



# Skin Remodeling with Copper Peptides

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(English Version Below)

**Loren Pickart PhD**

(Interview with Dr. Loren Pickart - April 2004)



Интервью с доктором Лореном Пикартом

Я давно мечтала встретиться с доктором Пикартом. Во-первых, я не раз встречала в американской прессе статьи о медьсодержащих пептидах, которые он открыл. Во-вторых, выяснилось, что мы с ним почти соседи - его офис расположен в получасе езды на машине от моего нынешнего дома. И вот встреча состоялась. Поводом послужила публикация статьи доктора Пикарта в нашем журнале. Конечно, я воспользовалась этой возможностью, чтобы задать ему все те вопросы, которые у меня возникли после знакомства с его работами.



- Мистер Пикарт, я правильно поняла, что медь содержащие пептиды - это ваше открытие? До вас об их свойствах было ничего не известно?

- Я не могу сказать, что медь и пептиды, содержащие медь, до нас никто не изучал. Например, было уже известно, что медь необходима для работы такого важного антиокислительного фермента, как супероксиддисмутаза (СОД). Химики также исследовали связывание меди с различными пептидами. Однако вот эту молекулу, модель которой я держу сейчас в руке, - медьсодержащий пептид человеческого организма - до нас не изучал никто.

Это все произошло в 70-е годы, когда я работал в университете Калифорнии в Сан-Франциско. В те годы на медицину возлагали большие надежды. Многие ученые верили, что в ближайшие 10 лет им удастся придумать вакцину от рака. Я же решил заняться старением, рассудив, что в этом случае я никогда не останусь без работы.



До



После



Мы работали с клетками крови и открыли пептиды, содержание которых в молодых клетках было выше, чем в старых клетках. Позже мы обнаружили, что мы можем сохранять стареющие клетки крови дольше, просто добавляя к ним эти вещества. Однако нам потребовалось еще 15 лет, чтобы понять, как они работают. Сейчас мы знаем, что медьсодержащие пептиды являются сигналом для восстановления кожи, костей и волосяных фолликулов. И я подозреваю, что они являются универсальным сигналом к восстановлению для всех тканей.

- То есть они являются факторами роста?

- Нет, их роль гораздо шире. Давайте посмотрим на повреждение кожи. Сначала формируется тромб. Затем в поврежденной ткани начинают генерироваться активные формы кислорода, которые очищают рану от бактерий. Затем, клетки начинают вырабатывать трансформирующий фактор роста TGF-?, который побуждает кожу формировать рубцовую ткань. И все это время в поврежденной ткани накапливаются медьсодержащие пептиды, которые в какой-то момент ингибируют как продукцию свободных радикалов, так и продукцию TGF-?...

- Интересна связь медьсодержащих пептидов и свободных радикалов. Я читала, что, по мнению ряда ученых, свободные радикалы являются сигналом к восстановлению тканей, и что чрезмерное увлечение антиоксидантными продуктами может угнетать восстановление тканей.

- Я верю, что хорошее окисление на ранних этапах необходимо для заживления ран. Можно существенно ускорить заживление ран, применяя сначала агенты, усиливающие окисление, и затем медьсодержащие пептиды. Можно также применять на ранних этапах средства, содержащие TGF-?, а затем уже наши пептиды.

- В ваших статьях говорится, что эти пептиды обладают антиоксидантным и противовоспалительным действием, препятствуют образованию шрамов, усиливают ангиогенез (рост новых сосудов), привлекают макрофаги к ране, стимулируют рост волосяных фолликулов, усиливают разрушение коллагена и стимулируют образование нового коллагена...

- Да, они словно выключают окисление, разрушение ткани и формирование рубца и затем включают процесс воссоздания нормальной структуры ткани.

- Трудно поверить, что одна молекула способна оказывать все эти эффекты.

- Для нас это тоже было сюрпризом. Ведь далеко не все эти результаты были получены нами. Часть исследований была проведена во Франции, Германии, других странах. Например, данные о том, что пептиды стимулируют рост нервных отростков, получили французские ученые, влияние на ангиогенез исследовали в Национальном онкологическом институте США, антиоксидантное действие изучали в Университете Юты и т.д. Между прочим, в России тоже есть группа, которая изучает роль медьсодержащих пептидов при восстановлении печени.

- Кстати, в вашей статье вы упоминаете о том, что мокрые и окклюзивные повязки подавляли эффект медьсодержащих пептидов. Я же слышала, что влажное покрытие ускоряет заживление ран.

- Раньше, когда не было антибиотиков, врачи старались сохранять рану как можно более сухой, чтобы предотвратить развитие инфекции. Но затем, действительно, ученые обнаружили, что под влажной повязкой рана заживает быстрее и вероятность образования шрамов меньше. Поэтому мы тоже

пробовали применять влажные и водонепроницаемые повязки. Однако оказалось, что в этом случае рана, обработанная медьсодержащими пептидами, становится слишком мокрой. Вероятно (мы не исследовали это достаточно подробно, поэтому я не упоминаю об этом в статье), они вызывают расширение сосудов, что приводит к повышению содержания влаги в коже. Так что мы решили, что нанесение кремов или гелей на рану под легкую повязку или без повязки - это лучшая стратегия.

- Мы все время говорим о заживлении ран, о медицинском применении медьсодержащих пептидов. Но сейчас, как я поняла, они применяются не в медицине, а в косметике.

- То, что произошло, очень характерно для современной косметологии. Изначально мы разрабатывали эти препараты для врачей. Однако мы столкнулись с тем, что врачи очень неохотно соглашались пробовать что-либо новое. К тому же процедура регистрации лекарственного средства в США невероятно усложнена. На это требуются огромные средства. В косметологии все наоборот - зарегистрировать новый косметический ингредиент просто, а женщины обожают пробовать новые продукты. Я знаю, что во многих косметических средствах сейчас применяются ингредиенты, которые могут в будущем стать лекарствами. Разумеется, для того, чтобы вещество могло применяться в косметологии, оно должно быть безвредно. Но мы не нашли у медьсодержащих пептидов никаких побочных эффектов, никакой токсичности. Они абсолютно безопасны, они присутствуют в нормальном организме и являются лишь сигналом к восстановлению, а не модифицируют этот процесс. На наш взгляд, это идеальные свойства для косметического ингредиента.

- То есть при бесконтрольном применении косметики, содержащей высокую концентрацию медьсодержащих пептидов, нет опасности, например, воспаления или образования рубцов?

- Нет, напротив, вероятность образования рубцов и воспаления уменьшается. Некоторые женщины, использующие наши продукты, даже утверждают, что у них исчезают шрамы и растяжки. Вообще мы получаем поразительно хорошие отзывы. Особенно нравятся наши продукты женщинам 40-50 лет. Они покупают у нас образцы, затем возвращаются и покупают еще, а потом начинают буквально обмазываться нашими кремами с ног до головы, а также пользоваться ими детей, мужей и домашних питомцев. Наверное, это главным образом заставляет нас продолжать исследования, поддерживает наш интерес к этим веществам.

- Как я поняла, ваши продукты существенно вмешиваются в физиологию кожи. Между тем FDA по-прежнему разграничивает косметику и лекарство, оставляя за косметикой право лишь украшать, очищать и защищать кожу, но не влиять на ее физиологию.

- Любое вещество влияет на кожу. Простейшие эмульсии, даже обычная вода, нанесенные на поверхность кожи, влияют на нее. Эксперты FDA это прекрасно понимают. И они понимают также, что сейчас все больше людей хотят хорошо выглядеть и иметь здоровую кожу, хотят, чтобы косметика действовала. Сейчас FDA просто закрывает глаза на существование косметических ингредиентов, но я не сомневаюсь, что в недалеком будущем законы будут изменены.

- Я знаю, что ряд косметических компаний производит косметику по вашей технологии, и в будущем таких компаний, вероятно, будет больше. Вы верите, что все они будут использовать достаточно высокие концентрации медьсодержащих пептидов?

- К сожалению, большинство косметических компаний не очень заботится о том, чтобы их продукты действовали. Им главное добавить модный ингредиент в рецептуру, поместить его название на упаковке и в рекламном тексте, и остальное их не интересует. Я знаю, что компании, которые производят достаточно сильные продукты, тратят огромные средства на тестирование и разработку рецептур.

Ведь проблема тут не только в концентрации. Медьсодержащие пептиды - деликатные молекулы, они могут терять активность и даже разрушаться в процессе приготовления косметики. Поэтому нужно обязательно проводить дерматологические исследования готовых продуктов.

- Получается, что пока производить действенную косметику, за которой стоят серьезные научные исследования, менее выгодно, чем косметику, содержащую красиво и заманчиво звучащие, но бесполезные ингредиенты?

- К сожалению, это так. Но ситуация уже меняется. Чем больше появляется косметики, которая может решать какие-то проблемы кожи, тем ближе то время, когда производить действующую косметику станет выгоднее, чем создавать иллюзию эффективности.

- Как я знаю, вы практически не производите косметику на продажу и в основном занимаетесь исследованиями. Вы не думали о создании собственной профессиональной косметической линии? Такой, в которой будет достаточно высокая концентрация медьсодержащих пептидов, где не будет вредных для кожи ингредиентов и которая будет помогать людям сохранять кожу молодой и здоровой?

- Думал, и не раз. Но, наверное, я все-таки не буду это делать. Производство и продвижение косметики - хлопотное занятие, требующее ежедневного напряженного труда. Я предпочитаю научную работу. Мне 65 лет, и я уже хочу не только работать, но и наслаждаться жизнью.

Беседу провела Анна Марголина (февраль, 2004, Белвью, США).

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Медицинская рекламная сеть!

## English Translation

### Skin Remodeling with Copper Peptides - Loren Pickart PhD

Skin remodeling is a process that restores normal skin morphology after various types of wounds, injuries, and skin damage. Development of effective cosmetic skin remodeling is becoming an increasing focus of dermatologists and their clients. As we age, the dermis and epidermis thins and accumulates blemishes, lesions and imperfections. Extracellular matrix proteins such as collagen and elastin become damaged and lose their resiliency while the water-holding proteins and sugars diminish. The capillary network becomes less functional which produces a "graying" of the skin, the subcutaneous fat cells diminish in number, and fewer protective oils are secreted on the skin's surface. These aging effects are intensified by exposure to ultraviolet rays, irritants, allergens, and environmental toxins. The end result is a dry, wrinkled, inelastic skin populated by unsightly lesions.

Restoration to a biologically younger skin requires two linked processes: first, the removal of damaged proteins and aberrant skin lesions, and second, their replacement with normal, blemish free skin. This process is similar to the remodeling phase of wound healing in which scar tissue is removed, slowly restoring the skin to its original state.

Many skin renewal techniques are used that produce skin remodeling but all have drawbacks. Retinoic acid

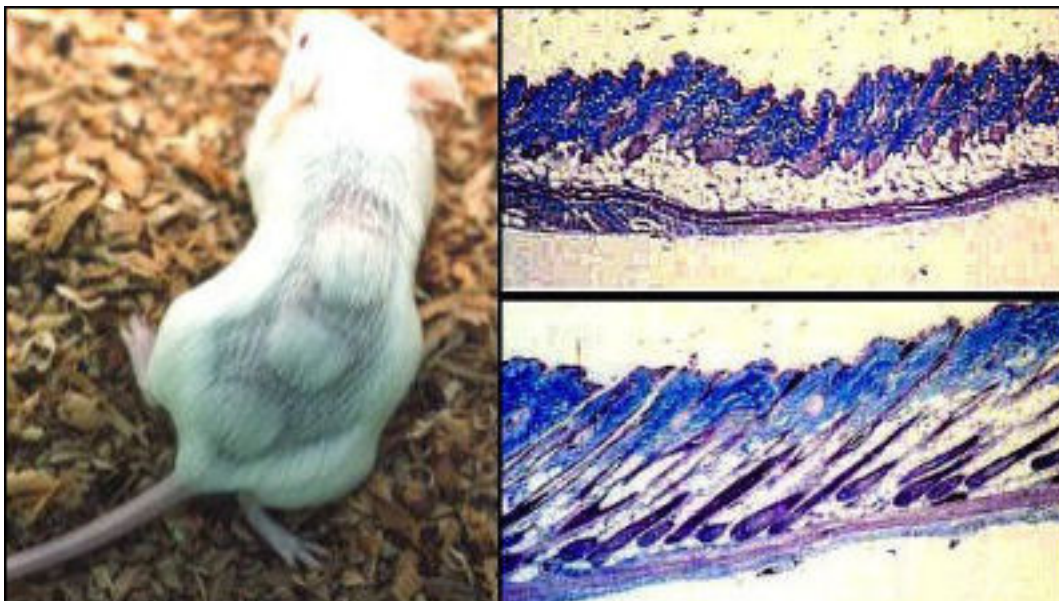
slowly remodels skin but at the price of chronic irritation and redness. Certain peptides, melatonin, and vitamin C increase skin collagen but skin also needs replacement of elastin, water-holding proteoglycans, and its microcirculation must be rebuilt. A class of pentapeptides and aminopeptides, that function like TGF-beta-1, are the latest “hot” product in cosmetic creams. Such peptides increase the skin's extracellular matrix proteins and were extensively tested in the 1990s for wound healing, but produced unacceptable skin thickening and scarring because they do not adequately remove older pre-existing proteins. Lasers, chemical peels, and dermabrasion work well only if there is a vigorous post-therapy regenerative response from the damaged skin.

### **Cosmetic Skin Remodeling and Wound Healing**

Children have beautiful skin because remodeling processes function efficiently and skin damage is rapidly removed. Sadly, in adults, remodeling slows drastically and various skin lesions may persist for years or decades.

Skin remodeling is best understood in the context of wound healing. Cosmetic remodeling of uninjured skin appears to be a similar process since the human body uses the same, or slightly modified, biochemically mechanisms, over-and-over again, for closely related purposes. Many dermatological techniques (lasers, dermabrasion, chemical peels) used for skin remodeling actually induce a mild wounding to trigger the remodeling process.

After skin wounding, blood clotting forms a covering over the injury, followed by the activation of a variety of anti-microbial sterilising and tissue-destructive processes. Neutrophils infiltrate the wound area and secrete toxic oxygen radicals to kill invading bacteria. Production of the cytokine interleukin-1 activates an inflammatory response. Fibroblasts enter the region and produce TGF-beta 1, a protein that induces the formation of protective scar tissue over the wound. After this initial phase, the oxygen radicals are neutralized and the production of interleukin-1 and TGF-beta-1 is suppressed. Metalloproteinases and macrophages remove the scar tissue and cellular debris. The extracellular matrix is rebuilt with new collagen, elastin, and proteoglycans. Recent work, in the last few years, with genetically modified mice, has also emphasized the key role of hair follicles and their associated sebaceous glands in the production of new skin cells. Stem cells for skin are now thought to arise from enlarged hair follicles, primarily the follicles that produce the fine vellus hair on the human body. (1)



Top Right. Mouse skin treated with one injection of saline. Bottom Right. Mouse skin after one injection of GHK-Cu. Note the much larger hair follicles (colored dark-purple) that grow larger and further down into the skin. It is from such enlarged vellus hair follicles in humans that new stem cells are seeding into the skin for remodeling.

## Glycyl-L-histidyl-L-lysine:copper(II) as the Activator of Remodeling

It now appears that a human copper peptide complex, GHK-Cu (glycyl-L-histidyl-L-lysine:copper(II)), is the primary activator of skin remodeling, and that remodeling is a more complex process than originally envisaged. GHK-Cu and certain copper peptide complexes, are increasingly used in cosmetic skin and hair care products, and after clinical skin renewal procedures; such as chemical peels, laser resurfacing, and dermabrasion, to improve post-treatment skin recovery. GHK-Cu exerts protective and regenerative effects on several organ systems including skin, hair follicles, bone, gastric and intestinal linings, and the liver. Although the understanding of the biochemical actions of GHK-Cu is still incomplete, the situation is like a jigsaw puzzle where enough pieces have been assembled to understand the overall picture.

GHK-Cu is found in human plasma, saliva and urine.

In plasma, it appears to be bound to plasma albumin at a concentration of approximately 200 ng/ml at age 20 which declines to 80 ng/ml by age 60 (2). GHK is a rare sequence, existing mainly in inflammation-associated and of the extracellular matrix proteins, such as collagen, thrombospondin, fibrin  $\alpha$ -chain, prokininogen, complement C1q, interleukin 4, skin collagenase, coagulation factor XI and SPARC (3). During episodes of tissue damage, GHK is generated by proteolysis (4). Numerous cell culture studies have found that the biologically effective levels GHK-Cu are approximately  $10 \times 10^{-9}$  M (5).

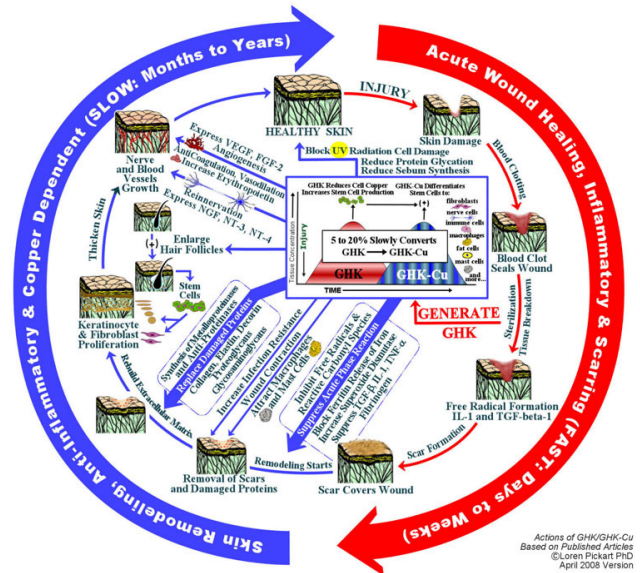
In vivo, GHK probably exists as a mixture of GHK and GHK-Cu. GHK has a high binding affinity for copper (II) ( $pK=16.2$ ) that is similar to albumin's copper (II) binding ( $pK=16.4$ ). GHK can obtain copper (II) from albumin. However, under physiological conditions only about 5% to 20% of GHK molecules would be expected to exist as GHK-Cu complexes with copper (II) (5). Biological actions have been reported for both GHK and GHK-Cu, although GHK is likely to chelate available copper while, conversely, GHK-Cu may lose copper to other binding proteins. Experiments using either molecule are actually studying a mixture of both. Free GHK-Cu, not bound to albumin, is a fragile molecule sensitive to carboxypeptidase actions and degrades rapidly (6).

### Biochemical Actions of GHK-Cu and Skin Remodeling

GHK-Cu takes a role in many biochemical events involved in skin remodeling (Table 1). Most surprising is that the molecule possesses a diverse multiplicity of actions all connected with skin remodeling. These include powerful anti-inflammatory actions that function to shut-down the initial phase of wound sterilization and scar formation (7-10). The molecule activates m-RNAs for both metalloproteinases that remove damaged protein and for extracellular matrix proteins such as collagen, elastin, and proteoglycans. (11-14) It chemoattracts tissue-repairing macrophages (15) while also stimulating angiogenesis (7,16) and neuronal outgrowth (17,18).

When used for wound healing, GHK-Cu markedly increases the size of hair follicles and their sebaceous glands, adjacent to the wound edge (19-20) and analogs of GHK-Cu are marketed by ProCyte and American Crew for hair transplantation ("Graftcyte") and stimulation of hair growth ("Tricomin"). A link between hair follicles and skin repair was postulated over 60 years ago during World War II when surgeons observed that skin recovery after burn injuries could be predicted by observing the return of hair follicles to the wound edge. If an abundant number of dermal hair follicles were observed at the wound edge, then scar removal followed by the re-estab-

### SKIN RENEWAL CYCLE



ishment of normal skin would occur. However, if there was a deficiency of hair follicles, then inadequate healing would follow and scar tissue remained. This action of GHK-Cu on hair follicles, in accord with the studies on hair follicles and stem cells cited above (1) further strengthens evidence that GHK-Cu functions as a remodeling signal.

**Table 1. Actions of GHK-Cu on Skin Remodeling**

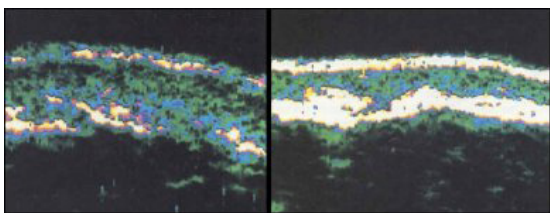
Biochemical Reaction	Acts by	Result	Reference
1. Suppression of initial oxidative sterisation, inflammation, and scar formation	Blocks ferritin channels that release ferric ions	Stops iron induced tissue oxidation	8
	Suppresses TGF-beta production by fibroblasts	Stops production of scar forming proteins	10
	Concentrates copper (II) ion in wound area	Activates Cu, Zn Super-oxide Dismutase	7
	Blocks cell damaging actions of interleukin-1	Stops post-wounding cellular damage	9
2. Removal of damaged molecules and cellular debris	Stimulating production of M-RNA, and synthesis of, metalloproteinases and anti-proteinases	Remove damaged collagen and elastin, Reduce blemishes and scars while smoothing skin	11 to 14
	Stimulating production of M-RNA and synthesis of collagen, elastin, and proteoglycans	Rebuilding of extracellular matrix proteins, Increases elasticity, firmness, and water-holding properties of skin	11 to 14
3. Repair Phase - Scar Tissue and cellular debris removed and replaced with normal skin	Chemoattractant for capillary cells and induction of angiogenesis	Rebuilding of the skin's microcirculation, increase youthful "glow"	7, 16
	Chemoattractant for macrophages that remove debris and release cellular growth factors	Enhance repair processes	15
	Promotes nerve out-growth	Restores innervation of damaged skin	17, 18
Markedly increases hair follicle size	Follicles produce stem cells that produce new skin cells	Newer, younger-looking skin	19, 20
Repairs and tightens skin barrier	Restores protective actions of skin	Reduces water loss, More resistance to entry of viruses and bacteria	33-36

### **Skin Repair and Remodeling**

Initially GHK-Cu was studied as a factor that increased the survival of many types of cell cultures and organ cultures. The first in vivo effect that I observed in 1984 was an acceleration of wound healing in a variety of animal models (21). In 1985, I started a company, ProCyte Corporation, to develop GHK-Cu into products for

human use. A few examples of healing actions include: the healing of pad wounds in dogs (22), more rapid wound closure and production of granulation tissue (23). Healing with GHK-Cu works best with light bandaging. Wet bandages nullified the effects (22). In immunosuppressed rats, healing is impaired and collagen synthesis is 23% of that in normal rats. GHK-Cu more than tripled collagen synthesis in these rats, raising it to 77% of normal; restoring normal wound healing (24). In punch biopsy wounds in pigs, intradermal injections of GHK-Cu produced highly localized patterns of healing. Thus, in animal or human studies, it is possible to test several potential formulations on a given test subject (25). A GHK-Cu cream used after Moh's surgery increased wound healing and skin re-epithelialisation (26). An open study of wounds in 60 patients in 1987 with diabetic and venous stasis ulcers gave evidence of rapid healing (27). This study used high concentrations of GHK-Cu and very low concentrations of anti-microbial agents. This apparently successful GHK-Cu formulation was never used in later clinical studies, which did not achieve therapeutic goals in FDA controlled trials.

The first suggestion that GHK-Cu was a remodeling agent came from studies that indicated that both collagen synthesis and breakdown were stimulated by GHK-Cu. In 1987, I also found, that the application of skin creams containing GHK-Cu, increased the thickness of the epidermis and dermis, increased skin elasticity, reduced wrinkles, and resulted in a removal of skin imperfections such as blotchiness and sun damage marks, while producing a significant increase in subcutaneous fat cells (28). But this observation was not pursued until recently. Finally, between 1998 and 2002, more extensive human studies solidified these observations. Abulghani et al reported GHK-Cu was more effective in stimulating new collagen development than vitamin C, retinoic acid, or melatonin (29). Appa et al reported that in eight weeks, a GHK-containing liquid foundation improved epidermal thickness, increased skin elasticity, and improved skin appearance (30). Leyden et al found, in another eight week study, such creams to reduce visible signs of photodamage and increased skin density in eight weeks on facial skin (31) and also in a further, placebo-controlled study (71 females, 12 weeks) found that GHK-Cu-containing face creams reduced wrinkles and fine lines while increasing skin elasticity, density and thickness while another placebo-controlled study (41 females, 12 weeks) found that a GHK-Cu containing eye cream reduced wrinkles and fine lines and improved eye appearance (32). Cosmetic products that contain GHK-Cu include lines such as Visibly Firm by Neutrogena and Neova by ProCyte. We expect more products using GHK-Cu to be marketed in the future since ProCyte's patent on cosmetic uses of GHK-Cu expires in May 2004.



Skin of 51 year old woman.

Left - before treatment.

Right - after three weeks of treatment with GHK-Cu.

*The skin became tighter and denser with more collagen (bright areas).*

### **Development of Improved Skin Remodeling Copper Peptides.**

The first generation products designed around GHK-Copper performed well in many controlled tests, however, the products failed in FDA clinical trials on the healing of very difficult-to-heal human wounds (as have many other approaches). The actions of GHK-Cu are limited by its fragility and tendency toward breakdown and also its lack of adhesion to the skin surface.

Therefore, in 1994, I started Skin Biology to develop improved second generation, skin regenerative/remodeling, copper peptides with enhanced potency, breakdown resistance, and high adherence to skin. We isolated peptide fragments from soy protein digests that possessed the desired qualities when chelated to copper (II). Such peptides have a very low antigenicity and long history of safe use in cosmetic products. In veterinary studies, creams made from these new copper complexes produced rapid and scar-free healing in dogs after spaying operations, and in young horses after leg-straightening operations. This allowed the dogs to be returned to their owners in four days instead of the usual five, while the foals were returned in five days instead of seven. How-



ard Maibach and colleagues (UCSF) tested these new copper peptides in four small, placebo-controlled human studies. They found that creams made from these new copper complexes produced significantly faster skin healing and reduced redness and inflammation after mild skin injuries brought on by tape stripping (33), acetone burns (removal of skin lipids) (34), 24-hour detergent irritation (35), and nickel allergy inflammation (36).

### **Current Research on Remodeling Copper Peptides**

**Scarless Healing** – Our current research at Skin Biology is opening an approach to scarless or nearly-scarless healing of surgical incisions. GHK-Cu markedly reduces scarring after surgery if injected (an aqueous solution of 1 mg/ml) down the incision line. However, the second generation copper peptides appear to be superior for such uses. In veterinary studies, the application of 2nd generation copper peptides in creams immediately after surgery produced rapid and scarless healing in dogs after spaying operations and in young horses after leg-straightening operations. This allowed the dogs to be returned to their owners in four days instead of the usual five, while the foals were returned in five days instead of seven. For such uses, the incisions should be left open to air or only lightly covered with gauze. Occlusive dressing and wet bandages nullify the positive effect.

**Post-Procedure Treatments** - Both GHK-Cu and the second generation copper peptides function well to improve the recovery of skin after procedures such as deep peels, laser resurfacing, and dermabrasion. ProCyte Corporation markets their “Cu-3” line for such uses. If the skin is treated with copper peptides within two hours after the procedure, post-treatment redness and inflammation is avoided without the use of corticosteroids. Skin rebuilding is hastened while scars and infections are greatly lessened. At Skin Biology, we are developing a water based product, called CP Serum, that works especially well for these uses. This product is often followed by either emu oil or squalane which act as moisturizers and as penetrating agents that push more copper peptide into the skin.

**Removal of Skin Lesions** - The second generation copper peptides work well for the removal of skin lesions. Our research finds that most skin imperfections (hypertrophic scars, pitted scars, skin tags, moles, actinic keratosis) can be removed or greatly reduced by repeated daily use of hydroxy acids to loosen and dissolve the lesions followed by strong copper peptides to aid skin regeneration. Hydroxy acids such as 2% salicylic acid (pH=3.2) or 14% glycolic acid (pH=3.9) are effective with copper peptides but obtaining a cosmetically satisfying result may require several months of applications. The use of stronger hydroxy acids, followed by the application of copper peptides greatly speeds the removal of lesions and scars, but can be very irritating if not expertly applied. For example, to remove moles, 70% glycolic acid is applied for 6 minutes, washed off, then the strong copper peptides are applied to the moles. Two to three days of this procedure often removes moles permanently.

### **Safety of Copper Peptides**

Numerous safety tests of skin regenerative copper peptides have failed to find any toxicity problem. Extremely small amounts penetrate the skin and no rise in blood copper has ever been found in animals or humans treated with copper peptides. Further reassurance as to the safety of copper peptides is that in nutritional studies, increased supplementation with copper has been reported to increase DHEA levels (37), raise brain enkephalins (38), reduce carcinogenesis and cancer growth (39-41), reduce the development of cardiovascular disease (42), reduces the markers of osteoporosis (43), reduce rheumatoid arthritis (39), improve immune function (44), reduce protein glycation (45) and deleterious peroxidation of fats and red blood cells (46), reduce brain developmental defects in offspring (47), and increase anti-oxidant defenses by activation of superoxide dismutase (48). Indeed, many researchers have noted that copper supplementation appears to counter many of the degenerative diseases of aging.

## Formulating Copper Peptides into Products

When formulating copper-peptide products, great care must be taken to minimize interactions with the ionic copper. Other ingredients of creams, lotions, and solutions may interact with the ionic copper and neutralize the positive copper-peptide actions and, in some cases, generate copper-complexes that inhibit cell replication.

Some companies have sell cosmetic skin products using copper complexes such as EDTA-copper but many complexes of copper with chelating molecules inhibit fibroblast function and skin repair (49). All products should be carefully tested in actual human skin repair tests. Also, not all copper peptide complexes are skin regenerative. Only products based on GHK-Cu or the newer complexes from Skin Biology are supported by credible, published evidence of efficacy.

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## **Skin Remodeling with Copper Peptides - Interview with Loren Pickart PhD**

- Mr. Pickart, am I right that you were the first scientist who started research on Copper-Peptides and there was nothing known about them before?

*- I would not say that proteins associated with copper were completely unknown. Chemists had been investigating the ability of copper to make complexes with some peptides. And there is a lot of research on copper and enzyme superoxide dismutase. But this molecule, the model of which I'm holding now (Seen Here), was unknown to scientists.*

*It all happened in 1970s when I was working at the University of California at San Francisco. It was time of great belief in medicine. Many scientists wanted to do big things, such as fighting cancer. I decided to find the way to reverse human aging.*

*We worked with blood cells and discovered that young cells contained some Copper-Peptide complex. We found out, that old cells lasted longer if we supplied them with this peptide complex. But it took us 15 years to understand how they work. Now we know that Copper-Peptides work as a restorative signal in skin, bones, and hair follicles. And it is possible that they work the same way in other tissues.*

- So they work as growth factors?

*- Not exactly. Let us look at wound healing. After damage, there are mostly destructive and sterilizing processes involving free radicals. Then cells begin to release transforming growth factor TGF-beta-1 that stimulates scar formation. But damaged tissue also releases Copper-Peptides. At some point their concentration reaches the level where they suppress TGF-beta-1 production and block oxidation.*

- I have read that free radicals could be a restorative signal and because of this too much antioxidants might delay wound healing.

*- I believe in good oxidation. You can accelerate wound healing by applying oxidizing agents first and Copper-*

*Peptides second.*

- In your article you are saying that Copper-Peptides work as antioxidants and anti-inflammatory agents; they also inhibit scar formation, stimulate angiogenesis, attract macrophages to wound, stimulate hair follicles, speed up both collagen destruction and new collagen synthesis...

- *Yes, that's correct. They remodel skin, you may say that they turn off destruction and turn on reparation.*

- It is hard to believe that one molecule can be so powerful.

- *We hardly could believe it too. But numerous other laboratories all over the world extended our observations. French scientists found that Copper-Peptides stimulate nerve growth, scientists from National Cancer Institution researched angiogenesis, scientists from Utah investigated antioxidant capacity of this molecule and so on.*

- We keep talking about medical use, but now they are used in cosmetic industry.

- *Yes, initially we developed these products for medical use, but physicians don't like trying new inventions; they prefer well-known remedies. Besides, the procedure of drug approval is ridiculously complicated in USA. It takes years and you have to spend a fortune. It is much easier to get approval for cosmetic products, and women love to explore new cosmetics. I can assure you, that many cosmetic products already contain the medicine of the future, because their developers do not want to bother with drug approval. But I agree that unlike drugs, cosmetic products should be perfectly safe. We tested Copper-Peptides and didn't find any toxicity, any side effects. They are safe, and they are meant to be safe, because they are found in human body and they don't modify any physiological processes in skin. They protect skin and give the signal to restoration. Don't you think it is perfect role for cosmetic ingredients?*

- You mean that there is no risk of scar formation or inflammation even if people use high concentrated products?

- *On the contrary, Copper-Peptides prevent scars and inflammation. Some women using our products report disappearance of stretch marks and scars. We have very good testimonials, especially from middle-aged women. Usually they buy one or two products for start, then come back for more, and then start to recommend them to all their friends and relatives. Their praises keep us going.*

- It seems that your product affects the skin physiology after all. But FDA still requires cosmetic products to be inert in skin.

- *There are no such things as inert cosmetic ingredients. All substances that we put on our skin, such as Vaseline and other emollients (even plain water) affect skin in some way. And people in FDA understand this. They also understand that modern people want cosmetics to improve skin, to make it better. I have no doubt that the definition of cosmetics will be changed soon.*

- Today many cosmetic companies make cosmetics using your Copper-Peptides. Do you believe they use efficient concentrations of Copper-Peptides?

- *Unfortunately many cosmetic companies just don't care. They want a popular ingredient on the label and that is all. But some companies make very good products and spend a fortune on testing. It is not only a matter of concentration, it is important to know how Copper-Peptides will behave in a complex mixture, and how a technical process will affect them. That is why dermatological testing of finished products is so important.*

- It seems for majority of cosmetic manufacturers it is still easier to make fake claims rather than develop potent cosmetic products?

- *Unfortunately it is true. But this situation is changing now. The more great cosmetic products come to the market, the closer the future in which only efficient cosmetics will be profitable.*

- As I understand, your company does a very little manufacturing, and your main occupation now is still science of reversal of skin aging. But don't you ever dream to be famous with your own cosmetic line?

- *Yes, I have been thinking about this a lot. But I prefer to be a scientist. Manufacturing and promotion of new cosmetics is a tough business. I'm 65 years old and I want to enjoy life.*