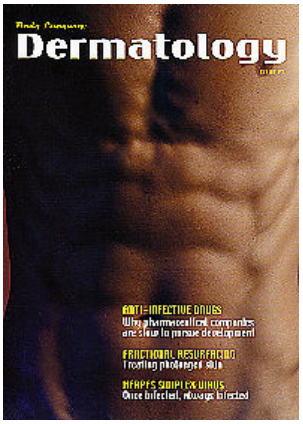
Improving Hair Growth with Skin Remodeling Copper Peptides

(English Translation)

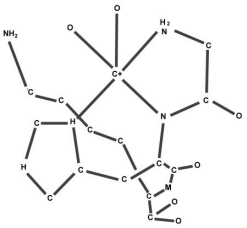


Loren Pickart PhD

Cosmetics & Medicine (Russia) July 2004
Also published in London's Body Language:
Dermatology Journal (December 2004)

When we are young, our hair is thick, well-pigmented and grows rapidly on our head. But with the passage of time, the hair thins or vanishes, growth slows, and becomes grayer. While the search for methods to restore healthy, younger hair is ancient, the reality is that, even today, in the era of minoxidil (Rogaine) and finasteride (Propecia), all existing therapies give at best a marginal restoration of hair health.

Skin remodeling copper peptides, or SRCPs for short, are the latest candidate being tested for the improvement of hair health. What are SRCPs? They are types of copper peptides that are based on a human copper peptide complex called glycyl-l-histidyl-l-lysine:copper (II) or GHK-Cu for short.



See Figure 1.

Figure 1 Legend: Solution structure of GHK-Cu

GHK-Cu is a normal component of human blood plasma, urine, and saliva. (1) It is increasingly being used in products sold for reversing the effects of aging on human skin. SRCPs are defined as having actions similar to GHK-Cu which include anti-inflammatory effects, skin repair actions, and the ability to increase the size of hair follicles. It should be emphasized that not all copper-peptides have such positive actions; indeed, some copper-peptides can inhibit these effects. (2-4)

Causes of Hair Thinning and Loss of Vitality

Before discussing the use of SRCPs on hair, it is best to first focus on the causes of hair thinning and loss in healthy humans. These causes are more diverse than generally realized although most attention has been focused on blocking the actions of DHT (dihydrotestosteone). For example, most theories of hair loss and thinning hair have focused on the metabolic actions of DHT, but in reality, other factors can also induce or modulate these effects. So it is best to consider each factor that influences hair growth separately.

DHT – The actions of the androgens testosterone and DHT are major factors in scalp hair growth and male

pattern baldness (androgenetic alopecia). Such androgens also stimulate axillary, pubic and beard hairs to grow. However, hairs such as eyebrows and eyelashes are not regulated by androgens. Testosterone is enzymatically converted by 5-AR to DHT in the hair follicle and DHT is thought to be the major factor in male pattern baldness.

But many men have high testosterone metabolite levels but never suffer hair loss. The ultimate factor in hair loss appears to be not DHT itself, but damage to the hair follicle. A recent study of 3,000 individuals found no link between baldness and the genes (5-alpha reductase) controlling the the production of testosterone metabolites. (5,6) Some researchers are of the opinion that if follicular health is improved or maintained, it is possible that hair loss can be reversed or minimized.

Miniaturized follicles – At age 15, hair follicles actively produce thick, heavy terminal hair for about 3.6 years during the anagen phase then shrink during the dormant telogen phase for about 4 months. As we age, the follicle's anagen phase progressively shortens while the telogen phase lengthens. The net result is a progressive shrinkage of follicle size during the anagen phase and this produces thinner, slower growing hair. (5,6) Hair conditioners are used to thicken the hair shaft with fats and proteins to give the appearance of fuller, more-youthful hair.

Increase in length of dormant follicle phase – While this change is usually attributed to DHT actions, other factors such a damage caused by excessive heat, coloring agents, and relaxers may also produce follicle damage that results in less functional follicles.

Inadequate follicle microcirculation – The synthesis of new hair necessitates a very high nutrient flow to the follicle bulb. Morphological studies often observe a markedly diminished capillary blood supply in aged, miniaturized follicles. This alone may be the cause of follicle miniaturization and inadequate hair syntheses. (5-7)

Inflammation around follicles – Many dysfunctional follicles appear to have an auto-immune inflammation around the follicle. It has been proposed that follicular inflammation is the final step in the sequence of events that ultimately produces inactive follicles that are incapable of producing thick, terminal hair. (5-7)

Decreased subcutaneous fat layer – The layer of fat at the base of the skin, also known as subcutaneous adipose tissue or colloquially called “baby fat”, diminishes with age. Researchers have noted the accumulation of this fat around healthy follicles that are vigorously growing hair, and its relative lack in around dormant follicles, and have postulated that these fat cells serve a supportive function for the hair follicle. Conditions that inhibit hair growth such as chemotherapy or starvation, also decrease the subcutaneous fat layer (5-7).

Damage from relaxers, excessive heat, coloring agents and dyes – Numerous common procedures damage scalp health and hair follicles. Scalp damage from relaxers, permanents, color cosmetics with their organic dyes and metallic salts, and excessive heat from blow dryers and hot oil treatments that can literally boil the follicles, all can combine to damage the hair follicle and reduce hair growth. This is often most noticeable in women as a decrease or loss of eyebrows and eyelashes by age 40.

Lack of sulfur donors – Hair is composed of 35% sulfur containing amino acids. Only feathers in birds have similar levels of such amino acids. Nutritional surfer supplements such as MSM (methyl sulfonyl methane) have long been used to improve the hair coats of racehorses and are increasingly being used to improve hair health in humans.

Graying of hair – The hair colors are produced in pigment cells in the follicles. The amino acid tyrosine is converted by the copper-containing enzyme, tyrosinase, into black pigments called melanin or eumelanin and a reddish pigment, produced by a separate gene, called heomelanin (or sometimes called phaeomelanin). In most

persons, hair color slowly decreases with age and may vanish to produce white hair in the elderly.

Excessive hair cutting – Dr. George Michael (founder of the George Michael Long Hair Clinics) emphasized that longer hair is healthier hair. It is possible that hair follicles require some tension produced by the weight of a heavy hair shaft in the same manner that muscles and bones whither when not stressed and exercised. Michael remembered that, in the Russia of his youth, women in their sixties often had healthy, waist-length hair. Later, when he worked in New York City, he found that virtually no women of this age possessed such healthy hair.

SRCPs to Stimulate Hair Growth

One of the more exciting developments in skin research in recent years is the finding that hair follicles are the source of stem cells for the skin. (8,9) But long before these discoveries that linked hair follicles and skin repair, I had observed that, after treating skin wounds with GHK-Cu, that there was a profound enlargement of the hair follicles of the skin at the wound edge. To develop these discoveries for commercial uses, in 1985 I started a company called ProCyte. Further work with radioisotopes in mice indicated that the SRCP was present at the site of injection for only about 30 seconds before being cleared from the area. This meant that a very brief exposure of the follicle to the SRCP was sufficient to produce an increase in hair follicle volume of 4 to 8-fold and increased hair growth within 12 days.
See Figure 2

.

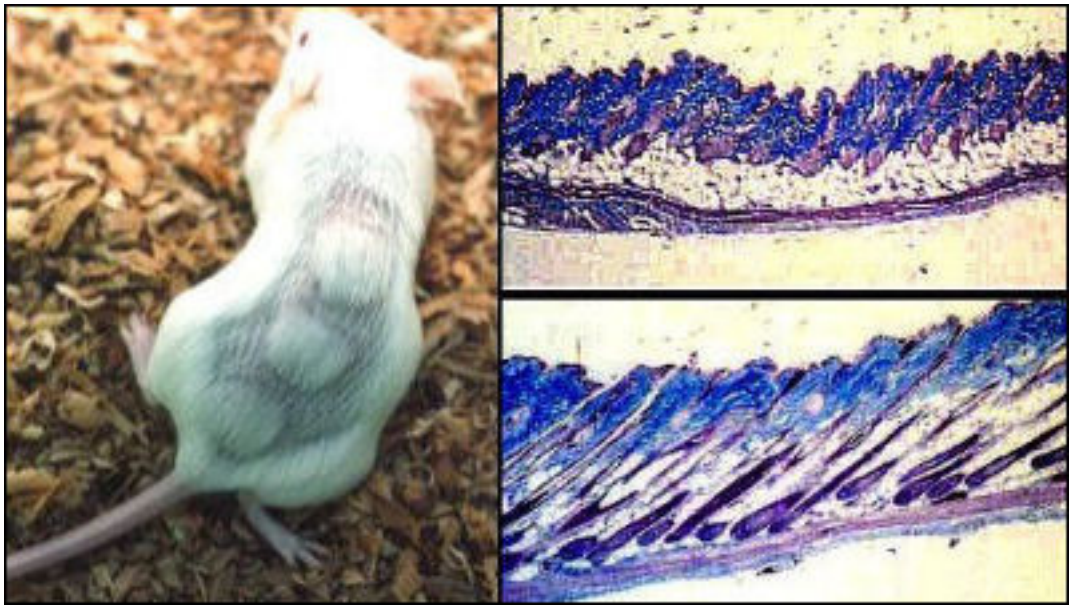


Figure 2 Legend. A 25 day-old mouse was shaved and injected intradermally in three spots with a SRCP. Twelve days later, there was a very strong stimulation of hair growth at the injection sites.

Further work by Steven Lovejoy (University of Washington) and myself found that the chemical addition of fat-like molecules, such as fatty acids or hydrophobic amino acid residues, to GHK-Cu, resulted in an intensified follicle enlargement action and more strongly stimulated the rate of hair growth in young mice. Even in undamaged mouse skin, one intradermal injection of the SRCPs induced accelerated hair growth after twelve days. Work with radioisotopes indicated that the SRCPs was present at the site of injection for only about 30 seconds before being cleared from the area. (10)

These discoveries were later verified and extended by Hideo Uno at the University of Wisconsin. Uno had written The UpJohn Company's textbook for physicians when Rogaine (minoxidil) first was marketed. Using hair growth models in mice and rats, Uno found that SRCPs convert fine, short vellus hairs into thicker pigmented terminal hairs.

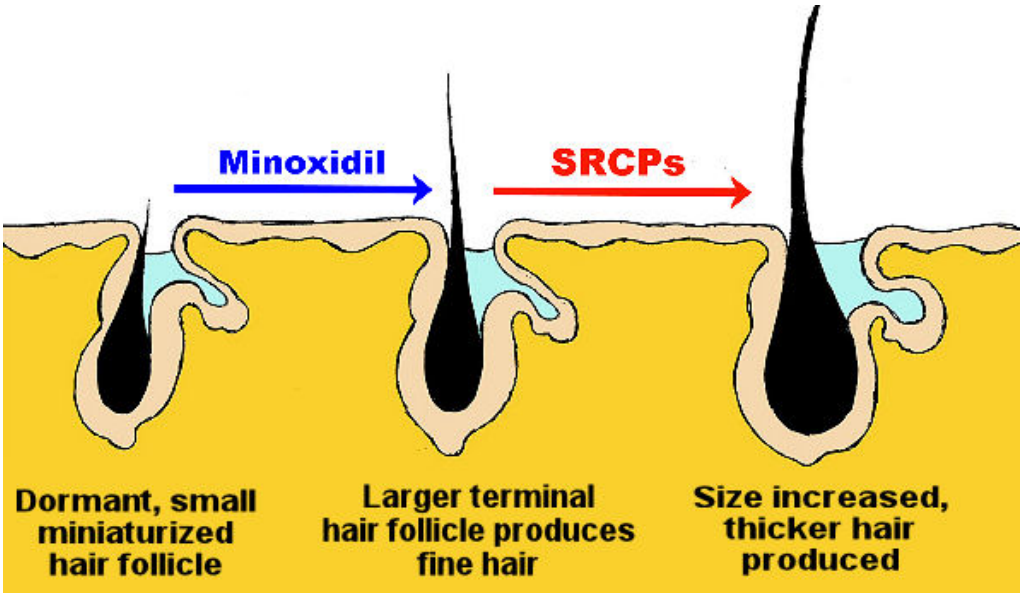
Uno studied the details of hair stimulation by SRCPs in C3H mice and "Fuzzy" rats by 1) phototrichogram, 2) folliculogram (micro morphometric analysis), and 3) the rate of DNA synthesis in the follicular cells. He found that in C3H mice, the SRCPs stimulated of the follicular cell proliferation, resulting in an enlargement of the anagen follicles from vellus types that produce small, thin hair to terminal follicles that produce thick, long hair. type The SRCPs also maintained follicles in the anagen phase longer. In Fuzzy rats, a genetic strain that has only short vellus hair, the SRCPs had the effect of enlarging the small vellus follicles. (11-12).

Also of interest were studies by Awa and Nogimori of Kaken Pharmaceuticals reported, that in mice, pretreatment with SRCPs blocked hair loss induced the cancer chemotherapy drugs cytosine arabinoside and doxorubicin. If mice were first treated with chemotherapeutic drugs to induce hair loss, subsequent treatment with SRCPs accelerated the recovery of lost hair. (13)

Bernard Kalis (University of Reims) was the first to demonstrate that SRCPs also had positive actions on hair follicle functions in humans. His studies used phototrichogram analysis that found SRCPs caused a greater proportion of human follicles to switch from the dormant telogen state into the hair-growing anagen state. (14) A later placebo-controlled, three-month study in male humans found a SRCP (Ala-His-Lys: copper(II)) in a product called Tricomin increased the terminal hairs and was 32% more effective than the control group that used 2% minoxidil in this study. (15)

Hideo Uno has commented that while minoxidil primarily stimulates new vellus hair growth, the SRCPs are more effective in the conversion of vellus hair into terminal hairs and suggested that the combined use of minoxidil and SRCPs would have a synergistic actions and be most effective. See Figure 2.

Note – Figure 3 is self explanatory about the actions of minoxidil and SRCPs.



SRCPs and Hair Transplantation

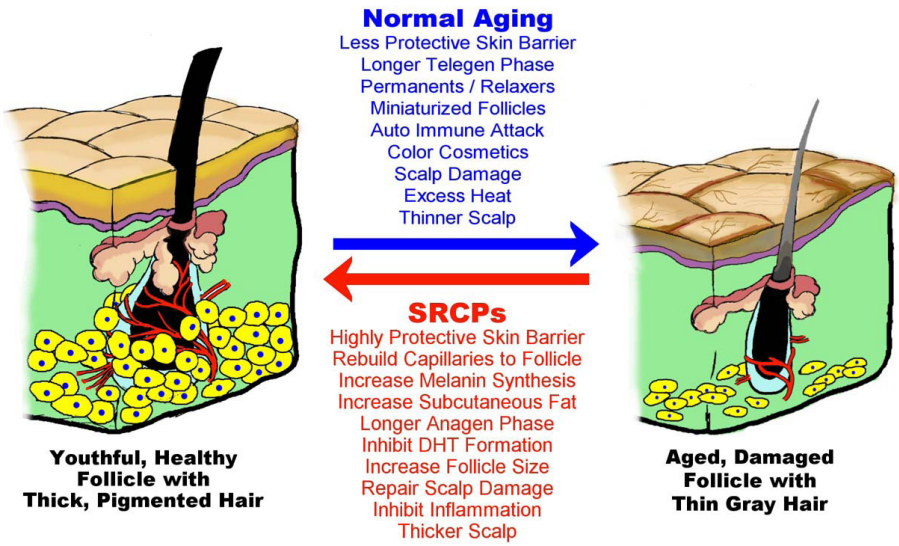
Another developing use for SRCPs is their use to improve human hair transplantation. GraftCyte, a copper peptide product sold by ProCyte, when used in the post-operative regimen results in faster healing of transplants and earlier regrowth of the hair shafts. GraftCyte is sprayed on the wound area after transplants. Controlled studies by Perez-Meza et al found that the GraftCyte system provided enhanced healing of the transplanted follicle and less post-operative hair shedding along with a more immediate hair growth. Patients see new hair growth in 6 weeks, versus the normal 10 to 14 weeks of other procedures. The normal skin crusting after transplantation has been reduced from 10 to 14 days to 5 days in most cases. (16).

A second controlled study of Graftcyte by Gary Hitzig on 30 hair transplant patients found that Graftcyte reduced percent of patient with shedding of transplanted hair from 30% with saline to 10% with Graftcyte. The time to healing of the transplant wounds using Graftcyte and Dr. Hitzig's procedure was 10-14 days with saline and 5-10 days with Graftcyte. Regrowth of new hair from the transplants occurred in 6-8 weeks with saline and 4-6 weeks with Graftcyte. Patient satisfaction after transplantation rose from 80% to 95%. (17) Graftcyte can be obtained from www.procyte.com.

Improving General Hair Vitality with SRCPs

While the above studies were encouraging, it is also apparent that the SRCPs are not miracle hair growth therapies. A more important future use of SRCPs may as a regular scalp treatment or hair tonic, used once or twice weekly, for the general improvement of hair and scalp health. SRCPs have numerous actions that may improve hair health. See Figure 4. These include:

Note – Figure 4 is self explanatory about aging and follicle damage.



Reduce DHT formation in the hair follicles – 5-alpha reductase exists in 2 forms; type 1 which function in hair follicles and type 2 which acts in prostate tissue. Follicle damaging DHT is produced in the hair follicles. Propecia (finasteride) inhibits 5-AR throughout the body and improves hair growth. But it works best on the type 2 form, and is best suited for for controlling prostate enlargement. It also must be administered by pills that spread the drug throughout the body. However, increased copper ions in the skin is better at inhibiting the type 1 5-AR that damages hair growth. Sugimoto et al (Sugimoto 1995) found that copper (II) ions could give up to a 90% inhibition of type 1 5-AR. at At 0.12 micrograms copper ion per milliliter, there was a 50% reduction in activity of type 1 alpha reductase but copper (II) ions were 10-fold less active on inhibiting the type 2 prostate type. Thus, copper ions are more specific inhibitors of 5-AR than finasteride. (18)

Human transdermal studies have found that concentrations up to 0.50 micrograms of copper ion can be introduced into the skin with SRCPs without skin irritation. For comparison, the blood plasma copper level is approximately 1 milligram per milliliter.

Improve Microcirculation to Hair Follicle – Hair follicles have very high rates of metabolic activity. However, morphological studies of aged follicles often find an inadequate capillary circulation and some have suggested that the resultant lack of nutrient flow may be a causative factor in the thinning of hair shafts with age. SRCPs have angiogenic activity may possibly correct this problem. (2)

Protective Anti-inflammatory Actions – The final event in the sequence of degenerative changes that produce involuted non-functional hair follicles are tissue-damaging auto-immune inflammatory and free radical reactions around the follicle. SRCPs may reduce such effects since they block both the inflammatory actions of both interleukin 1and TGF-beta-1 actions in inflammation. (19-21) Also during tissue injury, the release of ferrous iron from ferritin increases the formation of tissue-damaging free radicals, but SRCPs block the release of iron from ferritin. Finally, copper, zinc superoxide dismutase (SOD) is normally only about 50% activated due to a lack of copper in the protein. SRCPs can supply additional copper to SOD and increase its anti-oxidant effectiveness. (22)

Autoimmune damage causing hair loss exists in conditions such as alopecia areata, diabetes, vitiligo, certain types of thyroid disease, and pernicious anemia. The treatment for these conditions is usually a short course of any cortisone-type drugs which often restores hair growth. But cortisone injections into the bald spots bring the hair back only temporarily. The problem is that costicosteroids inhibit skin repair and often produce and thinner, less functional skin that is less able to support hair follicle functions. In studies on nickel allergy patients, Zhai et al wrote that SRCPs to be as potent as cortisone in reducing redness and inflammation while also stimulating skin repair in nickel allergy patients. (23)

Enhancement of the skin's subcutaneous fat layer and thickening of the scalp – During human aging, there is a thinning of the scalp. Part of this is due to a diminishment of the scalp's subcutaneous fat layer that surrounds the hair follicles diminishes with age. Pathologists have noted that large subcutaneous fat cells are associated with large, healthy hair follicles and are postulated to provide nutritional support to the follicles. Conditions that cause hair loss such as cancer chemotherapy are associated with a sharp decrease in the volume of subcutaneous fat cell. SRCPs increase both the hair follicles size and the amount of subcutaneous fat. (24)

SRCPs also help increase skin thickness by increasing the dermal levels of collagen, elastin, and the water-holding proteoglycans and glycosaminoglycans. (2-3)

Repair of Damaged Scalp – Hair loss, especially in women, may often be caused by scalp damage from relaxers, permanents, coloring chemicals, and excessive heat from blow dryers and hot oil treatments. This is often evident in women who have seriously thinned eyebrow by age 40 after decades of application of color cosmetics. SRCPs might be used after various hair procedures to speed repair of scalp damage.

Reduce Graying of Hair - Hair becomes gray with age but the speed that this happens may depend on the adequacy of available copper in the scalp. Melanin and other hair pigments are produced from the amino acid tyrosine by the action of tyrosinase, a copper-containing enzyme. Additional scalp copper might slow this graying process and our clients at Skin Biology have often reported the re-pigmentation of gray hair after using our Folligen products.

Future Development of SRCPs for Hair Health

While research between 1983 and 1991 established the potential uses of SRCPs, it also became apparent that much more effective and stable SRCPs were needed to develop practical and truly effective products. Therefore, in 1994, I founded Skin Biology to develop improved SRCPs.

Previously when I was at ProCyte, I had used chemical modifications of molecules to create more-active SRCPs. But the problem with this chemical approach is that the human body often has difficulty metabolizing alien molecules. Peptides from soy protein digests have a long history safe use in products ranging form solutions used for intravenous alimentation to hair conditioners used to add body to hair. At Skin Biology, we isolated a special from the soy protein digests. When this fraction when chelated to copper (II) produces a very strong stimulation of hair growth in standard models in mice, strongly stimulated skin rebuilding, and had anti-

inflammatory actions. (23,25-28)

To enhance the uptake of SRCPs into the skin and hair follicles, we focused on natural penetrating agents such as emu oil or squalane from olives to push more SRCP into the skin. We also are testing the use of encapsulating the SRCPs in newer types of advanced liposomes to increase potency. Several products based on this new technology are being test marketed at www.folligen.com.

There is also the possibility that some variant of SRCPs could be used to induce hair follicle multiplication. Often during studies in mice, we have observed what appeared to be an increased production and density of hair follicles. This effect was often observed during skin transplantation experiments and may more complex than the more simple enlargement of hair follicle size that we most often observed. See Figure 5. Dermatological dogma is that hair follicles never multiply but, in the era of stem cells and DNA cloning, anything is possible.

References

1. Pickart, L. A tripepeptide in human serum that promotes the growth of hepatoma cells and the survival of normal hepatocytes, Ph.D. thesis, Univ. of California, San Francisco, 1973

2. Pickart, L. , Copper Peptides for Tissue Regeneration, Speciality Chemicals 2002 (October) pages 29-31

3. Pickart, L., Reversing Skin Aging with Copper Peptides, Body Language Dermatol. 2003 (April) pages 12-13

4. Pickart, L., Copperceuticals and the Skin, Cosmetics & Toiletries 2003; 118, 24-28.

5. Ellis, J.A., Stebbing, M., Harrap, S.B., Genetic analysis of male pattern baldness and the 5-alpha reductase genes, J Invest Dermatol 1998; 110, 849-853

6. Uno, H., The Histopathology of Hair Loss (Publisher: The UpJohn Company, Kalamazoo, MI) 1988

7. The Molecular and Structural Biology of Hair (Stenn K.S., Messenger A.G., and Baden H.P, (eds). Ann NY Acad Sci; New York: New York Academy of Sciences) 1991.

8. Jahoda, C.A., Whitehouse, J., Reynolds, A.J., Hole, N., Hair follicle dermal cells differentiate into adipogenic and osteogenic lineages. Exp Dermatol. 2003; 12, 849-859.

9. Lavker, R.M., Sun, T.T., Oshima, H., Barrandon, Y., Akiyama ,M., Ferraris, C., Chevalier, G., Favier, B., Jahoda, C.A., Dhouailly, D., Panteleyev, A.A., Christiano, A.M., Hair follicle stem cells, J Investig Dermatol, 2003; 8, 28-38

10. Pickart, L., New metal peptide complexes and derivatives used for stimulating growth of hair in warm-blooded animals, especially humans, US Patent 5,120,831; Compositions for stimulating hair growth containing cupric complexes of peptide derivatives including. glycyl-l- histidyl-l-lysine n-octyl ester. US Patent 5,177,061; New glycyl-histidyl-lysyl copper compounds used in stimulating hair growth; US Patent 5,214,032; Metal-peptide compositions and methods for stimulating hair growth, US Patent 5,550,183

11. Trachy, R., Fors, T.D., Pickart, L. Uno, H. The hair follicle stimulating properties of peptide copper complexes. Results in C3H mice. Ann N Y Acad Sci 1991;642, 468-469

12. Uno, H., Kurata, S. Chemical agents and peptides affect hair growth. J. Invest Dermatol 1993; 101, 143S-147S

13. Awa, T., Nogimori, K., Trachy, R. Hairloss protection by peptide-copper complex in animal models of chemotherapy-induced alopecia. J Dermatol Sci 1995; 10, 99-104

14. Trachy, R., Patt, L., Duncan, G., Kalis, B., Phototrichogram Analysis of Hair Follicle Stimulation: A pilot clinical study with a peptide-copper complex, in: Dermatological Research Techniques, (Edited by H.I. Maibach, CRC Press), 1996, pp-217-226

15. Press release, Procyte Corporation, 1997

16. Perez-Meza, D., Leavitt, M., Trachy, R. Clinical evaluation of GraftCyte Moist Dressing on hair graft viability and quality of healing. Inter J Cos Surg 1998; 6, 80-84

17. Hitzig,G. Enhanced healing and growth in hair transplantation using copper peptides, Cosmetic Dermatol 2000 (June) ; 13, 18-21

18. Hitzig,G. Enhanced healing and growth in hair transplantation using copper peptides, Cosmetic Dermatol 2000 (June) ; 13, 18-21

19. Pickart, L., New glycyl-histidyl-lysine ester copper complex compounds with anti-inflammatory and superoxide dismutase activity useful for enhancing wound healing. US Patent 4,877,770; New anti-oxidative and anti-inflammatory metal peptide complexes - containing. glycyl histidyl and lysine residues used to enhance or restore resistance to oxidative or inflammatory damage. US 5,118,665

20. Vinci C., Caltabiano V., Santoro A.M., Rabuazzo A.M., Buscema M., Purrello R., Rizzarelli E. Copper addition prevents the inhibitory effects of interleukin 1-beta on rat pancreatic islets. Diabetologia. 1995; 38:39-45

21. McCormack MC, Nowak KC, Koch RJ. The effect of copper tripeptide and tretinoin on growth factor production in a serum-free fibroblast model. Arch Facial Plast Surg 2001; 3:28-32

22. Miller D.M., DeSilva D., Pickart L., Aust S.D. Effects of glycyl-histidyl-lysyl chelated Cu(II) on ferritin dependent lipid peroxidation. Adv Exp Med Biol 1990; 264: 79-84
23. Zhai H., Chang Y.C., Singh M., Maibach H.J. In vivo nickel contact dermatitis: human model for topical therapeutics. Contact Dermatitis 1999; 40: 205-208

24. Pickart, L., Skin treatment composition comprises GHL-CU or derivatives for improving skin health, increasing subcutaneous fat, dermal thickness and density. US Patent 5,135,913

25. Pickart, L., Tissue protective and regenerative compositions, US Patents 5,382,431, US 5,888,522, US 5,554,375

Note on reference 25 – The title of all three patents is the same. But they make different claims on the same text.

26. Zhai H., Poblete N., Maibach H.J. Stripped skin model to predict irritation potential of topical agents in vivo in man. Inter J Dermatol 1998; 37: 386-389

27. Zhai H., Leow Y.H., Maibach H.R., Human barrier recovery after acute acetone perturbation: an irritant dermatitis model. Clin Exp Derm, 1998: 23: 11-13

28. Zhai H., Leow Y.H., Maibach H.R., Sodium lauryl sulfate damaged skin in vivo in man: a water barrier repair model. Skin Res Tech, 1998: 4: 24-27

29. For more references, see www.skinbiology.com/copperpeptideregeneration.html