



## PRODUCT INFORMATION & OUR SCIENCE

# StemceleX

## Hair Restorative Topical Lotions



### StemceleX: Our Unique Scientific Approach

StemceleX is the latest medical breakthrough within the field's major areas of hair loss study and medical knowledge: functional genomics, steroid hormones, and signal transduction, all focusing on the relationship between steroid hormone, adenyl cyclase in the cell membrane and cell survival (including stem cells) in the human scalp. The hair follicle is one of a few human tissues containing stem cells. The stem cells are interspersed within the basal layer of the outer sheath and in an area called the bulge. From this reservoir stem cells migrate to hair matrix and start to divide and differentiate. Their behaviour is controlled by numerous cytokines produced by cells of the dermal papilla. Dermal papilla cells and some cells of the inner and outer sheaths of the follicle from androgen-dependent hairs have androgen receptors in their cytoplasm and nucleus. Androgens indirectly control hair growth by influencing the synthesis and release of cytokines from the dermal papilla cells.

Testosterone is the principal circulating androgen in humans and is converted to dihydrotestosterone in a reaction catalyzed by the enzyme 5-alpha reductase. The effect of androgens on scalp hair loss may be mediated through changes in intracellular concentrations of cyclic AMP (cAMP). The effect of various sex hormones on the activity of adenyl cyclase in the follicles of scalp hair has been tested with results indicating that dihydrotestosterone inhibits adenyl cyclase activity and that testosterone does not. (Richardl.De Villez et al.) It has been suggested that dihydrotestosterone level in hair follicle can initiate baldness by inhibiting adenyl cyclase.(Vera Price et al.)

An article published J. Soc.Cosmet. Chem., 21, 901-924 (Dec.9, 1970) Human Hair Follicle; Metabolism and Control Mechanisms\* Kenji Adachi, M.D. Ph.D., Susumu Takayasu, M.D. Iwao Takashima, M.D. Motonari Kano, M.D. and Shigeo Kondo, M.D. Presented May 26-27, 1970, New York City. Synopsis:- Recent investigations on the METABOLISM and metabolic mechanisms of HUMAN HAIR FOLLICLES to elucidate certain molecular bases for the etiologic factors of common baldness are summarized. Studies on CARBOHYDRATE metabolism, TESTOSTERONE metabolism, and the ADENYL CYCLASE system of human hair follicles, suggest the following mechanisms of transformation of the hair follicles from the terminal to the vellus type: Testosterone carried in plasma reaches the hair follicles, where it is converted to 5 $\alpha$ -dihydrotestosterone, a tissue active androgen. Since the hair follicles have sufficient 5 $\alpha$ -reductase to catalyze this conversion, the intracellular level of TPNH is presumed to be the rate-limiting factor at this step. The growing hair follicles appear to generate sufficient TPNH via the pentose cycle. Probably 5 $\alpha$ -dihydrotestosterone but not testosterone is the tissue – active androgen,



since adenyl cyclase in the hair follicles is markedly inhibited by 5 $\alpha$ -dihydrotestosterone but not testosterone. Inhibition of adenyl cyclase decreases the intracellular level of cyclic AMP. This decrease of cyclic AMP, in turn will create premature completion of the anagen state. Years of repetition of this premature completion probably produces the short vellus type hairs and hair follicles. Although solid proof for the entire process of BALDNESS is not yet available, the initial roles played by 5 $\alpha$ -dihydrotestosterone and adenyl cyclase are highly significant in these complex mechanisms.

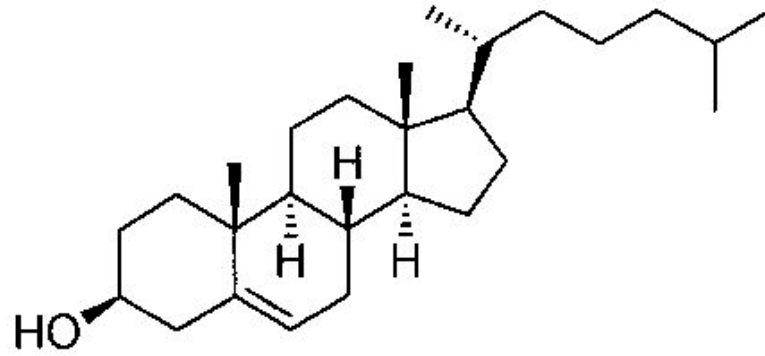
In simple terms four types of relationships between hair growth and androgens can be defined: (1) no androgen dependence lanugo, eyebrows eyelashes (2) dependence upon adrenal androgen and hence equal growth in men and women, axillary and lower pubic hair; (3) dependence upon testicular androgen upper pubic, facial, ear, extremity and truncal hair; and (4) inhibition by testicular androgen, scalp hair. The reason different body regions respond differently to the same or similar androgen is unknown. (Harrison's Principals of Internal medicine)

The sonic hedgehog pathway may also play an important role in male and female pattern baldness. In the skin, sonic hedgehog (Shh) is required for hair follicle morphogenesis during embryogenesis and for regulating follicular growth and cycling in the adult. Recent studies indicate that topically applied hedgehog (Hh) agonist can modulate cycling in adult mouse skin. The Hh-agonist stimulated the transition from the resting (telogen) to the growth (anagen) stage of the hair cycle in adult mouse skin, suggesting that topical application of Hh-agonist could be effective in treating conditions of decreased proliferation and aberrant follicular cycling in the scalp including androgenetic alopecia (Paladini et al, Journal of Investigative Dermatology. 2005; Volume 125 page 638).

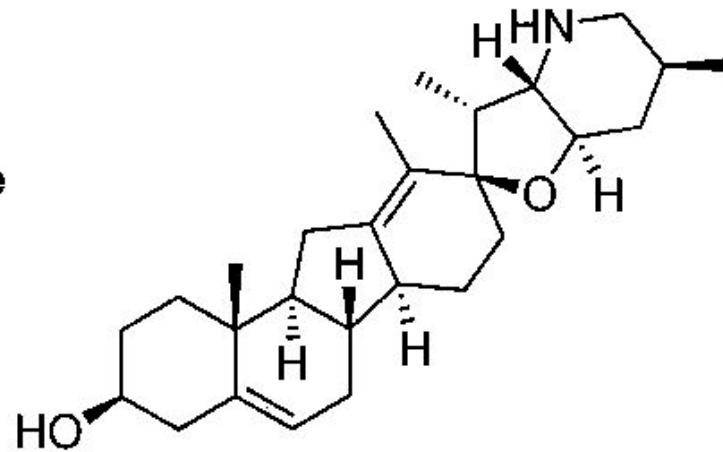
There is growing evidence that implicates a role for sonic hedgehog (SHH) in morphogenesis of the craniofacial complex. Mutations in human and murine SHH cause midline patterning defects that are manifested in the head as holoprosencephaly and cyclopia. In addition, teratogens such as jervine, which inhibit the response of tissues to SHH, also produce cyclopia. (Hu, 1999).

Plant-derived steroidal alkaloids are potent teratogens and block response to sonic hedgehog signaling. An additional experimental model for HPE derives from the occurrence of epidemics of congenital craniofacial malformations among newborn lambs on sheep ranches in several National Forests of the western USA ( W. Gaæeld, R.F. Keeler, J. Toxicol. et al 15 (1996) 303^326). The most dramatically affected lambs showed severe HPE, including true cyclopia and other craniofacial malformations characteristic of HPE. The occurrence of these defects was traced to grazing by pregnant ewes on the range plant *Veratrum californicum*. ( W. Binns, L.F. James, J.L. Shupe, G. Everett, Am. J. Vet. et al Res. 24 (1963) 1164^1174). The compounds responsible were identified by Keeler and Binns (R.F. Keeler, W. Binns, et al, Teratology 1 (1968) 5^10), as a family of steroidal alkaloids; the structures of two of these, cycloamine and jervine, are shown as compared to cholesterol in Fig. 1.

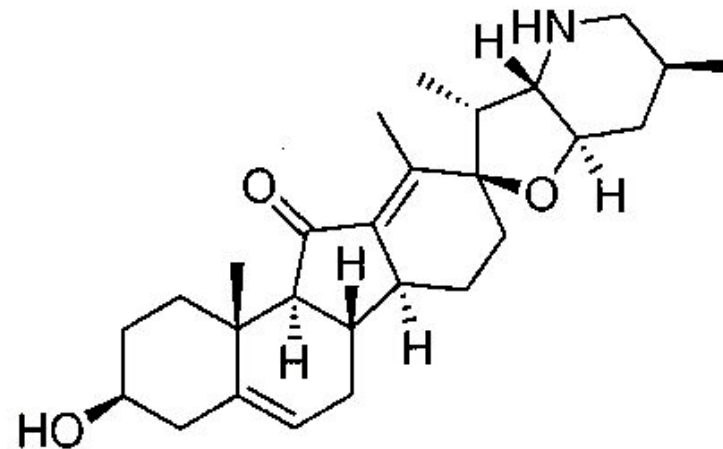
cholesterol



cyclopamine



jervine



**Fig.1.** Cholesterol and two plant-derived teratogens, jervine and cyclopamine. Despite similar ring structures and other shared features (e.g. hydroxyls in the B orientation at position 3 as well as an olefin



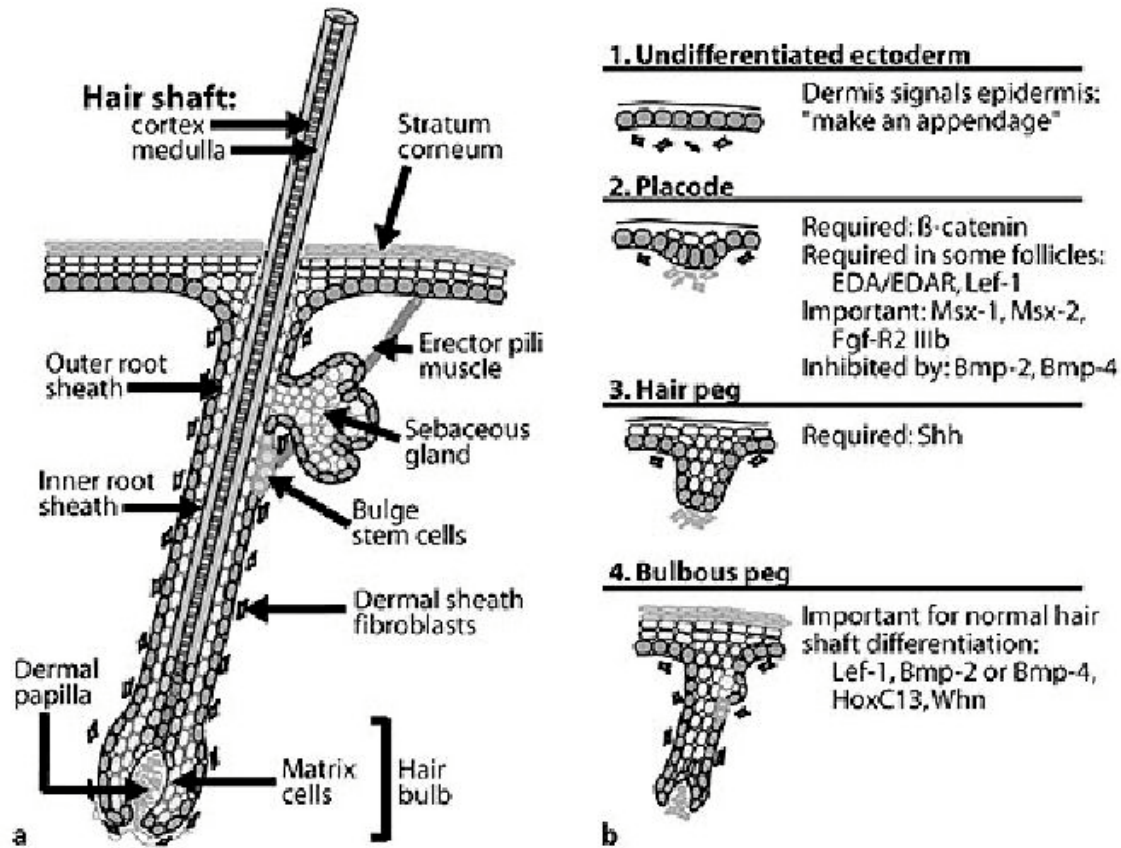
at position 5) these teratogens do not interfere with the cholesterol modification of Hedgehog *in vivo* or *in vitro*.

This signaling system controls the development of many different organs. "If we can find out more about how the signaling system regulates the behavior of stem cells, we may be able to develop new treatments for not only hair loss but also for cancer", (says Amel Gritti-Linde, associate professor in oral biochemistry at the Sahlgrenska Academy.)

According to recent study of George Cotsarelis, MD. Chair of the Department of Dermatology at the University Of Pennsylvania School Of Medicine has found that Male Pattern Balding may be due to stem cell inactivation and researchers surmised that balding may arise from a problem with stem-cell activation rather than the numbers of stem cells in follicles. In male pattern balding hair follicles actually shrink; they don't disappear. The hairs are essentially microscopic on the bald part of the scalp compared to other spots. Cotsarelis says we are surprised to find the number of stem cells was the same in the bald part of the scalp compared with other places, but did find a difference in the abundance of a specific type of cell, thought to be a progenitor cell, this implies that there is a problem in the activation of stem cells converting to progenitor cells in bald scalp.

The SHH also regulates sebaceous gland development and activation leads to a striking increase in both the size and number of sebaceous glands. Remarkably, ectopic hedgehog signaling also triggered the formation of sebaceous glands from foot pad epidermis in regions normally devoid of hair follicles and associated structures. (Am Pathol et al, American Journal of Pathology, Vol. 163, No. 6, 2173-2178, December 2003 Copyright © American Society for Investigative Pathology)

A new study published in Science Daily on June 14, 2011 by researchers at NYU Langone Medical Centre has shown that, for first time, Wnt signalling, already known to control many biological processes, between hair follicles and melanocyte stem cells can dictate hair pigmentation. Using genetic mouse models, researchers were able to examine how Wnt signalling pathways enabled both hair follicle stem cells and melanocyte stem cells to work together to generate hair growth and produce hair color. Research also showed the depletion (or inhibition or abnormal) Wnt signalling in hair follicle stem cells not only inhibits hair re-growth but also prevents melanocytes stem cell activation required for producing hair color. The lack of Wnt activation in melanocyte stem cells leads to depigmented or gray hair.



**Fig. 2. Basic hair follicle morphogenesis.** a Schematic of fully developed mid-anagen hair follicle. Cells of the dermal papilla and the dermal sheath are mesenchymal in origin; all other cells depicted derive from the epithelium. Layers not shown: outer root sheath: companion cell layer; inner root sheath: Henley's layer, Huxley's layer, cuticle; hair shaft: cuticle. Note the capillary bed in the dermal papilla and the erector pili muscle which inserts at the bulge and is associated with a network of nerves. b Schematic of hair follicle morphogenesis. Several important signaling steps are noted to the right. EDA = Ectodysplasin; EDAR = ectodysplasin receptor; Lef-1 = lymphoid enhancerbinding factor 1; Fgf-R = fibroblast growth factor receptor; Bmp = bone morphogenetic protein; Shh = sonic hedgehog; Whn = winged-helix nude. dergo(Source:- Molecular Genetic and Endocrine Mechanisms of Hair Growth Laura C. Alonso, Robert L. Rosenfield. The Rockefeller University, New York, N.Y. and The University of Chicago Children's Hospital, Chicago, Ill., USA)

Hair and sebaceous glands almost always occur in association as the duct of sebaceous gland opens into the associated hair follicle. The dermis contains smooth muscle. In the hairy skin this forms the pilo-erector muscle attached to the follicle. The orientation of the hair is determined by the angle of the



follicle to the epidermal surface. The hairs can be erected by the sympathetically innervated pilomotor (or arrector pili) muscles.

Dandruff is the shedding of scales from the scalp. The rate of growth of the horny layer of the scalp is generally more rapid than of skin elsewhere. Entrapment of the scales in the hair makes the normal loss of the superficial layers of the stratum corneum more noticeable. The admixture of skin secretions (sweat and sebum) with the scales makes the appearance of dandruff even more obvious. One of the constituents of the sebum (dandruff) or the oil secretion of sebaceous glands is a chemical known as squalene. Recent research reports have indicated that this chemical, in adequate concentrations, act as a depilatory on animal skin it is most harmful for normal hair growth. ( Illustrated Medical and Health Encyclopedia , Morris Fishbein,M,D.)

Pattern baldness is a common type of baldness in adult males. It is of various type but all are genetically determined. Affected males are usually heterozygous for the gene and it is on an autosomal chromosome; its expression requires high levels of circulating androgen, and castration before puberty prevents the occurrence of baldness. Homozygotes for the gene respond to lower levels of androgens and are affected earlier in adult life and occasionally baldness occurs in female who are homozygous for the trait; the source of androgens being the adrenal cortex. Substances alleged to be of benefit in correcting alopecia include cholesterol and jaborandi (an extract of the leaves of the plant from which pilocarpine is obtained) there is no convincing evidence that they are effective. (W.C Bowman/M.J.Rand, Textbook of Pharmacology second edition page # 32.9)

Hair loss can also be caused by underlying medical problems, drugs, infections and a variety of other factors. Medical problems that can cause diffuse hair loss include: anemia, connective tissue diseases (such as Lupus), severe nutritional deficiencies, surgical procedures, general anesthesia, and severe emotional problems and in patients with hypofunction of the anterior pituitary or thyroid glands. In women, obstetric and gynecologic conditions, such as post-partum and post-menopausal states, and ovarian tumors can cause hair loss.

The hair follicle is one of a few human tissues that contain stem cells. Stem cells of the hair follicle are gathered in the basal layer of the outer roots sheath and it is from these cells that the matrix cells are formed. The matrix sits over the dermal papillae and contains actively dividing, immunologically privileged cells. Together, the dermal papillae and the matrix are referred to as the hair bulb. The size of the bulb and the number of matrix cells will determine the width of the fully-grown hair. The cells of the matrix differentiate into the three main components of the hair follicle: Outer Root Sheath (ORS), Inner



Root Sheath (IRS) and the hair shaft. The ORS or tricholemma (Greek for coating sac) surrounds the hair follicle in the dermis and then blends into the epidermis on the surface of the skin, forming the structure commonly referred to as the pore (from which the hair emerges).

The epithelial stem cell niche is located in the hair follicle bulge, which is part of the ORS that is in continuity with the interfollicular epidermis and sebaceous Gland. Hair grows from cells located at the base of the hair follicle. Hair follicles continuously cycle through growth, rest, and re-growth phases. It is suspected from our clinical research and scientific understanding that stem cells, located within the follicle bulge, are partially responsible for hair growth.

### **Who may use Stemcelex?**

Stemcelex may only be used (topically applied) by adult men and women 18 years of age and older who are expecting or experiencing gradually thinning hair or hair loss from the scalp or outer 1/3 of eye brows.

### **Who should not use Stemcelex?**

Pregnant or breastfeeding women, children under age of 18 years, patients with previous skin disease, low blood pressure, hyperthyroidism and broken scalp skin should not use Stemcelex. Pilocarpine and veratrum (active ingredients of Stemcelex) has shown to increase the rate of birth defects in animal studies.

### **Should I perform a topical patch test before using Stemcelex?**

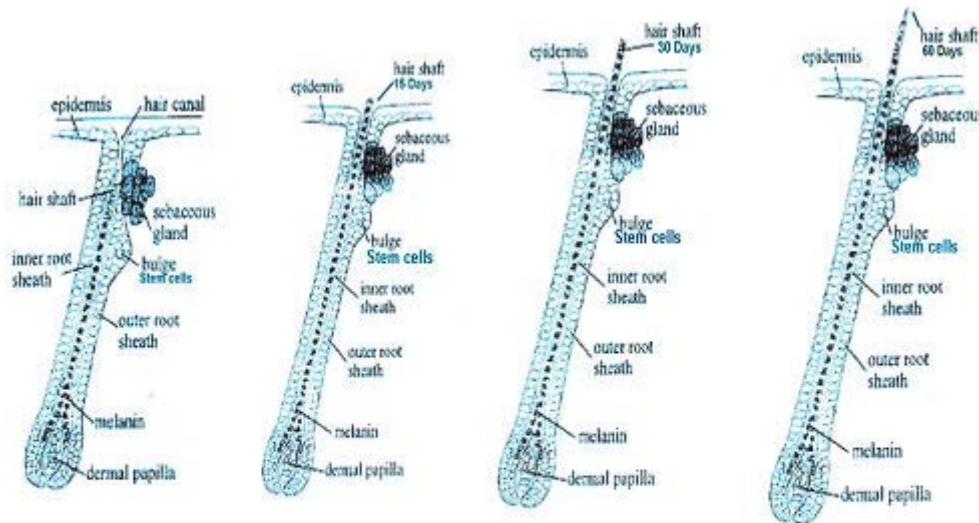
It is advised to perform a patch test before applying Stemcelex, according to the suggested dosage and application coverage (see label information), to scalp. To conduct a patch test, place a small amount of lotion on a pad or swab and apply to a small area of the scalp. Leave the Stemcelex application in place and monitor your skin closely for a period no less than 24 hours and to a maximum of 72 hours. Each Stemcelex lotion is to be tested separately not together and on different areas of the scalp.

### **Will Stemcelex work for everyone?**

The amount of hair re-growth may be different for each person and may also depend on each individual's genetics factors. A Stemcelex user may respond better if you have been losing hair for a shorter period of time. In clinical studies mostly males subject were either in the initial stages of baldness or completely bald. These subjects, in addition to using the Stemcelex topical applications, also took a tincture of Fucus vesiculosus (5-10 ml; prepared as per the Homeopathic Pharmacopeia) orally before meals. These subjects observed a thickening and darkening of the very thin and weak hair within 1-3 days of using the combined Stemcelex lotions. After 4-6 weeks of applying the combined Stemcelex lotions the conversion



of new hair into terminal hair was observed. The new hair becomes thicker and darker within 4-6 weeks of continuous use of Stemcelex. Please do not use Medicago sativa (alfalfa) herbal tablets or androgenic hormonal treatments during periods of using Stemcelex topical lotions.



## Differentiation of the hair shaft using Stemcelex in 15, 30 and 60 days

All subjects were individually and carefully instructed on the proper scalp application of all three separate Stemcelex lotions and oral consumption of a supplemental herbal tincture (not included in Stemcelex packaged kits). All subjects demonstrated new hair growth after properly using the Stemcelex lotions. The re-growth of hair was first noticed in some subjects as early as two weeks into the treatment. By the third week a substantial number of men and women demonstrated moderate re-growth, with both fine vellus hairs and darker pigmented intermediate and terminal hairs being observed. There was partial and general whitening of hair re-growth observed in some patients during the Stemcelex treatment.

Apart from our clinical research, some of the active medicinal ingredients of Stemcelex have been traditionally used in shampoos, head lice lotions, dandruff treatments, hair shine and grooming products, and also used in ancient Europe to promote new hair growth. Our investigative research has uncovered that some of the active ingredients used to formulate Stemcelex lotions have been used by ancient people for hair re-growth. Although the broadly accepted references to our active ingredients in general pharmacopeia recommends their use for various conditions of hair, the Stemcelex lotions represent a unique combination and use of these active herbal ingredients for hair re-growth.



## How do plant materials help us understand StemceleX hair re-growth?

The relationship between man and plants by means of their remedy activity has always been very close during all cultural epochs. Despite the significant achievement of synthetic organic chemistry in the field of pharmaceuticals the interest in the medicinal plants and the medicines isolated from them is constantly increasing. Because of the fact that biologically active compounds of plants are products of living organism than the chemically foreign synthetic pharmaceuticals. Therefore, the phytotherapy is much appropriate than the synthetic medication therapy. For an example amino acids are best known as the building blocks of protein, and that is the main function of the 20 amino acids that are commonly found in proteins (both plant and animal). Hair is composed of protein, and it grows from the hair follicles that lie within the skin's dermis layer. Protein, including hair protein, is composed of linear amino acid chains. Amino acids help build new cells and play important roles in cell metabolism.

Cysteine, methionine, cystine, arginine and lysine are the five types of amino acids that seem to have an effect on hair growth. Mixtures of plant proteins can serve as a complete and well-balanced source of amino acids for meeting human physiological requirements. Steroids also play a role as essential hormones in plants as well as in animals. Plants produce numerous steroids and sterols some of which are recognized as hormones in animals.

Steroidal alkaloids are an important class of natural products characterized by the cyclopentenophenanthrene ring with the incorporation of nitrogen. These alkaloids occur both in plants and animals and are interesting from their structural viewpoint. Such alkaloids display a wide range of pharmaceutical and chemical properties. Biogenetically, they are related to cholesterol, and both the steroidal alkaloids and cholesterol having common biogenetic precursors. In the chemistry of the steroids the extensive range of widely occurring natural substances, possessing a tetracyclic carbon skeleton which plays such a profound role in biological processes.

Jervine and cyclopamine are two steroidal alkaloids derived from plants of the genus *Veratrum*. Both substances are found in *Veratrum* plants and both block the synthesis of cholesterol. It has been demonstrated that jervine exert teratogenic effects in several animal species. Prenatal exposure to these compounds has been shown to cause craniofacial and limb malformations in sheep, goat's cattle, chickens and two strains of mice. Research on jervine teratogenicity in mice established that the type of defects produced was related to the time of treatment, genetic background and the dose. In all cases, peak effectiveness of *veratrum*-teratogens occurred prior to morphological differentiation of the target tissue. Because of its temporal and tissue specificity, researchers have investigated jervine sensitivity as a potential marker of early prechondrogenic stem cell populations.

Research shows that an interesting comparison can be made between the action and effects of jervine and that teratogen, retinoic acid. Retinoic acid also causes limb defects in a proximodistal and cephalocaudal gradient which is dependent upon the time of treatment. (Campbell MA, Brown KS, Hassell JR, et al) It has also been shown that these compounds specifically block the SHH signaling pathway (Cooper et al). However, studies indicate that jervine acts specifically during an early phase of the differentiation of mesenchyme into cartilage. It is surmised that a specific stem cell population is the target tissue of this compound (Campbell MA, Brown KS, Hassell JR, et al). Jervine is similar to retinoic acid. All trans Retinoic acid was reported to in the 1980 to lengthen anagen, promote hair growth when applied topically to mouse and human skin. (Laura C Alonso & Robert L. Rosenfield et al.) The Rockefeller University, N.Y. and the University of Chicago Children Hospital, USA



The Steroids are a widely-occurring group of natural products mostly possessing the tetracyclic carbon skeleton I. The many analogous synthetic compounds are conveniently included in the class. The diversity of natural compounds comprised by the group results primarily from variation in the side chains R1 R2, and R3 and secondarily from differences in nuclear substitution and in the degree of unsaturation. R1 and R2 are generally methyl groups, which may occasionally be oxygenated as in isorubijervine (R1 = --CH<sub>2</sub>OH), strophanthidol (R2 = --CH<sub>2</sub>OH), aldosterone (R1 = --CHO) and strophanthidin (R2 = --CHO). R2 is absent in the oestrogenic hormones and other steroids having ring A and or B aromatic. The side chain R3 may comprise two, four, five, eight, nine or ten carbon atoms; if it is absent, the position is usually oxygenated. Steroid may be broadly classified in Table 1. Some representative of most of the types listed has been converted by dehydrogenation with selenium into the cyclopentenophenanthrene (II: R=H; 16,17- dihydro-15H-cyclopenta[x] phenanthrene or its 17-methyl derivative (II:R=Me; the "Diels hydrocarbon". (Rodd's Chemistry of Carbon Compounds , Second Edition Volume II Alicyclic Compounds Part D).

Steroids have a variety of uses in the human body, including but not limited to fat storage, muscle growth, immune function and nerve cell membranes. Aldosterone, steroid hormone secreted by the adrenal cortex helps the kidneys regulates the amount of salt and water in human body and thus regulates blood pressure. ACTH's principal function is to stimulate the cortex of the adrenal glands to secrete a group of steroid hormones called glucocorticoids, mineralocorticoids and androgens steroids. Glucocorticoid hormones control the body's use of sugar and also help regulate biological functions during stressful moments.

Mechanisms by which ACTH Activates Adrenocortical Cells to Produce Steroids—Function of Cyclic AMP. The principal effect of ACTH on the adrenocortical cells is to activate adenyl cyclase in the cell membrane. This then induces the formation of cyclic AMP in the cell cytoplasm, reaching maximum effect in about 3 minutes. The cyclic AMP in turn activities the intracellular enzyme that cause formation of the adrenal cortical hormones. Thus this is another example of cyclic AMP as a second messenger hormone. The most important of all the ACTH – stimulated steps for controlling adrenocortical secretion is activation of the enzyme desmolase that causes initial conversion of cholesterol to pregnenolone. This initial conversion is the "rate-limiting" step for all the adrenocortical hormones, which explains why ACTH normally is necessary for adrenocortical hormones to be formed. Long term stimulation of the adrenal cortex by ACTH not for only increases secretory activity but also causes hypertrophy and proliferation of the adrenocortical cells, especially in the zona fasciculata and reticularis where cortisol and the androgens are secreted. (Textbook of Medical Physiology Guyton An HBJ International Edition)

Pregnenolone for example, is highly effective but is almost devoid of androgenic potency (Selye and Albert, 1942) and an excellent sustainer of testis function in hypophysectomized rats, (Appelzweig, N 1962 "Steroid Drugs" McGraw-Hill, New York) and thus it's reduces body hair. Steroidal alkaloids have been used for inhibiting unwanted hair growth or inhibiting spermatogenesis. (Under US patent No. 708974 Issued on March 15, 2005 assignee Johns Hopkins University School of Medicine)

Steroidal alkaloids arise by the inclusion of a basic nitrogen at some point in the steroid molecule. Those of the C<sub>27</sub> group include the Solanum alkaloids in relation to their potential as steroid precursors, and the Veratrum alkaloids considered which have a similar structure. A second, C<sub>21</sub> group of which many examples are found in the Apocynaceae (Holarrhena and Funtumia) and in the Buxaceae probably arise from pregnenolone by amination at either C-3 or C-20. Conessine is a common alkamine of the group and represents a desirable starting material for the synthesis of some hormones, e.g. aldosterone.



(Pharmacognosy, page # 618, George Edward Trease and William Charles Evans, Baillere Tindall London.) Pregnenolone that activate adenyl cyclase as doe's forskolin; plant ingredient(see below).. (Forskoline drug is widely used in studies aimed at dissecting the intercellular signaling pathway)

Jaborandi /Pilocarpus, Traditionally it is used as an external hair tonic which is believed to open pores and clean hair follicles, prevent hair loss, and generally aid in the manageability of hair. It is frequently employed in alopecia. (References:- The Eclectic Materia Medica, Pharmacology and Therapeutics by Harvey Wickes Felter, M.D. (1922) and Tropical Plant Database present by Raintree Nutrition, Inc. Carson City, NV 89701)

In the scientific research refering to Chemistry of Natural Compound Vol. 42 NO.1 2006 the alkaloids accumulation dynamics in Veratrum lobelianum were investigated. Jervine was found 0.02 to 011% in the subterranean part all vegetation stages. The jervine content was greatest in subterranean plant organs, reaching a maximum (0.3%) during natural dying off of aerial organs. Jervine a natural analog of serotonin can be used as a specific fibroblast growth factor. Studies show that the mammalian skin can produce serotonin and transform it into melatonin. The hair follicle may be an important target for pharmacological intervention by melatonin. In this context, melatonin or its derivatives could be used in the management of alopecia and/or for regulation of hair growth and pigmentation. Moreover basic fibroblast growth factor (bFGF) and platelet- derived growth factor (PDGF) essential to affect hair growth.

Veratrum lobelianum traditional uses of the rhizome and root in Bulgaria include high blood pressure, asthenia, palpitations, apoplexy, diarrhea, whooping cough, gastrointestinal discomfort, headache, exhaustion , etc., and externally – against dandruff for hair strengthening and stimulate hair growth. It has been used in ointments for rheumatic joints, against scabies and lice. (References( [1], Medicinal plants in Bulgaria and their use, Second complete edition Sofia 1973, "Zemizdat" State Publishing House, [2], Modern Phytotherapy , Compiled by Corresponding Member of the Bulgarian Academy of Science, Prof.Dr.Vesselin Petkov, Medicine and Fitness, Sofia 1982, and [3], Vegetable Resource, Russian Academy of Science, N.K. ABUBAKIROV, L. BELENOVSKAA, I. GRUŠVICKIJ, I. S. KOŽINA, HA. KUZNETSOVA: 1994.

Forskolin extract from coleus forskohlii which is also known as Plectranthus barbatus, is a plant used in traditional Ayurvedic medicine for the treatment of various conditions, including hypertension, congestive heart failure, respiratory disorders, and hypothyroidism. Coleus Forskohlii commonly used biochemical tool to raise levels of cyclic AMP (cAMP) in the study and research of cell physiology. Forskolin resensitizes cell receptors by activating the enzyme adenyl cyclase and increasing the intracellular levels of cAMP. cAMP is an important signal carrier necessary for the proper biological response of cells to hormones and other extracellular signals. It is required for cell communication in the hypothalamus/pituitary gland axis and for the feedback control of hormones. The physiological and biochemical effects of a raised intracellular cAMP level include inhibition of platelet activation, inhibition of mast cell degranulation and histamine release; increased force of contraction of heart muscle; relaxation of the arteries and other smooth muscles; increased insulin secretion and increased thyroid function. Also it acts by activating protein kinase A signalling pathway.

Published an Original Research Article "Several Selective Protein Kinase C Inhibitors Including Procyanidins Promote Hair Growth" Tomoya Takahashi\* Ayako Kamimura\* Akio Shirai\* Yoshiharu Yokoo\* Skin Pharmacol Appl Skin Physiol 2000; 13; 133-142 shows Forskolin an adenylate cyclise activator promote hair epithelial cell growth and boost the growth promoting effect of procyanidinB-2.



Treatment with topical forskolin can promote skin pigmentation and protect against the UV light-induced damage. Fair-skinned individuals do not tan when exposed to UV light due to a defective melanocortin 1 receptor (MC1R) gene – one of several genes that regulate skin, hair and eye color. The gene plays a key role in determining if a person has red hair, light skin and sensitivity to UV light. However, a functional MC1R is not required to achieve skin pigmentation. Dr. David E. Fisher, from the Dana Farber Cancer Institute in Boston and colleagues investigated the effects of UV light in mice lacking a working MC1R gene. UV light exposure induced melanocyte stimulating hormone expression in keratinocytes (skin cells) of these red / blonde-haired mice, but pigmentation did not take place. Melanocytes are a type of skin cells that produce pigment. Topical application of forskolin, however, caused pigmentation to occur without the need for UV light, showing that functional MC1R is, in fact not required. Testing in skin cancer-prone mice showed that forskolin treatment protected the animals from UV light- induced skin DNA damage. Nature,2006.

Another study published in Journal of Natural Products J.Nat. Prod, 2009, 72 (4),pp 769-771 DOI; 10.1021/np800541k “ In Vitro Skin Diffusion Study of Pure Forskolin versus a Forskolin containing Plectranthus barbatus Root Extract”. Abstract :- An in vitro skin diffusion study of pure forskolin (1) versus a 1-containing Plectranthus barbatus root extract (P. Barbatus extract) in hairless guinea pig skin and human skin in a flow-through diffusion cell system was conducted and is being reported for the first time. Both topical agents were formulated in a solution of 70% ethanol and 30% propylene glycol (v/v). The results showed that forskolin can be delivered through the stratum corneum and that the flux of this compound was enhanced when 1 was delivered as a constituent of the P.barbatus extract as compared to an equivalent amount in pure form. These results suggest that the P. barbatus extract used contain permeation enhancement activity from other compound(s) contained in the crude root extract. It is possible that P. Barbatus root extract may be used as an economical source of 1 to perform topical manipulation of pigmentation in high-risk populations.

### **Parasympathomimetic Herbs**

Very few common medicinal herbs have overtly cholinergic constituents that produce overall physiological parasympathomimetic action. The exceptions are restricted herbs, poisons, or foods not generally used in herbal medicine, such as the pilocarpine-containing *Pilocarpus* spp. (*Jaborandi*) and muscarine from *Amanita muscaria* and related toxic mushroom species. The Asian masticatory spice *Areca catechu* contains the muscarinic alkaloid arecoline, which is also nicotinic at higher doses. *Areca* is not used therapeutically in Western herbal medicine although the isolated alkaloids have been shown to cause bronchoconstriction and may exacerbate extrapyramidal effects of neuroleptic drugs.

Several western herbs are considered "parasympathomimetic-like" by herbalists primarily because of cardiovascular effects that resemble muscarinic cholinergic activity (hypotension, bradycardia). The pharmacology of these agents is either unknown, or results from complex mechanisms other than direct muscarinic agonism. For example, the veratrum alkaloids of *Veratrum* spp. (*Liliaceae*) have some cholinergic activity but their predominant bradycardic and hypotensive actions are more due to sodium channel blocking. (Reference: The Authoritative Clinical Reference Tool for Integrative Medicine and Alternative Therapies, , Integrative Medical Arts Group, Inc. • IBISmedical.com)

Perturbations in thyroid hormone levels alter hair growth. Hypothyroidism causes a reversible alopecia characterized by dull, brittle hair and increases in the percentage of follicle in telogen (resting stage). Initiation of thyroid replacement therapy results in shedding of scalp hair, possibly related to release of



club hairs from telogen follicles as they enter anagen. Loss of the lateral one third of the eyebrows is a classical sign of hypothyroidism. Hyperthyroidism also causes a reversible alopecia; in this case characterized by, thin, fine hair. (Laura C Alonso & Robert L. Rosen field et al,) The Rockefeller University, N.Y. and the University of Chicago Children Hospital, USA

Normal thyroid function requires an adequate intake of iodine, and its formation into thyroxine for hair growth. The major form of thyroid hormone in the blood is thyroxine. An excess of iodine in the body can adversely affect the thyroid. In hypothyroidism, cell metabolism slows down and body cells and hair cells don't receive the energy they need to function properly. The sea plant Kelp uniquely tops the list for the following nutrients: calcium, potassium, magnesium, iron, iodine, and is also very high in sulfur. (Heritage F, Composition and Facts About Food, Health Research, 1971)

Interestingly, seawater and human blood are almost identical in chemical constituency. No fewer than 92 different mineral elements have been found in seaweeds, including some elements which we require only in trace amounts, but whose presence is nonetheless vital to our complete well-being. Seaweeds contain many times more minerals than land grown plants; as much as 50 time more according to Dr W Black. (Black W, Proc Nutr Soc (Eng), 32, 1953)

Cells require a constant supply of energy to generate and maintain the biological order that keeps them alive. This energy is derived from the chemical bond energy in food molecules, which thereby serve as fuel for cells. Nutrients contain energy in low-energy covalent bonds, which are not very useful to do most of kinds of work in the cells. These low energy bonds must be translated to high energy bonds, and this is a role of adenosine triphosphate ATP. Since ATP appears as a critically important macromolecule in the transfer of energy to cells, Engelhard decided to use its unique knowledge in cellular technology to develop a cosmetic active ingredient that specifically target this key molecule. A screening test was performed in order to select active compounds which act as cell energy booster through the specific stimulation of the enzymes responsible for the ATP synthesis. This ingredient selected for its highest performance is an algae extract based on Laminaria digitata, that is found in the North Atlantic rocky coasts. This product is now commercially available under the tradename Seanergilium BG. Its efficacy in cosmetic application to target dull and tired skins was demonstrated on a clinical study. (MARTIN LAURENT(Engeruhado · japan) Journal Title;FragrJ VOL.34;NO.3;PAGE.42-47(2006) Language;Japanese)

Study of OSAWA YUTAKA (Tekunoburu Raifusaiensuken) TAMAKI SHINOBU(Tekunoburu Raifusaiensuken) SAWAKI SHIGETOYO(Tekunoburu) TOMITA YASUSHI(Graduate School, Nagoya Univ., JPN) Journal Title;Journal of SCCJ, VOL.38;NO.1;PAGE.10-14(2004) Language;Japanese) Abstract :- The mechanism of hair growth has been clarifying itself by the improvement in the culture techniques for hair follicle cells. Recently stem cells inducing the anagen phase in the hair follicle cycle have been discovered in the bulge region of the outer root sheath (ORS). To find growth-promoting agents for the ORS cells, we evaluated the effect of various botanical extracts on the growth of cultured human hair follicles. We found that Laminaria angustata extract increased the ORS cell growth. Further, hair-growth in the shaved skin of C3H mice was also promoted by the topical application of the extract.



**STEMCELEX IS A THREE-PART, SEPARATELY-APPLIED, TOPICAL LOTION (FIRST, SECOND AND THIRD APPLICATIONS) TO BE USED IN SEQUENCE AND HAS SEPARATE BUT RELATED SCIENTIFIC EFFECTS ON SCALP HEALTH AND HAIR RE-GROWTH.**

### **FIRST APPLICATION**

Jaborandi Pilocarpus (Imidazol alkaloids) Leaf extract, Ethyl alcohol 93% Propylene glycol 2%

#### **Route of Administration: Topical**

Directions for use: - Wash hair and scalp with mild shampoo then apply to dry thoroughly. Apply 5-10 drops twice daily to balding area or the area from hairs shedding. Use fingertips slowly to penetrate lotion thoroughly into the scalp and continue rubbing for one minute. Wait to dry at least 1-2 minutes before applying second application.

**Benefits:** - Jaborandi extract to clean the hair follicle, remove dandruff, and open the pores (from which the hair emerges) of the scalp skin blocked due to sebum and other constituent triglycerides, squalene, cholesterol wax esters and cellular debris. Pharmacologically and traditionally applied pilocarpus and pilocarpine are accredited with the rather singular effect of causing the hair to become darker in color, and to stimulate the growth of that appendage it is frequently employed in alopecia. The smooth muscles of organs respond in general to both pilocarpine and muscarine as such the hair can be erected by using this first application lotion on scalp. Jaborandi extract has ability to induce sweating and producing the secretion of saliva.

#### **Side Effects**

No adverse side effects for topical application except in cases of mild itching. Over dose or after oral administration, the most common side effects are sweating, urinary and gastrointestinal disturbances are also frequently reported. Pilocarpine is a parasympathomimetic drug and there is some risk of cardiovascular and pulmonary effects that make systemic administration somewhat dangerous.

Both jaborandi and pilocarpine may cause headaches and can irritate the stomach and cause vomiting and nausea, rapid pulse, contracted pupils, diarrhea or fatal pulmonary edema. Those with cardiac or circulatory conditions should not take jaborandi. Jaborandi may induce dehydration due to excessive perspiration and urination.

### **SECOND APPLICATION**

Names: -

- a) Veratrum Lobelianum (Steroidal alkaloids) Rhizome and root extract= 50%
- b) Plectranthus barbatus (Coleus forskohlii) Rhizome and root extract= 50%, Ethyl alcohol 93% propylene glycol 2%.



### **Route of Administration: Topical**

Directions for use:- Apply 20-40 drops two times daily same area(s) of first application. Use fingertips slowly to penetrate lotion into scalp and continue rubbing for one minute. Wait to dry at least 1-2 minutes, before applying third application.

### **Benefits**

Veratrum & Forskohlii extract to penetrate through skin into hair follicle and stimulate hair nerves around the bulge region of the follicles, supplying natural pregnenolone and diterpene to increase the interacellular concentration of cyclic AMP and to down regulate the dihydrotestosterone (DHT). Activate dormant hair follicle stem cells modulating signaling in the hair follicle resulting rapid reversal the balding process and re-growth hair, on the scalp. Promote skin and hair pigmentation as does melanocytes, also removes parasites and louse.

### **Side Effects**

No adverse side effects for topical application except skin burning sensation and sneezing. Low blood pressure and sensation of dryness in the mouth and throat related to a need or desire to drink water and salt, if dryness is excessive increased 5-10 drops of first application.

Over dose or after oral administration, the most common side effects are veratrum is irritating and ingestion can result in a burning sensation in the upper abdominal and breast bone, followed by salivation, vomiting, gastric erosion, vertigo, headache bradycardia, and lowers blood pressure, lowers heart rate, blurry vision, hazy mind, arrhythmia lowers respiration rate. There have been several poisonings reported in humans with the different species, but all known had favourable outcomes.

### **THIRD APPLICATION**

Name: - Kelp (*Laminaria digitata* (Fucoidans)) stem extract, Ethyl alcohol 93% Propylene glycol 2%

### **Route of Administration: Topical**

Directions for use: - Apply 30 -50 drops twice daily same patch of second application. Use fingertips slowly to penetrate lotion into scalp and continue rubbing for one minute. Wait to dry at least 1-2 minutes, before applying comb.

### **Benefits**

Laminaria extract to supply nutrition to the new grown fine hair, stimulate thyroids receptor in the scalp, incassated the ORS cell growth decreasing skin thickness and promote healthy growing hairs.



### **Side effects**

No adverse side effects for topical application.

Over dose or after oral administration hyperthyroidism can be caused by the excessive ingestion of iodine. Typical symptoms of hyperthyroidism include: weight loss, sweating, fatigue, heart palpitations and frequent soft stools. The iodine content in kelp products has been associated with acne eruptions and may aggravate pre-existing acne. Elevated urinary arsenic concentrations have also been traced to the ingestion of kelp products. As such, alginate extracts used as a food and/or for a medicinal product should not exceed arsenic levels above 3.0 ppm and lead levels above 10.0 ppm based on the internationally recognized Food Chemicals Codex. More than 2000 mcg a day may also lead to interference of normal thyroid functions and other harmful side effects. People with thyroid disease should check with a doctor before taking supplements that contain kelp.

### **Precautions of three lotions**

For external use only (prepared with ethyl alcohol)

Keep from heat and open flame.

Keep this and all alcoholic lotion out of the reach of children.

Accidentally ingestion may cause serious effects. Call poison control centre immediately.

After using any of the lotions wash hands with soap and water.

### **Does StemceleX reduce body or unwanted hair in men women?**

StemceleX supplying pregnenolone in the hair follicle and activate adenylyl cyclase therefore the conversion of testosterone to dihydrotestosterone and the degree of 5- $\alpha$  reductase activity is low. Moreover, hedgehog signal transduction pathway e.g. which involve the use of steroidal alkaloids inhibiting unwanted hair growth or inhibiting spermatogenesis.

### **What should be taken orally during using of StemceleX for faster results?**

There is available powder or tablet form of *Coleus forskohlii* dietary supplements can be taken orally 200 mg to 500 mg along with tincture of *Fucus vesiculosus* 1-2 ml before breakfast, as per suggestion of physician. This would be helped to grow hair faster than the StemceleX using alone.

### **What happens if I completely stop using StemceleX?**

Hair needs regular nutrition and StemceleX, other than the active ingredients, is comprised of vitamin minerals and amino acids to supply the nutrients needed for the healthy growing of hair. Dandruff never stops and scalp-shedding skin cells are part of the normal cell production. With dandruff, scalp cell production is abnormally rapid. Therefore, using StemceleX lotions should continue reducing doses to keep hair health and re-growing. If you stop completely using StemceleX your natural pattern of hair loss may continue.



## **HOW TO CONTACT US?**

Contact person:-  
Mohammed Alal Khan  
Scientific Director  
Email:- [makhan@nf.sympatico.com](mailto:makhan@nf.sympatico.com)  
[canadamakhan@yahoo.com](mailto:canadamakhan@yahoo.com)

### **Island Laboratories Inc.**

Office:-  
160 Main Street St. George's, NL, Canada A0N 1Z0  
Tel: 709-6473551 Fax: 1-709-647-3487

Laboratory:-  
13, Lakeview Drive, Kippens NL. Canada A2N 3B9  
Tel: 709-6436140

Websites: [www.stemceleX.com](http://www.stemceleX.com)