REPLENOLOGY®

21 *to* GROW

21 Natural Scientific Pathways Shown to Stimulate Hair Growth and Prevent Hair Loss

Welcome to

REPLENOLOGY®

We're so glad you've made the decision to join us on this journey, where science, nature, and specifically formulated nutrition all converge to bring you better health. Replenology is the study of replenishing the nutrients we lose with aging or that are lacking in our daily diet, and the Replenology Hair System focuses on the nutrients linked to stronger, thicker, fuller, and more resilient hair.

In this guide, we've included our list of "21 to Grow" – 21 naturally occurring proteins, hormones, and signals shown through our rigorously tested and collected scientific data to help prevent typical hair loss and stimulate normal hair growth.

As scientists, we're interested in harnessing everything the latest studies and research can tell us about how natural processes in the body can re-energize follicles, support hair strength and re-stimulate the normal hair growth process. We personally know how hair loss can affect our lives and relationships, and we have dedicated ourselves to discover a different, more comprehensive approach to the challenge.

We are actively engaged in advanced research to demonstrate how the natural, regenerative powers of the body – combined with the right botanicals, vitamins and minerals – can be the key to a multi-pathway solution to thinning hair.

We know how important it is for you to understand what you're putting in and on your body; so, we created this guide to expand your knowledge of the real science behind the Replenology Hair System.

Please use this guide, glossary and the handy references included, and as always, feel free to contact us at info@replenology.com to ask us any questions!

TABLE OF CONTENTS

Each of your body's 5 million hair follicles, including the 100,000 to 150,000 follicles on your scalp, is a dynamic "mini-organ" according to the world-leading dermatologist and hair loss researcher, Ralf Paus[1].

As a mini-organ, there is a complex balance of molecular interactions required to keep each follicle normal to grow thick and healthy hair. Healthy scalp hair has a growth phase called anagen, which can last from 2 to 7 years, and a short resting phase, called telogen, which can last from 2 to 4 months between growth cycles. A normal scalp will have approximately 10 to 15% or 10,000 to 22,500 of the hair follicles in this resting phase at any time, therefore losing approximately 80 to 120 scalp hairs per day is normal.

When an imbalance occurs in the follicle, the growth phase can become shorter and the resting phase can become longer. Hair growing from these imbalanced follicles may also experience changes in rate of growth, thickness, strength and color. The visual effect can be noticed as thinning, when hair density in an area of the scalp is reduced by 25%. This thinning may or may not have a pattern. Sometimes these impacted follicles may still grow hair, although it may be shorter, thinner and colorless. This is known as vellus hair, which is similar to hair found on other parts of the body.

MOST LOST HAIR FOLLICLES REMAIN ACTIVE

Normal hair loss can be attributed to various non-disease related causes such as aging, stress, nutrient deficiency, pharmaceutical side effects, damage from hair treatment chemicals or chronic tension caused by various hair styles. Some hair loss conditions are permanent and others are temporary. Fortunately, more than 95% of both male and female hair loss sufferers have compromised, yet active, hair follicles. We have now found a way to wake those follicles up and support the growth phase. This is one of the key functions of the Replenology Hair System.

SOME HAIR LOSS IS LINKED TO AGING: SOME IS LINKED TO OUR DIET!

As a hair loss sufferer, you may ask why you are experiencing this condition. The rate of men experiencing hair loss is generally described as the same percentage as their decade in life, i.e. 20% in their twenties, 30% in their thirties, 40% in their forties and so on. For women, it is generally 30%, yet stage of life tends to be a greater influencing factor just before, during and after menopause. But younger women are also affected: today young women in their twenties and thirties are also experiencing hair loss in greater numbers[2].

Aside from the normal physiological and hormonal changes experienced with aging, many studies have confirmed the nutrient value of common foods has declined over recent decades while calorie consumption has increased. Strong evidence is also being published that sustained microdoses of exposure to many chemicals used in the food chain and cosmetics are also disrupting the body's normal biochemistry and hormonal balance. This results in reduced ability to absorb necessary dietary vitamins, minerals and other nutrients impacting healthy hair growth.

You may also be asking why, up to now, there has been no hair loss treatment with a substantial success rate. Hair loss can be an unwanted side effect of many medications, however there are 2 classes of drugs that have new hair growth as an unexpected side effect. These drugs are approved for hair loss treatment, however they have success rates as low as 25% and unfortunately, very different results for women compared to men. Each drug has its own side effect profiles including sexual dysfunction, itching, and in some cases abnormal and typically undesired hair growth, for example, facial hair on women.

Other approved products for hair loss include low level light laser therapy devices, although these too can have varying success rates based on gender and skin type. So the search for an alternative, definitive and scientifically proven proven answer was not successful - until the creation of Replenology.

There are new drugs and interventions in development and many surgical methods for lost hair, but these can be invasive and painful or have unwanted side effects. The nutrition and cosmetic communities have rallied to the challenge as well, with many products making claims of a "silver bullet" or magic ingredient, yet they have very limited – if any – success and no knowledge of how these processes work on a molecular level.

We know that traditional Chinese, Ayurvedic, and other Asian cultures have successfully used herbs for medicinal and theraputic purposes for thousands of years. Unlike modern medicine, traditional herbal methods often view hair loss as a result of a deficiency in the quality of blood due to various organ dysfunctions such as liver, kidney, or spleen, and the overall blood flow around the scalp.

Our scientists have discovered many of the molecular interactions and pathways that promote or inhibit hair growth, by combining ancient knowledge and the use of safe and effective botanicals with the latest in research at the molecular level. In fact, the positive effects of vitamin nutrients, minerals and many botanicals used in traditional healing can create a delicate symphony of molecular interactions in and around a hair follicle.

HOW FAST DOES REPLENOLOGY WORK, AND WHAT ARE GOOD SIGNS WE ARE ON OUR WAY TO FOLLICLE AWAKENING?

Replenology starts to work on the first day you start the program, acting both on and deep below the scalp. Hair loss does not happen overnight, so it will take some time to see the full benefits of Replenology. Telogen (resting) follicles can awaken and begin to grow new hair within 4-6 months.

Very often, an increase in shedding will occur in the first month of using Replenology, as compromised late stage anagen hairs transition to the telogen phase. This is a positive sign indicating follicle renewal and improved hair follicle health which will result in faster growing and stronger hair. Increased natural color (melanization) also frequently occurs with the improvement in follicle health.

OUR COMMITMENT

At Replenology we are dedicated to solving the hair loss question by understanding the genetic, hormonal and other biochemical events in the body required to grow hair normally. We believe that a delayed aging effect or tissue repair process requires stem cells to regenerate those tissues, and we view this as the optimal way for the body to heal itself. We also believe the body's own stem cells possess the ultimate solution to stimulate normal hair growth in out-of-balance follicles. Our scientific team is actively conducting advanced research with independent scientists to determine how botanicals, vitamins and minerals stimulate hair stem cells to re-activate follicles and normal growth processes.

And unlike drugs, Replenology is committed to formulating products that are free from harmful side effects, harmful chemicals and common allergens. In short, we have created Replenology for you. We have succeeded in developing a system which weaves the 21 molecular pathways in and around hair follicles with carefully selected nutrients that are not normally found in a modern diet. Replenology's 21 to Grow approach offers targeted nutrient replenishment to support normal hair growth, benefitting intrinsic scalp and hair follicle functions.*

1 Schneider, et al. "The Hair Follicle as a Dynamic Miniorgan" Curr Biol. 2009 Feb 10;19(3):R132-42. doi: 10.1016/j.cub.2008.12.005. http://www.cell.com/current-biology/pdf/S0960-9822(08)01626-6.pdf

2 Ramos & Miot. "Female Pattern Hair Loss: a clinical and pathophysiological review" An. Bras. Dermatol. Vol 90 No 4. Rio de Janeiro July/Aug. 2015. http://www.scielo.br/pdf/abd/v90n4/0365-0596-abd-90-04-0529.pdf

* These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

THE IMPORTANCE OF BALANCE

Homeostasis, from the Greek words for "same" and "steady," refers to any process that living things use to actively maintain fairly stable conditions necessary for survival. In its simplest terms you can think of homeostasis as "balance".

Homeostasis keeps the body's internal environment under control and keeps the conditions right for cells to live and function. Without the right body conditions, certain processes such as growth, and various proteins such as enzymes and hormones will not function properly. Homeostatic mechanisms act as buffers to correct deviations and restore balance to keep the body environment as close to optimum condition as possible.

So what does homeostasis have to do with healthy hair? As you may be aware, hair growth and density are influenced by many factors, such as nutrition, immunity, hormones, prescription drugs, stress and ageing just to name a few – you will learn about others throughout this book. Any disturbance to hair follicle homeostasis can disrupt the normal cycle of hair growth, which can lead to a shortened anagen phase, impaired hair quality and very often a prolonged or indefinite telogen phase.

By understanding and being able to favorably influence homeostatis, normal healthy hair growth may be more effectively attained and sustained.

1 to GROW

DHT (DIHYDROTESTOSTERONE) AND 5α-R (5-ALPHA-REDUCTASE)

WHAT ARE THEY?

- DHT is a more powerful form of the steroid hormone testosterone and 5α-R is a naturally occurring enzyme.

HOW DO THEY WORK?

- DHT production involves converting testosterone into DHT by an enzyme called 5α-R. In addition, a cofactor known as NADPH (Nicotinamide adenine dinucleotide phosphate) is required by 5α-R to effectively convert testosterone to DHT.
- Scientists believe DHT diffuses into hair follicle cells and restricts the ability to produce hair.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE DHT AND 5α-R TO PROMOTE NORMAL HAIR GROWTH?

- Popular drugs have been FDA-approved to inhibit 5α-R, but these have nasty, unwanted side effects including decreased libido.
- Numerous natural substances in Replenology are known to lower DHT, inhibit 5α-R and decrease the availability of NADPH without these side effects.

To read more on the roles of DHT and 5α-R and their impact on hair biology please see:

Inui & Itami. "Androgen Actions on the Human Hair Follicle: Perspectives." Exp Dermatol. 2013 March. 22(3):168-71. https://www.ncbi.nlm.nih.gov/pubmed/23016593

2 to GROW

BOOSTING THE IMMUNE SYSTEM MICROENVIRONMENT (IMMUNOMODULATION)

WHAT IS IT?

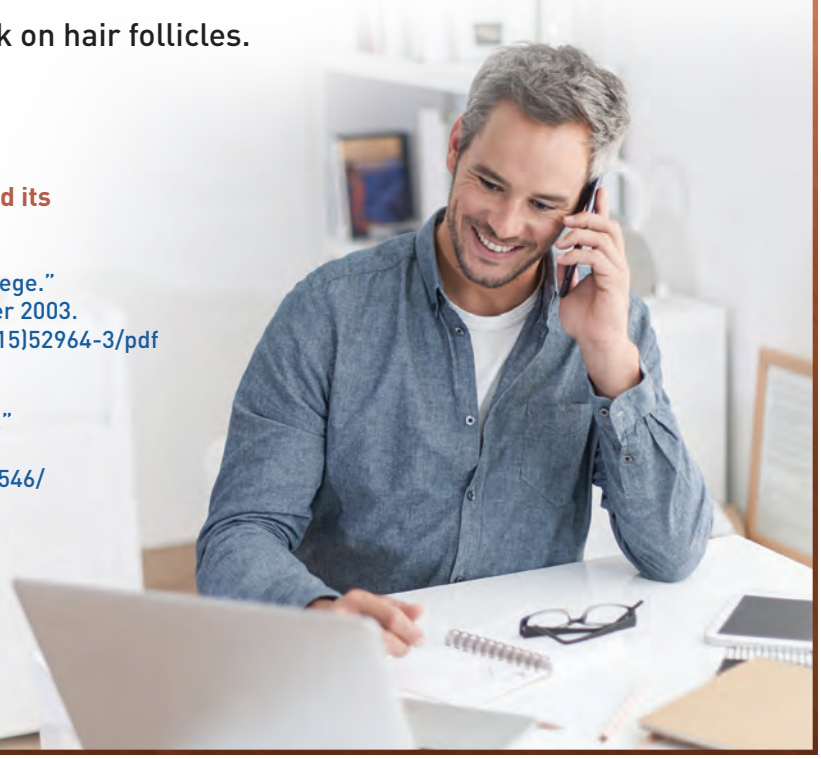
- Think of your hair follicle like a small organ in your body, with its own immune and hormonal makeup – what we call a 'microenvironment'.

HOW DOES IT WORK?

- This microenvironment uses something in your body called 'immune privilege' to protect your hair from unwanted immune reactions.
- When the hair follicle begins to break down, autoimmune reactions happen in the hair follicle that can cause unwanted loss of existing hair and inhibit normal hair growth.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE IMMUNOMODULATION TO PROMOTE GROWTH?

- Our natural formula positively affects the immune state of the hair follicle, stimulating your body to naturally protect your hair from loss – in essence preserving or restoring the 'immune privilege'. In addition, ingredients within the Replenology formula have been shown to limit the unwanted effects of an over-active immune system attack on hair follicles.



To read more on the role of immunology and its impact on hair biology please see:

Paus, et al. "The Hair Follicle and Immune Privilege." Journal of Investigative Dermatology 8:2. October 2003. http://www.jidsponline.org/article/S0022-202X(15)52964-3/pdf

Ito. "Recent Advances in the Pathogenesis of Autoimmune Hair Loss Disease Alopecia Areata." Journal of Immunology Research. 2013. https://www.hindawi.com/journals/jir/2013/348546/

3 to GROW

PGD2 (PROSTAGLANDIN D2)

WHAT IS IT?

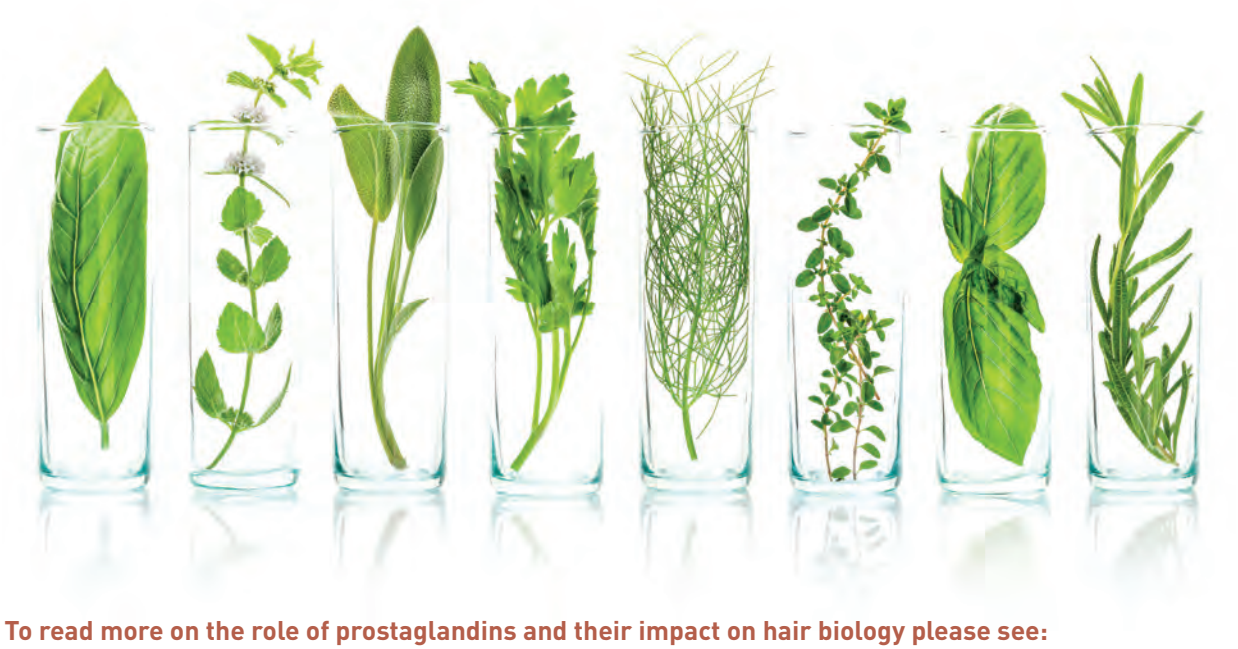
- Prostaglandins are a group of molecules that have hormone-like effects that help your body deal with injury and illness by regulating inflammation.
- A specific prostaglandin, PGD2 (Prostaglandin D2), has been determined to cause baldness in men.

HOW DOES IT WORK?

- PGD2 prevents hair follicles from maturing, and therefore growing hair.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE PROSTAGLANDINS TO PROMOTE NORMAL HAIR GROWTH?

- Numerous studies point to specific plant extracts, which are used in the Replenology formula, to be potent inhibitors of PGD2.



To read more on the role of prostaglandins and their impact on hair biology please see:

Garza, et al. "Prostaglandin D2 Inhibits Hair Growth and Is Elevated in Bald Scalp of Men with Androgenetic Alopecia." Sci Transl Med. 2012 March Vol 21.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3319975/pdf/nihms366359.pdf

Nieves & Garza. "Does Prostaglandin D2 hold the cure to male pattern baldness?" Exp Dermatol. 2014 April, Vol 23.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3982925/pdf/nihms568813.pdf

4 *to* GROW

COX (CYCLOOXYGENASE)

WHAT IS IT?

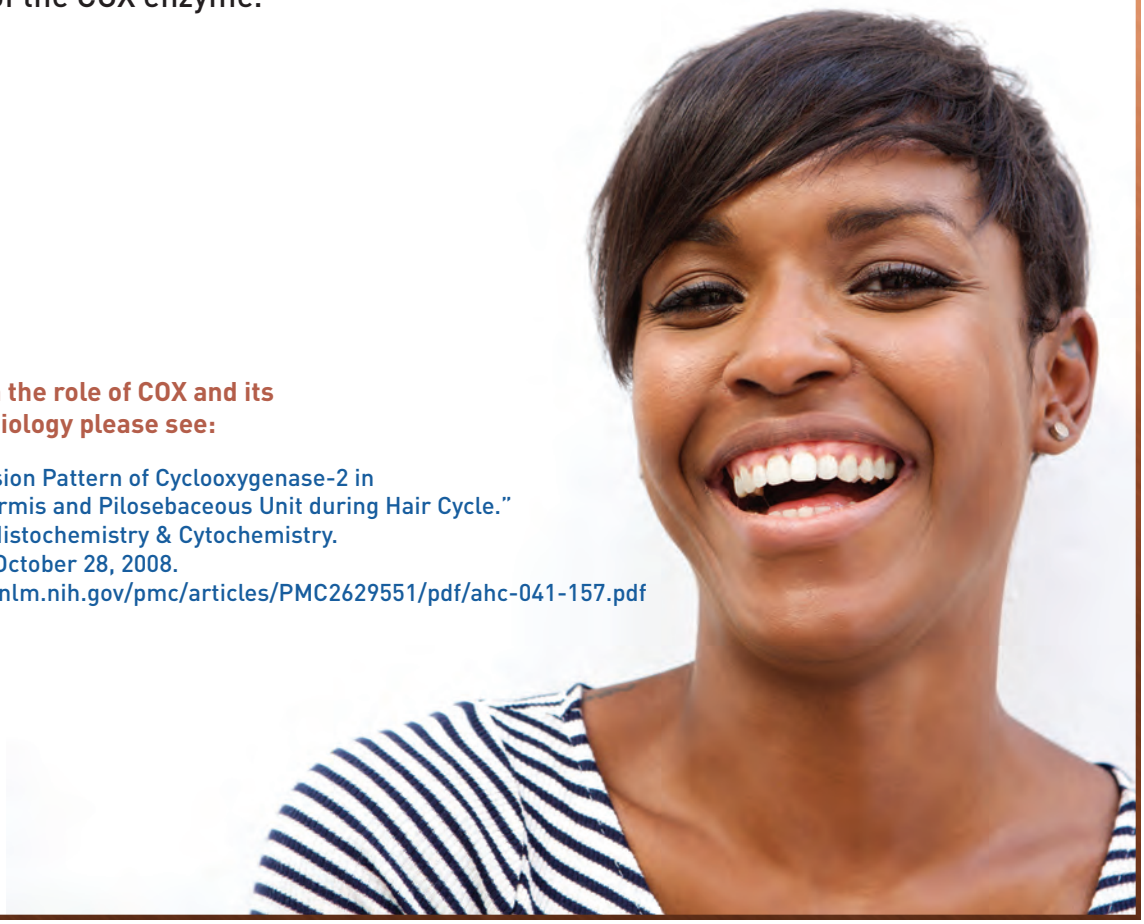
- COX is an enzyme that is responsible for the formation of prostaglandins and promoting inflammation.

HOW DOES IT WORK?

- Uncontrolled inflammation can lead to tissue injury. Numerous studies have shown that inflammation to the scalp exacerbates hair loss. More specifically, COX levels rise when the hair cycle enters catagen (phase where hair growth stops) and telogen (resting phase of the hair growth cycle).

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE COX TO PROMOTE NORMAL HAIR GROWTH?

- Numerous studies point to specific plant extracts and a variety of flavonoids, a diverse group of plant chemicals, which are in the Replenology formula, to be inhibitors of the COX enzyme.



To read more on the role of COX and its impact on hair biology please see:

Xu, et al. "Expression Pattern of Cyclooxygenase-2 in Normal Rat Epidermis and Pilosebaceous Unit during Hair Cycle." Japan History of Histochemistry & Cytochemistry. Published online October 28, 2008. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2629551/pdf/ahc-041-157.pdf

5 to GROW

IFN (INTERFERONS)

WHAT ARE THEY?

- IFNs are a group of signaling molecules called cytokines that are used for communication between cells.

HOW DO THEY WORK?

- Under normal circumstances IFNs trigger the protective defenses of the immune system to help eradicate foreign invaders such as viruses and bacteria. However, when uncontrolled they can lead to tissue damage and hair loss.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE INTERFERONS TO PROMOTE NORMAL HAIR GROWTH?

- Plant extracts in the Replenology formula have been shown to be inhibitors of IFNs. For example, certain ingredients within our formula have been shown in studies to modulate the effects of IFNγ (interferon-gamma, a type of IFN implicated in the phases of normal hair growth).

To read more on the role of interferons and their impact on hair biology please see:

Ito, et al. "Interferon-gamma is a potent inducer of catagen-like changes in cultured human anagen hair follicles." Journal of Dermatology. 2005 April, Vol 4. https://www.ncbi.nlm.nih.gov/pubmed/15840090

6 to GROW

IL (INTERLEUKINS)

WHAT ARE THEY?

- Interleukins are a group of over 35 secreted proteins and signaling molecules known to regulate cell growth and differentiation.

HOW DO THEY WORK?

- Interleukins are situation-specific and work by stimulating or inhibiting the activity of the immune system.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE INTERLEUKINS TO PROMOTE NORMAL HAIR GROWTH?

- It is vital to increase the presence of interleukins that have a positive impact on hair health, while decreasing the presence of interleukins that promote hair loss.
- Replenology has been formulated with botanical extracts that have been shown to increase the presence of the "good" interleukins (for example IL-10) and decrease the presence of the "bad" interleukins (for example IL-1 and IL-6).

To read more on the role of interleukins and their impact on hair biology please see:

Gregoriou, et al. "Cytokines and Other Mediators in Alopecia Areata." Mediators of Inflammation, Vol 2010. https://www.hindawi.com/journals/mi/2010/928030/

7 to GROW

TNF-α
(TUMOR NECROSIS FACTOR ALPHA)

WHAT IS IT?

- TNF-α is a chemical messenger (cytokine) produced by many cells in the body, that under normal circumstances, is required for a healthy immune response. Under abnormal situations (elevated levels) it can cause the immune system to attack healthy hair cells.

HOW DOES IT WORK?

- Recent studies have shown that TNF-α plays a central role in the programmed cell death (apoptosis) of hair cells. In fact, it has been suggested by several researchers to be the most significant factor in hair cell death, possibly more significant than DHT.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE TNF-α TO PROMOTE NORMAL HAIR GROWTH?

- TNF-α has been shown to modulate hair cycles.
- Replenology is formulated with botanical extracts that have been shown to block the negative effects of TNF-α on hair cells.

To read more on the role of TNF-α and its impact on hair biology please see:

Botchkareva, et al. "Apoptosis in the Hair Follicle." Journal of Investigative Dermatology, Volume 126, Issue 2.
http://www.jidonline.org/article/S0022-202X(15)32770-6/pdf

8 *to* GROW

TGF-ß
(TRANSFORMING GROWTH FACTOR BETA)

WHAT ARE THEY?

- TGF-ß is a member of a cytokine (cell messenger) super-family that has approximately 30 members that carry out their actions via specific message-receiving molecules.

HOW DO THEY WORK?

- These cytokines regulate cell proliferation or cell destruction in many cell types and have a central role in the inflammation process.
- Studies have shown that TGF-ß is associated with hair follicle shrinking and eventual hair loss.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE TGF-β TO PROMOTE NORMAL HAIR GROWTH?

- Replenology is formulated with botanical extracts that have been shown to block the negative effects of TGF-ß on hair cells and promote healthy hair growth.

To read more on the role of TGF-ß and its impact on hair biology please see:

Hibino & Nishiyama. "Role of TGF-ß2 in the human hair cycle." Journal of Dermatological Science. 2004 June, Vol 35. https://www.ncbi.nlm.nih.gov/pubmed/15194142

A WORD ABOUT CELL SIGNALING

Cell signaling is part of the communication process that cells use to govern basic activities and actions.

The ability of cells to perceive and correctly respond to their environment is important for normal development, tissue repair, and the maintenance of tissue in a normal state.

By understanding and being able to favorably influence cell signaling, healthy hair growth may be more effectively attained.

9 to GROW

WNT/BETA CATENIN CELL SIGNALING

WHAT IS IT?

- When hair stem cells are exhausted, no new hair can grow.

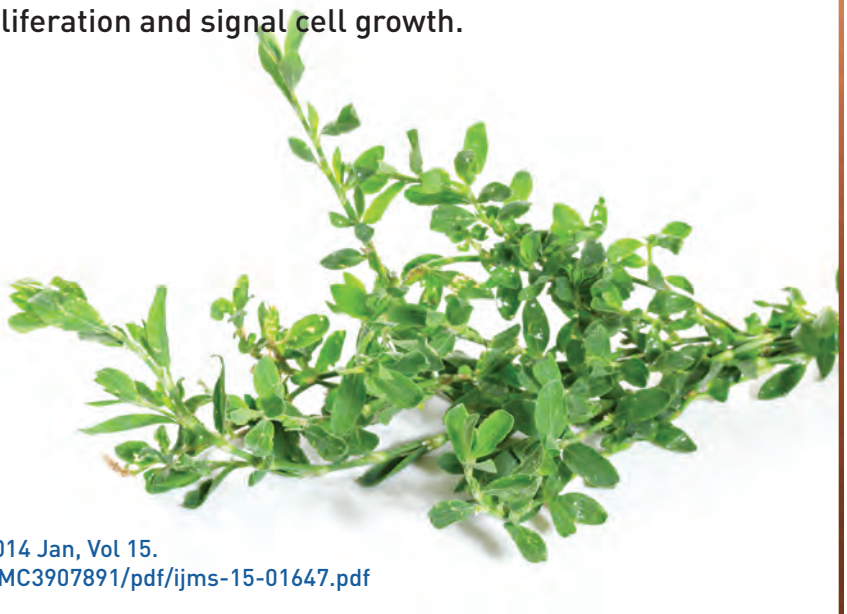
  Wnt/ß-catenin cell signaling is required to give stem cells the ability to change into various cell types and to allow exhausted stem cells the ability to self-renew. We're still trying to understand how this works as a scientific community, but when it comes to normal hair growth, optimum cell signaling is important!

HOW DOES IT WORK?

- Scientists have found that active compounds from plant extracts can activate the Wnt/ß-catenin pathway and increase cell proliferation – in other words, stimulate the appropriate signals that promote normal hair growth, and, in effect, "turn them back on".

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE CELL SIGNALING TO PROMOTE NORMAL HAIR GROWTH?

- Replenology's formula contains these active plant extract compounds in quantities known to increase stem cell proliferation and signal cell growth.



For more information on cell signaling in the hair follicle please see:

Rishikaysh, et al. "Signaling Involved in Hair Follicle Morphogenesis and Development." International Journal of Molecular Science. 2014 Jan, Vol 15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3907891/pdf/ijms-15-01647.pdf

Choi, et al. "Distinct functions for Wnt/ß-catenin in hair follicle stem cell proliferation and survival and interfollicular epidermal homeostasis." Cell Stem Cell. 2013 December, Vol 13. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3900235/pdf/nihms531630.pdf

10 to GROW

SHH (SONIC HEDGEHOG)

WHAT IS IT?

- You read that right!
- Sonic hedgehog is one of three proteins in a signaling pathway family called hedgehog.

HOW DOES IT WORK?

- SHH works with the dermal papilla (DP), the structural formation located in the uppermost layer of the skin, to provide oxygen and nutrients to the follicle promoting healthy hair.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE SHH TO PROMOTE NORMAL HAIR GROWTH?

- The Replenology formula contains several botanicals that are used in traditional healing to counter hair loss, and that have been demonstrated to influence SHH and induce the anagen (growth phase) of resting hair follicles.

To read more on SHH in the hair follicle please see:

Woo, et al. "Shh maintains dermal papilla identity and hair morphogenesis via a Noggin–Shh regulatory loop." Genes & Development, Vol 26. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3371411/pdf/1235.pdf

11 to GROW

BMP
(BONE MORPHOGENIC PROTEIN)

WHAT IS IT?

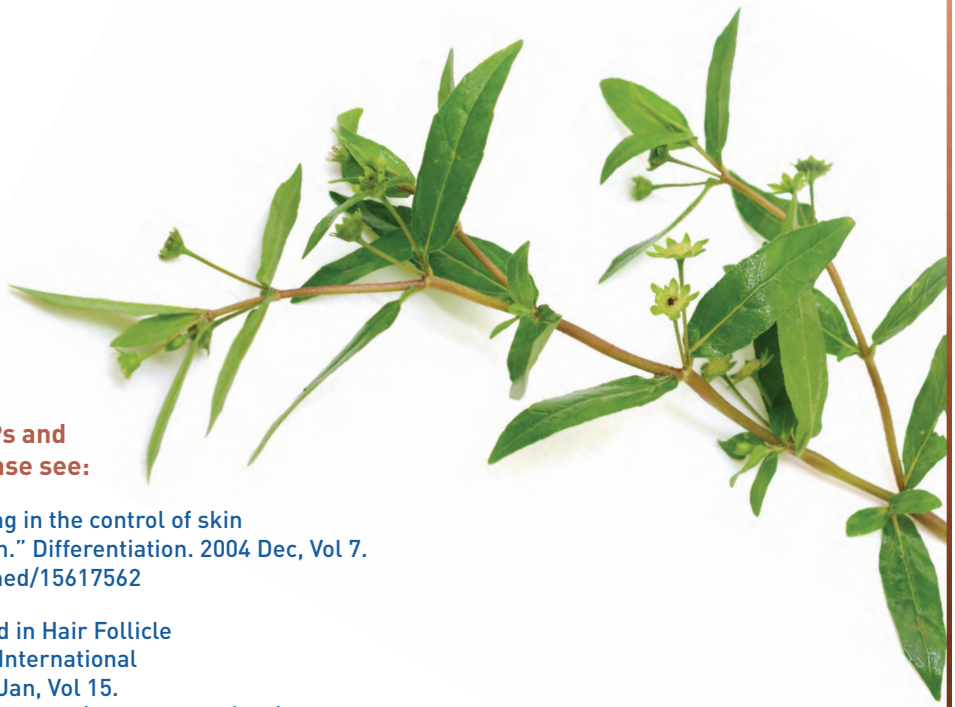
- BMPs have been associated with a variety of cellular functions
- To date, 20 different BMPs have been identified that control the formation of different types of cells as well as various cellular functions.

HOW DO THEY WORK?

- Under normal circumstances, as follicle growth is activated, waves of BMP (especially BMP-4) shut down the stem cells in hair follicles, halting growth.
- Inhibiting BMP-4 signaling would promote normal hair growth and inhibit hair loss.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE BMPS TO PROMOTE NORMAL HAIR GROWTH?

- Research has demonstrated that botanicals used in traditional healing to counter hair loss, and included in the Replenology formula, influence BMP and modulate the phases of normal hair growth. More specifically, these ingredients inhibit BMP-4.



To read more on the role of BMPs and their impact on hair biology please see:

Botchkarev & Sharov. "BMP signaling in the control of skin development and hair follicle growth." Differentiation. 2004 Dec, Vol 7. https://www.ncbi.nlm.nih.gov/pubmed/15617562

Rishikaysh, et al. "Signaling Involved in Hair Follicle Morphogenesis and Development." International Journal of Molecular Science. 2014 Jan, Vol 15. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3907891/pdf/ijms-15-01647.pdf

Pilkus. "New activators and inhibitors in the hair cycle clock: targeting stem cells' state of competence." Journal of Investigative Dermatology. 2012 May, Vol 5. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4033821/pdf/nihms582531.pdf

NOGGIN

WHAT IS IT?

- Noggin is a development protein that promotes certain growth in tissues.

HOW DOES IT WORK?

- Noggin modulates certain BMPs (bone morphonegentic proteins), and inhibits BMP-4 to stimulate normal hair growth.
- Studies have shown that Noggin was found to induce a new hair growth phase.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE NOGGIN TO PROMOTE NORMAL HAIR GROWTH?

- Our product contains botanical ingredients that have been shown to stimulate Noggin, inhibit BMP-4, and jumpstart the growth process in hair follicles.

To read more on the role of Noggin and its impact on hair biology please see:

Botchkarev, et al. "Modulation of BMP Signaling by Noggin is Required for Induction of the Secondary (Nontylotrich) Hair Follicles." Journal of Investigative Dermatology. 2002 Jan, Vol 118 , Issue 1, Pages 3-10. http://www.sciencedirect.com/science/article/pii/S0022202X15415234

Botchkarev, et al. "Noggin is required for induction of the hair follicle growth phase in postnatal skin." FASEB Journal. 2001 Oct, Vol 12. https://www.ncbi.nlm.nih.gov/pubmed/11641247

13 to GROW

PPARγ (PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA)

WHAT IS IT?

- PPARs are a group of molecules that play an essential role in regulating cell differentiation, development and metabolism.
- PPARγ has been extensively studied due to its role as a "master regulator" of inflammation.

HOW DOES IT WORK?

- Research points to PPARγ's ability to assist in hair follicle growth.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE PPARγ TO PROMOTE NORMAL HAIR GROWTH?

- Studies have demonstrated that a decrease of PPARγ is associated with hair loss. It is possible to stimulate PPARγ's production through the use of botanical blends, which we include in Replenology.

To read more on the role of PPARs and their impact on hair biology please see:

Di-Poi. "Functions of peroxisome proliferator-activated receptors (PPAR) in skin homeostasis." Lipids. 2004 Nov, 39(11):1093-9. https://www.ncbi.nlm.nih.gov/pubmed/15726824

Festa, et al. "Adipocyte lineage cells contribute to the skin stem cell niche to drive hair cycling." Cell. 2011 Sep 2, 146(5): 761–771 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3298746/

14 to GROW

MTORC1 (MAMMALIAN TARGET OF RAPAMYCIN)

WHAT IS IT?

- mTORC1 is a protein complex that senses the need for nutrients, energy and oxygen in cells and controls protein synthesis.

HOW DOES IT WORK?

- mTORC1 is responsible for activating proteins in the body.
- Hair is primarily composed of the protein keratin. As such, hair cells must have adequate energy resources, nutrient availability, oxygen abundance, and proper growth factors to develop and mature the keratin.
- Studies have shown that mTORC1 limits the negative effects of BMP-4 signaling, allowing hair follicle stem cell activation.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE MTORC1 TO PROMOTE NORMAL HAIR GROWTH?

- The Replenology formula includes botanicals that activate mTORC1 and keep the negative effects of BMP-4 on healthy hair growth in check.

To read more on the role of mTORC1 and its impact on hair biology please see:

Kellenberger & Tauchi. "Mammalian target of rapamycin complex 1 (mTORC1) may modulate the timing of anagen entry in mouse hair follicles." Exp Dermatol. 2013 Jan, 22(1):77-80. doi: 10.1111/exd.12062. https://www.ncbi.nlm.nih.gov/pubmed/23278901

15 to GROW

TERT
(TELOMERASE REVERSE TRANSCRIPTASE)

WHAT IS IT?

- TERT is a component of an enzyme called telomerase.

HOW DOES IT WORK?

- TERT functions to add a protective structure that "caps" chromosome ends to prevent damage that occurs either naturally from aging or from the environment.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE TERT TO PROMOTE NORMAL HAIR GROWTH?

- Research has demonstrated that botanicals included in the Replenology formula stimulate TERT activity.

To read more on the role of TERT and its impact on hair biology please see:

Choi, et al. "TERT Promotes Epithelial Proliferation through Transcriptional Control of a Myc and Wnt-Related Developmental Program." PLOS Genetics. 2008 Jan, Vol 4, Issue 1, E10. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2211538/pdf/pgen.0040010.pdf

Sarin, et al. "Conditional telomerase induction causes proliferation of hair follicle stem cells." Nature. 2005 August 18, 436(7053): 1048–1052. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1361120/pdf/nihms4712.pdf

GROWTH FACTORS

Growth factors are naturally occurring substances within the body capable of stimulating cellular growth, maturation, proliferation and cellular differentiation.

Growth factors are usually proteins, hormones or molecules called cytokines or messengers that are important for regulating a variety of cellular processes.

16 to GROW

FGF (FIBROBLAST GROWTH FACTOR)

WHAT ARE THEY?

- FGF family members possess the broad ability to encourage cell division and cell survival activities, and are involved in a variety of biological processes including cell growth and tissue repair.

HOW DO THEY WORK?

- FGFs work in what is referred to as a paracrine manner. That is, they are produced by a cell and the FGF has its effect on a nearby or neighboring cell.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE FGF TO PROMOTE NORMAL HAIR GROWTH?

- Two FGF family members have been implicated in normal hair growth: FGF-7 and FGF-18.
- Our products use botanicals that have been shown to activate FGF-7 and inhibit the formation of FGF-18, helping slow the loss of hair and promote healthy hair growth.

To read more on the role of FGFs and their impact on hair biology please see:

Pilkus. "New activators and inhibitors in the hair cycle clock: targeting stem cells' state of competence." J Invest Dermatol. 2012 May, 132(5): 1321–1324. doi:10.1038/jid.2012.38
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4033821/pdf/nihms582531.pdf

Pilkus & Chuong. "Macroenvironmental Regulation of Hair Cycling and Collective Regenerative Behavior." Cold Spring Harb Perspect Med. 2014, 4:a015198
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3869280/pdf/cshperspectmed-SKN-a015198.pdf

17 to GROW

HGF (HEPATOCYTE GROWTH FACTOR)

WHAT IS IT?

- Hepatocyte growth factor (HGF) is a multifunctional protein growth factor which acts to stimulate cell division.

HOW DOES IT WORK?

- HGF is a paracrine hormone found to influence hair length, promote follicular growth and stimulate DNA synthesis in hair follicles.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE HGF TO PROMOTE NORMAL HAIR GROWTH?

- Our Replenology formula use botanicals that have been shown to activate HGF helping to slow the loss of hair and promote healthy hair growth.

To read more on the role of HGF and its impact on hair biology please see:

Qi, et al. "Therapeutic role of human hepatocyte growth factor (HGF) in treating hair loss." PeerJ. 4:e2624; DOI 10.7717/peerj.2624
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5101615/pdf/peerj-04-2624.pdf

Yamazaki, et al. "Hair Cycle-Dependent Expression of Hepatocyte Growth Factor (HGF) Activator, Other Proteinases, and Proteinase Inhibitors Correlates with the Expression of HGF in Rat Hair Follicles." Society for Investigative Dermatology. 1999 Dec, Vol. 4 No. 3.
http://www.jidsponline.org/article/S1087-0024(15)30289-6/pdf

18 to GROW

IGF
(INSULIN-LIKE GROWTH FACTORS)

WHAT ARE THEY?

- IGFs are proteins very similar to insulin that are used by cells to communicate with their environment.

HOW DO THEY WORK?

- IGFs are important for the regulation of normal physiology. IGFs have been shown to play important roles in the promotion of cell proliferation and the inhibition of normal or programmed cell death (apoptosis). Research has demonstrated that one form of IGF called IGF-1 affects proliferation of the hair follicle and the normal hair growth cycle.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE IGF TO PROMOTE NORMAL HAIR GROWTH?

- Replenology products include botanicals that have been shown to activate IGF helping to slow the loss of hair and promote healthy growth.

To read more on the role of IGFs and their impact on hair biology please see:

Weger & Schlake. "IGF-I Signalling Controls the Hair Growth Cycle and the Differentiation of Hair Shafts." The Journal of Investigative Dermatology. 2005 Nov, 125:5. http://www.jidonline.org/article/S0022-202X(15)32532-X/pdf

Ahn, et al. "Effect of IGF-I on Hair Growth Is Related to the Anti-Apoptotic Effect of IGF-I and Up-Regulation of PDGF-A and PDGF-B." Ann Dermatol. 2012, Vol. 24, No 1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3283847/pdf/ad-24-26.pdf

IMPROVED CIRCULATION

An often-overlooked contributor to normal hair health is circulation. Even a perfectly designed solution for correcting hair loss would be ineffective without adequate blood flow delivering the necessary nutrients to the hair follicle.

It is beneficial to increase circulation in any regime targeted at improving hair health. This can be achieved with formulations that stimulate improved blood flow or blood supply.

19 to GROW

VEGF (VASCULAR ENDOTHELIAL GROWTH FACTOR)

WHAT IS IT?

- VEGF is a signal and growth factor protein produced by cells which stimulates the growth of blood vessels. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate.

HOW DOES IT WORK?

- VEGF's normal function is to create new blood vessels.
- Numerous studies demonstrate that increasing VEGF improves blood flow. In fact studies in normal hair biology demonstrate that when hair follicles leave telogen (resting phase) and enter anagen (growth phase) new blood vessel creation is stimulated in and around the follicle.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE VEGF TO PROMOTE NORMAL HAIR GROWTH?

- Replenology products have been designed to use botanicals that have been shown to activate VEGF helping to support hair during growth and also to increase the blood supply to the hair follicle supporting nutrient delivery.

For more information and further reading on VEGF and its role in hair biology please see:

Li, et al. "VEGF induces proliferation of human hair follicle dermal papilla cells through VEGFR-2-mediated activation of ERK." Exp Cell Res. 2012 Aug 15, 318(14):1633-40 https://www.ncbi.nlm.nih.gov/pubmed/22659165

20 to GROW

APOPTOSIS (PROGRAMMED CELL DEATH)

WHAT IS IT?

- A cell can die in one of two ways: necrosis or apoptosis. Necrosis occurs when a cell is damaged by an external force, such as poison, injury, infection or losing its blood supply. This type of cell death is not ideal and causes inflammation that can cause further distress or injury within the body. On the other hand, apoptosis, often called programmed cell death, is when a cell self-destructs in a process that follows a controlled, predictable routine. This type of cell death is a normal part of health and wellness and is the method by which damaged and no longer needed cells are removed without causing unwanted inflammatory reactions and illness.

HOW DOES IT WORK?

- Problems occur when programmed cell death malfunctions. Too much apoptosis can lead to degenerative diseases and too little apoptosis can lead to the accumulation of unwanted and inappropriately functioning cells.
- With the appropriate signals various proteins jump into action and carry out this orderly process of programmed cell death. The dying cells then send out distress signals, which are answered by cells of the immune system, which in turn clean up the dead cell matter.
- Because the hair follicle goes through cyclic activity it transits through periods of active hair growth (anagen) and apoptosis-driven catagen or regression. During growth, the activity of factors promoting proliferation and survival predominate, whereas during regression signals that induce apoptosis take over.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE APOPTOSIS TO PROMOTE NORMAL HAIR GROWTH?

- Our formulations use botanicals that have been shown to inhibit factors associated with cell death and promote the active growth phase of the hair follicle.

For more information and further reading on apoptosis and its role in hair biology please see:

Botchkareva, et al. "Apoptosis in the Hair Follicle." Journal of Investigative Dermatology. Volume 126, Issue 2. http://www.jidonline.org/article/S0022-202X(15)32770-6/pdf

21 to GROW

ANTIOXIDANTS

WHAT ARE THEY?

- An antioxidant is a molecule that inhibits the oxidation of other molecules. Oxidation reactions produce damaging molecules called free radicals. These radicals can start chain reactions in cells that cause damage or death of the cell. Under normal circumstances oxidation reactions are important for normal cell function.

HOW DO THEY WORK?

- Cells of all living organisms have complex antioxidant systems in place to keep oxidation reactions under control.
- Cells make use of various vitamins and enzymes such as superoxide dismutase and peroxidase as antioxidant molecules to keep oxidation reactions in check.
- Insufficient levels of antioxidants, or the inhibition of the antioxidant enzymes will lead to cellular stress that may damage and kill cells.

HOW DOES REPLENOLOGY'S ADVANCED SCIENCE INFLUENCE ANTIOXIDANTS TO PROMOTE NORMAL HAIR GROWTH?

- Studies suggest that oxidative stress seems to play a significant role in many human diseases.
- Therefore, having sufficient quantities of antioxidants or preventing the inhibition of antioxidant enzymes is critical for normal cell structure and function.
- The best sources of antioxidants are vitamins and plant polyphenols.
- Our formulations use botanicals that have been shown to provide a significant source of the necessary vitamins and antioxidants to support healthy normal hair growth.

To learn more about the role of antioxidants on health and disease please see:

Pham-Huy, et al. "Free Radicals, Antioxidants in Disease and Health." International Journal of Biomedical Science. 2008 June, Vol 4. No 2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3614697/pdf/IJBS-4-89.pdf

A WORD ABOUT NUTRITION

The integumentary system, of which hair, skin and nails are a part, is the largest system in your body. It is one of the most metabolically active systems in that its tissues never stop growing. It has enormous nutrient requirements which, in this day and age and depending on your health status and lifestyle, may not be adequately met.

Clinical trials have demonstrated that proper nutritional intake is critical for healthy hair growth, and conversely, nutritional deficiencies correlate with typical causes of hair loss not related to disease. Therefore, nutrition is a vital part of any regimen directed at maintaining or improving hair health. Despite having optimal health or the best regimen, if the "building blocks" for proper growth and development of hair are not available, the structure is most likely to be affected. The Replenology formulation contains all the necessary "building blocks" including vitamins, minerals (trace elements), amino acids, fatty acids and antioxidants to promote normal, healthy hair growth.

QUESTIONS ABOUT THE SCIENCE? We'd love to delve deeper with you and answer any questions you might have! Join us on FACEBOOK, or check out more information about how our 21 to Grow Formula will work for you HERE.

GLOSSARY

ANAGEN: The active growth phase of hair follicles.

ANTIOXIDANT: A molecule that inhibits the oxidation of other molecules.

APOPTOSIS: Also known as programmed cell death. The death of cells that occurs as a normal and controlled part of cellular growth and development. (As opposed to necrosis which is cell death caused by injury).

APOPTOSIS-DRIVEN CATAGEN: The second part of hair's lifecycle (catagen) that occurs as a consequence of apoptosis (programed cell death). Apoptosis-driven regression: Retreat or deterioration of a structure as a consequence of apoptosis (programmed cell death).

5α-R: 5-alpha-reductase. An enzyme which converts testosterone into dihydrotestosterone (DHT).

ß-CATENIN: A protein with dual function. It is involved in regulation and coordination of cell to cell adhesion and gene transcription. It acts as an intracellular signal transducer in the Wnt signaling pathway. Alterations in the localization and expression levels of ß-catenin have been associated with various disease states.

BMP: Bone morphogenic protein. A group of growth factors originally discovered to induce the formation of bone and cartilage but now associated with a variety of cell functions in various tissues and cells.

CATAGEN: A short transition stage that occurs at the end of the anagen phase. It signals the end of the active growth of hair. The phase typically lasts for two to three weeks

CELL DIFFERENTIATION: The process by which a less specialized cell becomes a more specialized cell type.

CELL SIGNALING: The part of the communication process that cells use to govern basic activities and actions.

COX: Cyclooxygenase. An enzyme (in humans there are two, COX-1 and COX-2) that, amongst other activities, is responsible for the formation of prostaglandins and promoting inflammation.

CYTOKINE: Secreted proteins released by cells that have specific effects on the interactions and communications between cells.

DHT: Dihydrotestosterone. A more powerful form of the steroid hormone testosterone implicated in hair loss.

FGF: Fibroblast growth factor. A family of proteins involved in a variety of biological processes, including embryonic development, cell growth, morphogenesis and tissue repair.

GROWTH FACTORS: Naturally occurring substances within the body capable of stimulating cellular growth, maturation, proliferation and cellular differentiation.

HGF: Hepatocyte growth factor. A multi-functional protein growth factor that acts to stimulate cell division (amongst other functions).

IGF: Insulin-like growth factors. A group of proteins that are very similar to insulin. IGFs are used by cells to communicate with their environment.

IFN: Interferons. A group of signaling molecules called cytokines, made by cells and used for communication between cells.

INTEGUMENTARY SYSTEM: The system that comprises the skin and its appendages, including hair and nails.

IL: Interleukins. A group of proteins that modulate the activity of the immune system both up-regulating and down-regulating its response. ILs mediate communication between cells and regulate growth and differentiation.

IMMUNOMODULATION: The regulatory adjustment of the immune system. It refers to any process in which an immune response is adjusted to the desired level.

IMMUNE PRIVILEGE: The ability of tissues to actively regulate and direct immune responses that take place in their environment.

INFLAMMATION: A complex biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Although protective under normal circumstances, uncontrolled inflammation can lead to further tissue injury.

MTORC1: Mammalian target of rapamycin. A protein complex that functions as a nutrient/energy/oxygen-reduction sensor and controls protein synthesis in cells.

NADPH: Nicotinamide adenine dinucleotide phosphate. A membrane-bound enzyme complex which functions as a cofactor in various cellular reactions. NADPH is a cofactor for 5α-R (the enzyme that converts testosterone to DHT, which has been implicated in hair loss).

NOGGIN: A development protein that promotes certain growth in a developing embryo.

PARACRINE: A form of cell-to-cell communication in which a cell produces a signal to induce changes in nearby cells, altering the behavior of those cells.

PPAR: Peroxisome proliferator-activated receptor. A group of proteins that regulate gene expression. PPARγ, a specific PPAR, has been implicated in hair follicle growth, tissue repair.

PROSTAGLANDIN: A group of molecules produced by cells at sites of tissue damage, involved in dealing with injury and illness. They control processes such as inflammation, blood flow, and the formation of blood clots. PGD2, a specific prostaglandin, has been noted for causing baldness in men.

SHH: Sonic Hedgehog. One of three proteins in a signaling pathway family called hedgehog. During development SHH plays a key role in regulating vertebrate organogenesis (organ development). In the adult, SHH remains important as it has been implicated in the control of cell division.

STEM CELLS: An undifferentiated cell that is capable of giving rise to indefinitely more cells of the same type, and from which certain other kinds of cell arise by differentiation.

TELOGEN: The third phase of the hair's cycle. It typically lasts between three and five months. During this stage, the hair ceases to grow and becomes fully keratinized.

TERT: Telemorase reverse transcriptase. A subunit of an enzyme called telomerase which together with a partner forms part of what is known as the telomerase complex – a cap which helps to protect chromosomes from damage.

TESTOSTERONE: The primary male sex hormone. In men, testosterone plays a key role in the development of male reproductive tissues as well as promoting secondary sexual characteristics such as increased muscle and bone mass, and the growth of body hair.

TGF-ß: Transforming growth factor-beta. A member of a cytokine (cell messenger) super-family involved in many cellular functions including cell growth, proliferation, differentiation, apoptosis. It has been implicated in hair loss.

TNF-α: Tumor necrosis factor-alpha. A chemical messenger (cytokine) produced by many cells in the body, which under normal circumstances is required for a healthy immune response. Under abnormal situations (elevated levels) it causes the immune system to attack healthy tissues throughout the body.

VASCULAR SMOOTH MUSCLE: A type of involuntary muscle that lines the walls of blood vessels.

VEGF: Vascular endothelial growth factor. A signal and growth factor protein that stimulates angiogenesis (the growth of blood vessels).

WNT SIGNALING PATHWAYS: A group of signal transduction pathways made of proteins that pass signals into a cell through cell surface receptors.