necessary according to directions for use.

5. STUDY POPULATION

All 28 subjects initially recruited were selected. The research began with 28 subjects approved, in order to complete it with at least 20 subjects.

Of the 28 subjects selected, 20 subjects completed the study after using the product 56 +/-2 days (T56). Seven subjects (numbers 003, 004, 009, 015, 017, 018 and 020) withdrew from the study for personal reasons unrelated to product use. One subject (number 010) used the product incorrectly; therefore his/her data were not included in the research.

Inclusion Criteria

1. Both sexes (with at least 51% of them male);
2. Between the ages of 18 and 60;
3. Complains of hair loss.

Exclusion Criteria

1. Pregnancy.
2. Breastfeeding.
3. Use of anti-inflammatory/immunosuppressant drugs.
4. Active cutaneous illnesses/injuries (localized or disseminated) that might interfere in the study's outcome.
5. History of adverse reactions to products in the same category as the one being tested;
6. Medicated or cosmetic treatments for hair loss

6. METHODOLOGY

6.1. Evaluation of Perceived Efficacy

The methodology used for Evaluation of Perceived Efficacy was based on the "Guidelines for the Evaluation of the Efficacy of Cosmetic Products" (COLIPA, 2008) and "Standard Guide for Sensory Claim Substantiation" (ASTM E 1958-06, 2006).

The subjects were asked to evaluate their skin using the Perceived Efficacy Questionnaire (Attachment 4) at the following times:

- T0: On the first day of the study, before applying of the test-product (Subject Profiles);
- T56: After using the product 56 +/2 days (Perceived Efficacy).

6.2. Type of Test

The test of Perceived Efficacy was performed by the Subject under a single-blind monadic test.

7. ETHICAL ASPECTS

The subjects were given explanations and instructed concerning the research objectives and methods. They also received instructions about the study and signed a Free and Clear Consent Form (Attachment 2) prepared on the basis of the Helsinki declaration and Resolution 196/96.

Each subject was informed that he/she could withdraw from the study at any time, with no reasons given.

8. STATISTICAL ANALYSES

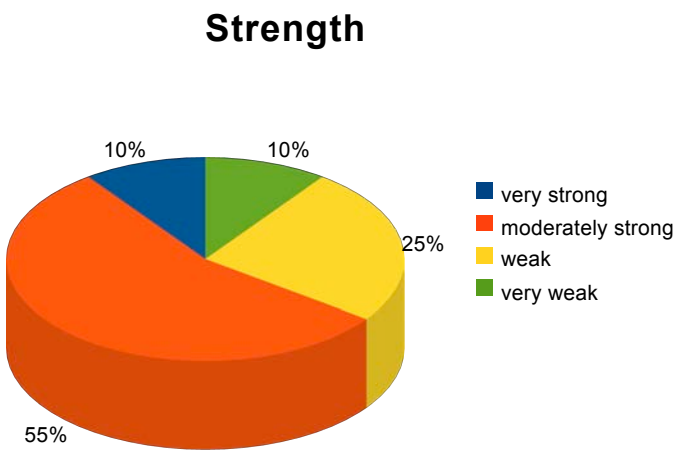
An exploratory analysis of the data was performed (percentages and bar graphs).

The number of subjects who completed the study was equal to 20 (HOUGH et. al., 2006 and STONE & SIDEL, 2004).

9. RESULTS

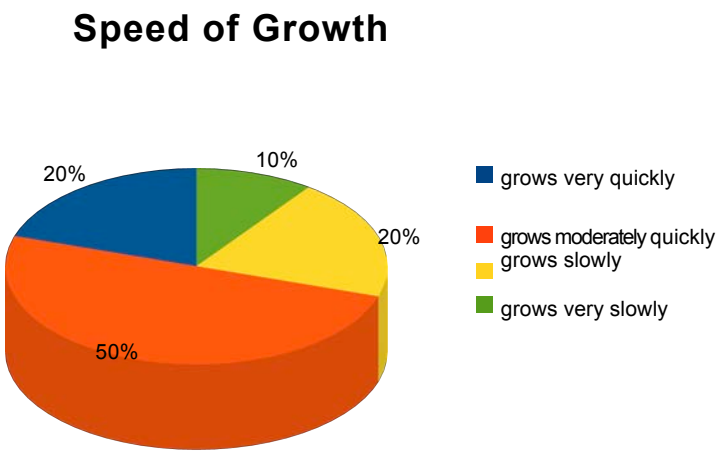
9.1. Subject Profiles

The Figures below (pie chart) shows the subjects' evaluation before using the product (Subject Profiles).



PERCEPTION

PROFILE OF THE JUDGES



9.2. Subjects' Evaluation of Perceived Efficacy

The following Table presents the subjects' percentage with respect to the perceived improvement of their hair after using the product 56 +/- 2 days (T56).

Attributes	T56 (%)
Hair Loss	95.0
Strength	90.0
Speed of Growth	75.0

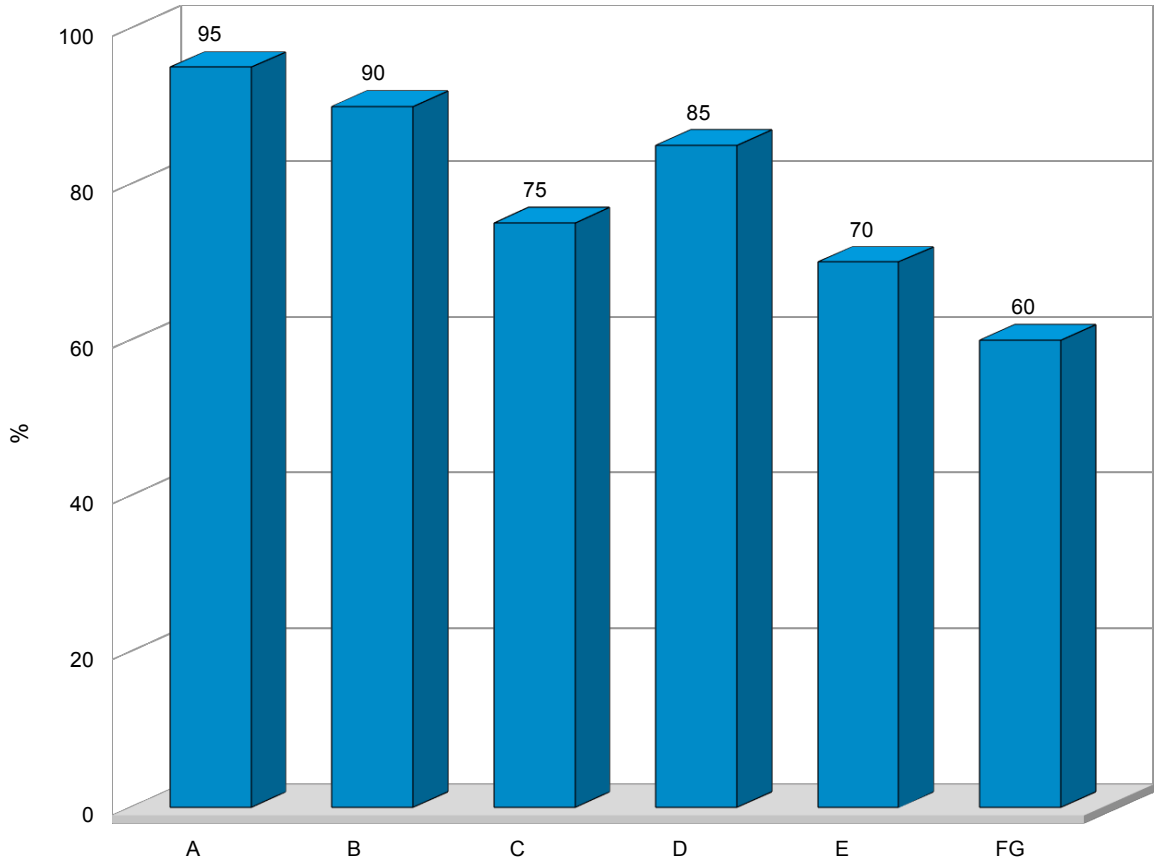
The table shows the subjects' percentages that refer to improvements in the skin and hair after product use.
Hair loss was considered the sum of the categories: *decreased a lot, decreased moderately* and *decreased a little.*
Strength and Speed of Growth were the sum of the categories: *increased a lot, increased moderately* and *increased a little.*

Affirmation	T56 (%)
"Using the product led to less hair loss"	85.0
"Using the product left my hair stronger"	70.0
"After using the product, I noticed an increase in hair growth"	60.0

The table shows the subjects' percentages that refer to improvements in the skin and hair after product use.
The statements made above were considered to be the sum of the categories *I fully agree and I agree.*

SUBJECTS' EVALUATION OF PERCEIVED EFFICACY

The figure below contains a summary of the percentage of acceptance of the Perceived Efficacy attributes evaluated on T56.



Attributes

A: Hair Loss

B: Strength

C: Speed of Growth

Statements

D: "Using the product led to less hair loss"

E: "Using the product made my hair stronger"

F: "After using the product, I noticed an increase in hair growth"

10. CONCLUSION

According to the methodology used to evaluate **SPECTRAL.DNC-N®**, ordered by **DS LABORATORIES,** one may conclude that:

Subjects' Evaluation of Perceived Efficacy

After 56 +/- 2 (T56) days of product use, the following results were obtained:

- 95.0% of subjects noticed less *hair loss*;
- 90.0% of subjects noticed increased *hair strength*;
- 75.0% of subjects noticed increased *hair growth*;
- 85.0% of subjects fully agreed or agreed with the statement "Using the product led to less hair loss";
- 70.0% of subjects fully agreed or agreed with the statement "Using the product left my hair stronger";

- 60.0% of judges fully agreed or agreed with the statement *"After using the product, I noticed an increase in hair growth."*

Vivian Pessoto Rosa
In Charge of Study

Fátima Ap. Ortigoza de Lima
Quality Assurance

12/20/2011

ANALI - 025

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See the scope on ANVISA's website:
http://www.anvisa.gov.br/reblas/bio/anali/index.htm

11 REFERENCES

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PERCEPTION

ATTACHMENT 1 – SUBJECTS WHO PARTICIPATED IN THE STUDY

Subject	Initials (name)	Age (years)	Sex	Status
001	SF	51	F	I
002	JGR	51	F	I
003	MASS	48	F	I
004	RFRA	36	M	I
005	MSCLN	35	F	I
006	SRRM	48	F	I
007	CMRS	51	F	I
008	OSR	56	F	I
009	ESG	29	M	I
010	RMVS	43	F	I
011	OP	49	M	I
012	LN	49	M	I
013	MAS	27	M	I
014	HJF	56	M	I
015	AMC	47	M	I
016	GBL	51	M	I
017	NSM	56	M	I
018	CAGS	29	M	I
019	JM	35	M	I
020	JA	36	M	I
021	CJAC	47	M	I
022	DBB	33	M	I
023	CCM	39	M	I
024	JL	55	M	I
025	RB	34	M	I
026	JDO	58	M	I
027	ALLN	37	M	I
028	EMA	F	M	I

I: Included
NI: Not Included
F: Female
M Male

ATTACHMENT 2 – FREE AND CLEAR CONSENT FORM

– You have been invited to participate in a study. We ask that you thoroughly understand all stages, and if you agree, sign this consent form;

– The purpose of the study is to verify the efficacy of a hair cosmetic product through the subjects' subjective perception by evaluating Efficacy under real conditions of use.

– The study will be carried out at ALLERGISA Pesquisa Dermato-Cosmética Ltda, located at Av. Dr. Romeu Tórtima, 452/466 – Barão Geraldo – Campinas – SP;

– You should use the product for up to 56 +/- 2 days based upon the recommended use explained by the technician in charge and/or indicated in the Daily Home Product Use;

– If you agree to participate in the study, you will complete a questionnaires before using the product and at the end of testing. You will receive the product to be tested to use at home, and a home product-use diary to be filled out regarding the frequency of product use and any complaint about its use deemed necessary. By signing this consent form you guarantee the veracity of the information reported, and at the end of the study, you will bring the test products and the duly completed diary;

– Attendance will be required twice, and you will have to stay 3 1/2 hours at the start (T0) and 3 hours at the end of the research (T56);

– The expected outcome is to prove the efficacy of the hair cosmetic product, through subjects' perception, under recommended conditions of use.

– You should be the only one using the product;

– Applications, as well as any adverse event, should be recorded in the Mini-Diary you will receive;

– You may be dismissed by the dermatologist after you sign the free and clear consent form if you present any criteria that could exclude you from the research, and also if the existing vacancies have already been filled.

– If you are a woman, you must state that you are not currently pregnant or breastfeeding and that you commit to refrain from getting pregnant during the study period;

– Your consent does not exempt the organizers of the research center from their obligations;

– You are aware of the fact that on occasion a representative of the sponsor company may be present to observe the study;

– You accept that, within the context of the study, your data will be collected and may be subject to electronic processing. If any changes are made to your registration data (telephone number, address, etc...), please ask the study organizers to update them;

– You will be evaluated prior to the study by a trained technician and monitored during the study by a dermatologist.

ATTACHMENT 2 – FREE AND CLEAR CONSENT FORM CONTINUED

– If you present with any clinical signs in the area where the study product is applied, the affected area will be photographed for recording purposes, but your identity will be kept confidential;
– Any questions that arise during and after the study will be promptly answered;
– Your contribution will ensure a safe and effective product for the community;
– According to current legislation, you will receive no cash payment;
– You will be reimbursed for travel expenses at each visit. At the end of the study you will be reimbursed for your participation in the form of Carrefour vouchers in the amount of R$ 30.00;
– You may withdraw from the study at any time, but you must inform the institute of your withdrawal.
– You can be removed from the study if you do not fulfill your obligations, based upon the study protocol, at the researcher's discretion
– The study will conducted on 28 volunteers;
– You will participate in the study for 56 days / 8 weeks;
– Your voluntary collaboration will be of great importance to our work; therefore, we ask that you arrive on time and on the dates listed throughout the course of the study.
– If there is any change to your habits, we ask that you please tell us so we may better interpret the results;
- Do not use any type of product (for example: deodorant or antiperspirant, talcum powder, bath oils, creams, lotions, perfumes, colognes, or topical medications) on the areas around the test area. If you use any of these products or take systemic medication, please let us know;
– In the event of intense itching or other strong signs of irritation, immediately report it and come to the test-application location, or call us at 19-3789-8615 (business hours) or 19-9778-0204 (24h);
– We guarantee that any adverse reaction caused by the tested product will be monitored by the dermatologist and/or specialist in charge of the project, and if necessary, proper medication will be provided.
– Potential indemnifications are insured.
– We guarantee that any new relevant information that may interfere with your consent with be reported;
– All raw materials used in the product are approved for topical use and are not toxic. However, like any product, it may cause unexpected reactions such as “reddening,” “swelling,” “itching,” and “burning” in the areas where the product is applied.

ATTACHMENT 2 – FREE AND CLEAR CONSENT FORM
CONTINUED

– All information collected volunteers will be kept confidential. However, when you sign this form, you allow the sponsor and regulatory authorities to audit all documents and research data;
– If you have any questions or problems, you may contact the medical team at 19-3789-8615.
– One copy of this form will remain on file at Allergisa and another will be given to the volunteer.

I agree to participate in the study **"EVALUATION OF PERCEIVED EFFICACY UNDER REAL CONDITIONS OF USE**" and I state that all of the aforementioned items have been explained to me.

01

Volunteer's Signature *(same as the R.G. or Driver's License C.N.H.)* Date

Witness *(complete first and last name, no abbreviations)*

Identification (R.G.) number

02

Area Code Telephone number

Witness' Signature *(same as the R.G. or Driver's License C.N.H.)* Date

Only complete this section if the volunteer is illiterate.

03

Signature of the Person In Charge of applying the TCLE Date

ATTACHMENT 3 – PRODUCT FORMULA

SPECTRAL.DNC-N®

ATTACHMENT 4 – QUESTIONNAIRES FOR THE SUBJECTS' EVALUATION

Subjects' Profile Questionnaire
Classification of hair characteristics before using the product (T0)

01 - With respect to **hair LOSS**, you have:

( ) intense loss

( ) moderate loss

( ) little loss

( ) no hair loss

02 - With respect to **STRENGTH**, your hair is:

( ) very strong

( ) moderately strong

( ) weak

( ) very weak

03 - With respect to **SPEED OF GROWTH,** your hair:

( ) grows very quickly

( ) grows moderately quickly

( ) grows slowly

( ) grows very slowly

ATTACHMENT 4 – QUESTIONNAIRES FOR THE SUBJECTS' EVALUATION

Perceived efficacy questionnaire

Comparison of Hair Characteristics after Using the Product – T56

01 - After using the product, your **hair** loss:

( ) decreased a lot

( ) decreased moderately

( ) decreased a little

( ) is the same, I didn't notice a change

( ) increased a little

( ) increased moderately

( ) increased a lot

02 -After using the product, the **STRENGTH** of your hair:

( ) increased a lot

( ) increased moderately

( ) increased a little

( ) is the same, I didn't notice a change

( ) decreased a little

( ) decreased moderately

( ) decreased a lot

03 - After using the product, the **SPEED OF GROWTH** of your hair:

( ) increased a lot

( ) increased moderately

( ) increased a little

( ) is the same, I didn't notice a change

( ) decreased a little

( ) decreased moderately

( ) decreased a lot

ATTACHMENT 4 – QUESTIONNAIRE FOR JUDGE'S EVALUATION CONTINUED

04 - Regarding the phrase **"Using the product led to less hair loss,"** you:

( ) fully agree

( ) agree

( ) neither agree nor disagree

( ) disagree

( ) completely disagree

05 - Regarding the phrase **"Using the product made my hair stronger,"** you:

( ) fully agree

( ) agree

( ) neither agree nor disagree

( ) disagree

( ) completely disagree

06 - Regarding the phrase **"After using the product, I noticed an increase in hair growth,"** you:

( ) fully agree

( ) agree

( ) neither agree nor disagree

( ) disagree

( ) completely disagree