



GHK-Cu

A wrapper for one atom of copper, and the fifty years spent arguing about what it does

GHK-Cu is three amino acids holding a single copper ion, and almost everything difficult about it follows from the fact that the copper is the interesting part. Copper runs the enzyme that gives collagen its tensile strength, the enzyme that disposes of superoxide, and the last step of respiration — and loose in solution it is one of the most efficient generators of oxidative damage in biology. Any organism that needs copper has to solve the problem of moving it without letting it react on the way. This molecule is one of the answers, and it is one the body builds for itself, out of its own torn collagen, at the site of an injury. What that fact does and does not license is the subject of this document.

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HOW TO READ THIS DOCUMENT

Every finding is labelled by the kind of study that produced it, in the sentence that reports it. A result in mice is called a result in mice. A dish of cultured fibroblasts is called a dish of cultured fibroblasts, and a computer match between two lists of genes is called that and nothing more — a distinction that matters unusually much for this compound, because its best-known claim rests on exactly such a match. Where a number can be traced only to the laboratory that discovered the molecule, this document says so. Nulls and failures appear beside the successes they belong

with. **This document recommends no human use of any compound and specifies no dose, route or schedule for any person.** Where doses appear, they are the doses a published study administered, reported with its species, population and duration attached.

PART ONE

The accident

01

A difference between young blood and old blood

In the early 1970s a doctoral student at the University of California, San Francisco was running an experiment that sounds, today, like something from a much more recent decade. Loren Pickart was keeping slices of human liver alive in culture and bathing them in human plasma. The plasma came from two groups of donors: people aged roughly twenty to twenty-five, and people aged roughly fifty to seventy. The question was whether the older tissue behaved differently depending on whose blood it was sitting in.

It did. Liver tissue from older donors, incubated in plasma from younger ones, shifted its protein output toward a younger pattern — specifically, it made less fibrinogen, the clotting protein whose production climbs with age and with inflammation (Pickart & Thaler, 1973). Something in young plasma was carrying an instruction, and the instruction was legible to old tissue.

This is worth pausing on, because the idea has since been rediscovered several times with much more publicity. The proposition that circulating factors carry age information, and that young circulation can partially reinstruct old tissue, is now associated with parabiosis experiments and with plasma-exchange trials. Pickart was working the same seam in 1973, with liver slices and a fibrinogen assay, and the substance he pulled out of it is the subject of this monograph.

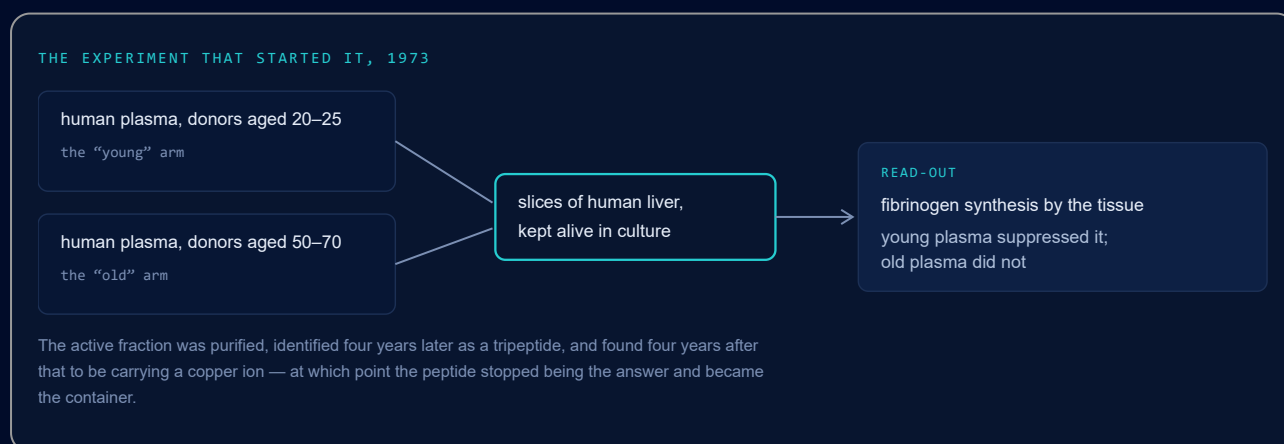


FIGURE 1 The founding experiment, redrawn from the described design. Two points are worth holding on to. The readout was fibrinogen suppression, not growth or rejuvenation; and the experiment compared plasma from two age bands, not the peptide against a placebo. The age-band framing of this experiment is frequently confused with a separate and later claim about how the peptide's own plasma concentration falls with age. They are different data.

The first two publications, both in 1973, describe the isolated activity and then confirm it with material made from scratch: a tripeptide, synthesised in the laboratory, reproduced what the plasma fraction did (Pickart & Thaler, 1973; Pickart et al., 1973). That is the right way to close such a loop, and it closed early.

There is a detail in those first papers that later accounts tend to leave out, and it deserves to be here rather than buried. The titles say the tripeptide *prolongs survival of normal liver cells and stimulates growth in neoplastic liver*. It made healthy hepatocytes last longer and it made hepatoma cells grow. Contemporary work described the compound's effects across cultured systems as ranging from stimulation of growth and differentiation to outright toxicity, depending on the system (Pickart et al., 1980). A molecule that begins its published life as a hepatoma growth stimulant, and is now sold as an anti-ageing agent, has had an interesting career, and the reader is entitled to know that.

02

Three letters

Identifying the active substance took four more years. In 1977 the sequence was published: glycyl-L-histidyl-L-lysine, three residues, no more (Schlesinger et al., 1977). Glycine, histidine, lysine — Gly-His-Lys, or GHK.

Three amino acids is very small. For scale, insulin has fifty-one, and the shortest peptide hormones in the human body run to nine or ten. A tripeptide is barely a molecule with a shape; it has no folding to speak of, no secondary structure, nothing that looks like a binding surface. That the activity survived reduction to three residues was a genuine surprise, and it created an obvious puzzle. What could a fragment that small possibly be doing?

The answer, when it came, was that the peptide was not doing it.

03

The metal was the point

The clue arrived as a nuisance. Purifying the tripeptide out of plasma was inefficient, and the losses were traced to metals: copper and iron were co-isolating with the peptide and interfering at several steps of the procedure. Stripping them out with a chelating resin raised recovery of the labelled peptide from plasma **eight-fold** (Pickart et al., 1979). The metals were not contaminants of the preparation. They were attached to the thing being prepared.

Follow-up work established that the tripeptide associates with copper, cobalt, iron, molybdenum, manganese, nickel and zinc at physiological pH, and has no affinity at all for calcium, potassium or sodium — and that its effects on cultured hepatoma cells required the metal to be present (Pickart & Thaler, 1980). Then, in 1980, a paper in *Nature* put the case together: the tripeptide readily forms complexes with copper(II) and enhances the uptake of copper into cultured cells

(Pickart et al., 1980). The same paper noted a structural resemblance the authors found suggestive — that the copper transport sites on albumin and alpha-fetoprotein also bind the metal at a histidine sitting next to a basic residue.

THE PIVOT, STATED PLAINLY

Between 1973 and 1980 the compound changed category. It was chased as a growth-modulating factor — a small hormone-like signal — and it turned out to be a carrier. The biological activity belonged to a copper ion, and the peptide’s job was to hold that ion in a form that could be moved around without doing damage. Nearly every subsequent argument about this molecule, including the arguments still running in 2026, is downstream of that reclassification. A carrier is judged by different criteria than a signal: what matters is what it delivers, where, in what quantity, and in what oxidation state.

FIFTY-THREE YEARS

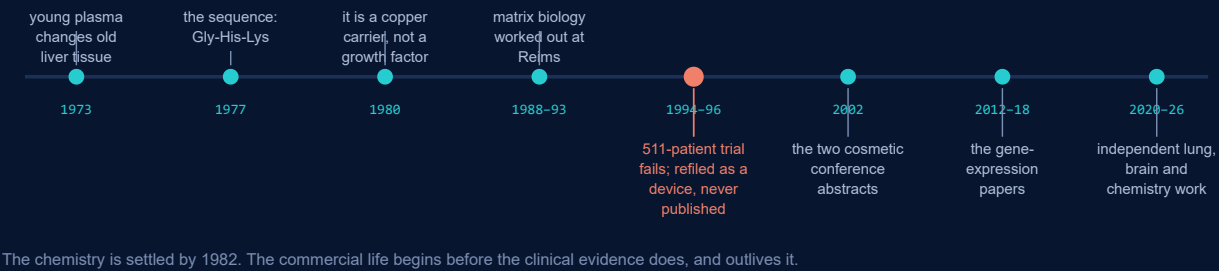


FIGURE 2 The sequence of events. The seven-year gap between the activity and its correct classification as a copper carrier is the interesting part of the first half; the fact that most of the commercial literature dates from after the pivotal trial failed is the interesting part of the second.

04

Names, and why they matter

Few compounds of this size carry so many names, and the differences between them are not cosmetic.

NAME	WHAT IT DENOTES	WHERE IT IS USED
GHK	the free tripeptide, no metal	chemistry and much of the animal literature
GHK-Cu	the copper complex	most biology, most commerce

NAME	WHAT IT DENOTES	WHERE IT IS USED
Copper tripeptide-1	the INCI name of the cosmetic ingredient	ingredient lists, regulatory filings
Tripeptide-1	the INCI name of the metal-free peptide	ingredient lists
Prezatide copper acetate	the pharmaceutical name of the same complex	the 1990s drug-development programme
Iamin, PC1020	trade and code names of that drug candidate	the clinical trials in section 18
Palmitoyl tripeptide-1	GHK with a fatty acid attached, no copper	a different cosmetic ingredient

Three of these distinctions cause real confusion in the literature. The first is **GHK against GHK-Cu**. Several of the most-cited animal studies used the uncomplexed peptide and said so; at least one set of authors stated explicitly that their experiment could not establish whether the copper complex would have worked better (Zhou et al., 2017). Reviews then cite those results as evidence about GHK-Cu. This document keeps them apart.

The second is **palmitoyl tripeptide-1**, which is neither the copper complex nor a source of copper. It appears in cosmetic literature under names that look adjacent to GHK-Cu and is sometimes swept into the same evidence pile. It is a different ingredient.

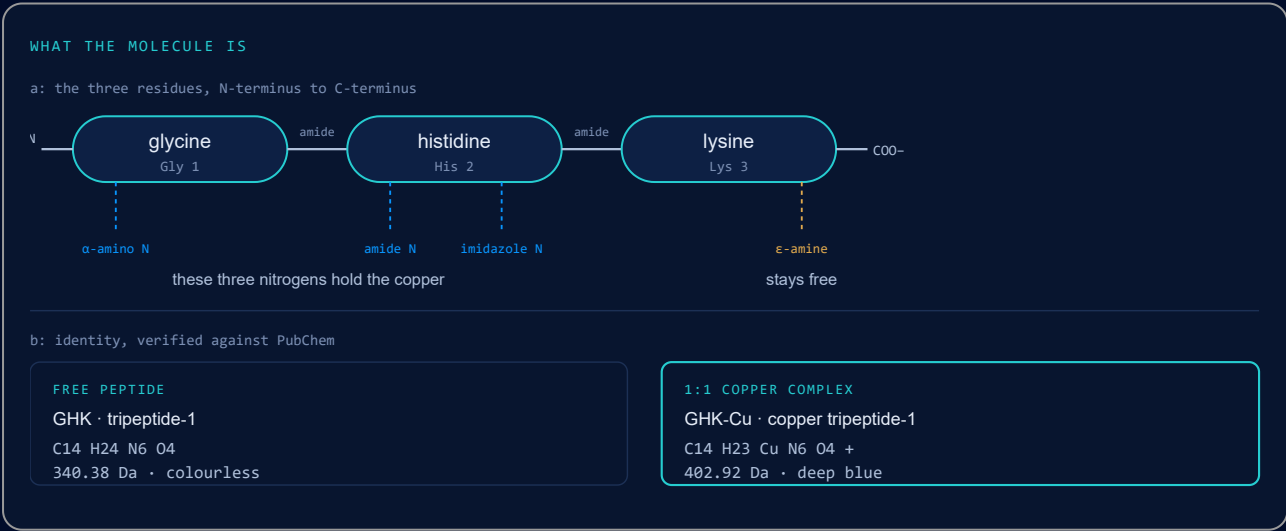


FIGURE 3 Identity. The three copper-donating nitrogens are contributed by the first two residues and the histidine side chain; the lysine side-chain amine is left outside the coordination sphere, which is why it is the usual attachment point for chemical modification. Formulae and masses were taken from PubChem records rather than from review text – a commissioned plate prepared for this monograph printed C₁₄H₂₆N₆O₄ for the free peptide, which is wrong by two hydrogens and inconsistent with the correct mass printed beside it, and that plate was withheld. A 2:1 species, Cu[GHK]₂, also exists and is the form named in the Cosmetic Ingredient Review assessment; it is not shown here.

The third is **stoichiometry**, and it is the least discussed and possibly the most consequential. The Cosmetic Ingredient Review's own safety assessment identifies copper tripeptide-1 with the formula $\text{Cu}^{2+}[\text{Gly-His-Lys}]_2^-$ — that is, *two* peptides per copper — and one published toxicity study records that its commercially supplied GHK-Cu reagent had a stated peptide-to-copper ratio of 2:1 (Li et al., 2016). Much of the biological literature treats GHK-Cu as a 1:1 complex. Both species exist and both are described in the chemistry. Material sold and studied under one name is therefore not guaranteed to be the same substance from one paper to the next.

A practical corollary follows for anyone reading a certificate of analysis. The free peptide has the molecular formula $\text{C}_{14}\text{H}_{24}\text{N}_6\text{O}_4$ and an average mass of **340.38 Da**. The 1:1 copper complex is $\text{C}_{14}\text{H}_{23}\text{CuN}_6\text{O}_4^+$ at **402.92 Da**. A document describing material as the copper complex while reporting a mass of 340 is describing either the free peptide or a paperwork error.

05

The copper problem

To see why a copper carrier would be worth having, it helps to look at what copper is for. Three enzymes make the case on their own.

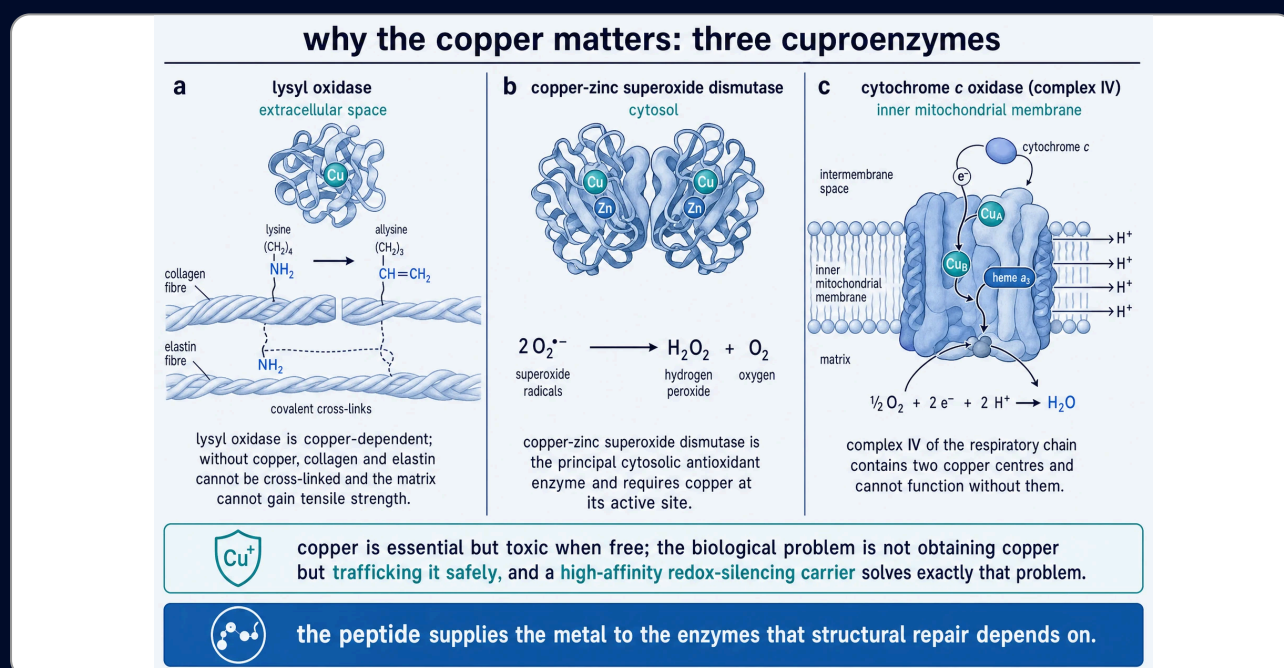


FIGURE 4 Why copper is worth carrying carefully. Three copper-dependent enzymes: matrix cross-linking, antioxidant defence and the terminal step of respiration. **ONE CORRECTION TO THE ARTWORK.** Panel (a) draws the product of lysyl oxidase as a vinyl group, $\text{CH}=\text{CH}_2$. The actual product, allysine, is an *aldehyde* — the side chain is $(\text{CH}_2)_3-\text{CHO}$ — and it is the aldehyde that goes on to form cross-links. The dismutase reaction in panel (b) also consumes two protons, which the drawing omits.

Lysyl oxidase works outside the cell, on collagen and elastin fibres that have already been secreted. It converts particular lysine side chains into a reactive aldehyde, and those aldehydes then form the covalent cross-links that turn a heap of protein strands into a material with tensile

strength. Lysyl oxidase is a copper enzyme. Without copper, connective tissue can be synthesised but cannot be made strong.

Copper-zinc superoxide dismutase is the principal antioxidant enzyme of the cytosol. It takes superoxide, the radical that leaks continuously from respiration, and converts it to hydrogen peroxide and oxygen. Its active site is a copper ion.

Cytochrome c oxidase is complex IV of the respiratory chain, the enzyme that finally hands electrons to oxygen and makes water. It contains two copper centres and does not work without them.

So copper is not optional. Neither is it safe. A free cupric ion in the presence of a reducing agent and oxygen will cycle between its two oxidation states and generate hydroxyl radicals, which attack essentially anything nearby. The body's response to this is to make sure there is almost no free copper anywhere: plasma copper is held on ceruloplasmin and albumin, and inside cells it is passed hand to hand by dedicated chaperone proteins. The concentration of genuinely unbound copper ion in a cell is often quoted as less than one atom per cell.

The biological problem, then, is not obtaining copper. It is trafficking copper. A small, soluble, high-affinity carrier that holds the metal in a non-damaging form and can hand it off is a solution to a real problem, and that is what GHK-Cu appears to be. The chemistry that follows in Part Two is about how well it does that job, and it is the part of this molecule's story that is not seriously contested.

PART TWO

The chemistry, which is not in dispute

06

The coordination sphere

The copper sits in a square-planar arrangement held by three nitrogen atoms that the peptide supplies, one from each of the first two residues plus one from the histidine side chain. In order along the chain they are: the free α -amino nitrogen at the glycine end; the nitrogen of the glycine-histidine amide bond, which loses its proton to make the bond; and one of the two nitrogens in the histidine imidazole ring. The fourth equatorial position is left open, and a water molecule sits loosely above the plane, completing a square pyramid.

That arrangement was established by a convergence of methods across the 1980s — X-ray crystallography, electron paramagnetic resonance, X-ray absorption and nuclear magnetic resonance — and it has been confirmed again since, most recently at 1.3 Å resolution in crystal structures where the tripeptide was fused to unrelated proteins purely as a copper-binding handle for solving their structures (Mehr et al., 2020). Nobody argues about it.

Two refinements matter for reading the rest of this document. First, the solid-state and solution structures are not the same. The crystal form is polymeric, with copper pairs bridged through oxygen and the fourth site occupied by a carboxylate from a neighbouring complex; in solution that polymer does not exist, and the complex is a discrete 1:1 species (Freedman et al., 1982). Second, the fourth site is not usually empty. It is an open coordination position on a copper ion in a solution full of imidazole rings, and it takes one whenever it can — from a second molecule of the tripeptide, from free histidine, or from a histidine side chain on a protein. What circulates is often not the bare complex but a ternary one (Bossak-Ahmad et al., 2020).

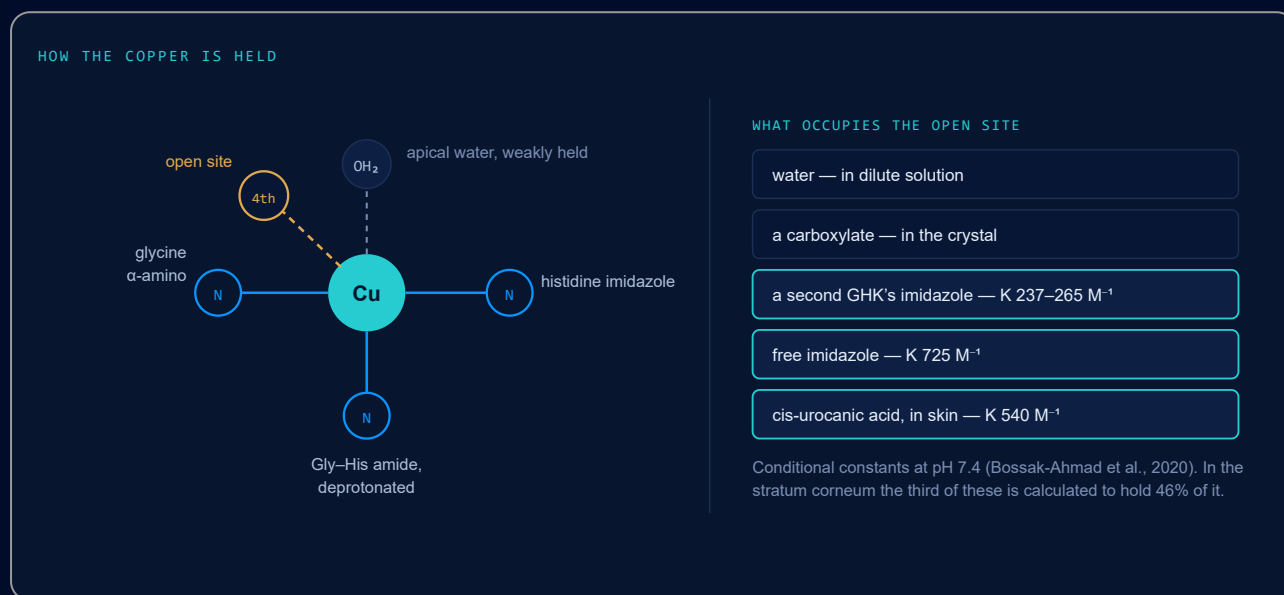


FIGURE 5 The donor set and the open site. Three nitrogens from the peptide hold the metal; a fourth equatorial position and an apical water complete the geometry. The fourth site is the part that is usually left out of summaries, and it is the reason the complex behaves differently in skin than in a cuvette. A commissioned plate covering this material drew a chemical skeleton that is not this molecule and was withheld; this figure replaces it.

07

How tightly, and tighter than what

The comparison that appears in almost every account of this molecule is that the tripeptide binds copper with a stability constant of $\log K\ 16.44$, against 16.2 for the high-affinity copper site at the N-terminus of serum albumin — from which it is concluded that the two are essentially equipotent and that the peptide can take copper directly from albumin. Those figures are reported consistently across the discoverer's reviews (Pickart et al., 2012; Pickart et al., 2015; Pickart & Margolina, 2018) and attributed there to a 1981 study by Lau and Sarkar.

The figures are not wrong. What is usually missing is the rest of that study's result. Lau and Sarkar measured the distribution of copper directly by equilibrium dialysis, and found that at equal molar concentrations of albumin and peptide, about 42 per cent of the copper sat on the peptide — consistent with near-equal affinity. But at the concentrations that actually obtain in plasma, where albumin is present in vast excess over any low-molecular-weight ligand, **only**

about 6 per cent of plasma copper is associated with low-molecular-weight components at all (Lau & Sarkar, 1981). Per molecule the two carriers are comparable. In the copper budget of blood they are not, because there is a great deal more albumin than there is tripeptide.

THREE NUMBERS, THREE DIFFERENT QUESTIONS

The affinity of this complex is quoted in at least three incompatible ways, and they are not in conflict — they answer different questions. **log K 16.44** is an overall stability constant, the figure used for the albumin comparison. **Conditional constants at pH 7.4**, which are what matter physiologically because they account for competing protonation, come out around $4.2 \times 10^{12} \text{ M}^{-1}$ — a dissociation constant of about 0.24 picomolar (Bossak-Ahmad et al., 2020). An isothermal titration calorimetry measurement quoted in the crystallography literature gives a dissociation constant of $7.0 \times 10^{-14} \text{ M}$ (Mehr et al., 2020). All three describe a very tight complex. Only the second is the right kind of number for asking what happens in tissue.

The practical upshot is that the tripeptide is a good copper carrier and a minor one. It will hold copper against almost everything except a dedicated transport protein, it will exchange with albumin readily in either direction, and it is present in plasma at concentrations three to four orders of magnitude below albumin's. Any claim that it materially redistributes the body's copper needs to reckon with that arithmetic.

08

Redox silencing, and where it stops

The safety case for putting copper into a cream rests on one claim: that copper bound in this coordination sphere is redox-silenced. Loose copper cycles between Cu(II) and Cu(I) and generates hydroxyl radicals; bound copper, according to the claim, does not, and so can be delivered without doing oxidative damage. The claim is repeated in essentially every review of the compound.

It is a real finding, and it is narrower than the way it is usually stated. Three independent lines of recent chemistry mark out where it holds and where it fails.

Against ascorbate, it holds

The classic pro-oxidant test is whether a copper species will catalyse the oxidation of ascorbate. Bound in the tripeptide, copper is inert against physiological levels of ascorbate. Better than inert, in fact: adding the tripeptide to a system in which copper is bound to amyloid- β and merrily oxidising ascorbate slows that oxidation in a dose-dependent way, and at 30 μM — an

excess over the amyloid peptide — brings the rate almost to zero (Tosto et al., 2023). The tripeptide wins the copper away from the damaging site and holds it quietly. This is the strongest form of the redox-silencing claim and it is well supported.

Against glutathione, it does not

Glutathione is the strongest reductant that naturally occurs in human plasma, and it is present inside cells at millimolar concentration. A 2021 study followed what happens when the two meet, in water at pH 7.4 and 37 °C, and the answer is: a great deal (Ufnalska et al., 2021). The copper is reduced — not slowly, but within the mixing time of the experiment, reaching about 60 per cent conversion at a 2.2-fold excess of glutathione and complete conversion at four- to six-fold. The reduction proceeds through a short-lived thiolate intermediate, and the stable product is not a reduced form of the complex at all: it is a $\text{Cu(I)}_4(\text{glutathione})_6$ cluster, with the tripeptide released intact and chemically unmodified. Under aerobic conditions the copper is then re-oxidised and re-captured by the peptide, and the cycle can be run again.

Two details make this more than a curiosity. Glutathione is consumed in excess of what the stoichiometry requires, which means the copper-peptide complex is *catalysing* additional glutathione oxidation rather than simply being reduced by it; and the re-oxidation step proceeds through superoxide. Cyclic voltammetry independently confirms that the complex is electrochemically active. The authors' own framing is not that the complex is inert but that it is a clean delivery vehicle for Cu(I) — the oxidation state that cellular copper importers actually accept — with the peptide surviving the transaction undamaged.

And it has measurable oxidase activity of its own

In 2026 a group characterising the complex as a catalyst reported that it behaves as a laccase mimic: it oxidises phenols and catecholamines using molecular oxygen, through a Cu(II)/Cu(I) cycle with superoxide as a trapped intermediate, and on several kinetic measures it outperforms the fungal enzyme it was compared against (Chen et al., 2026). Taken at face value that is awkward for the redox-silencing claim, and the paper does not attempt to reconcile the two.

The reconciliation is in the conditions. That assay runs at **80 °C**, at catalyst concentrations in the millimolar range, against millimolar phenolic substrate, in buffer. Human plasma concentrations of the tripeptide are sub-micromolar and body temperature is 37 °C. No activity data at 37 °C are reported. Most tellingly, the paper's own interference panel shows that **serum albumin substantially suppresses the catalytic activity** — and albumin is precisely the protein the complex is supposed to be sharing copper with in blood.

WHAT CAN ACTUALLY BE SAID

Copper held by this tripeptide is **redox-attenuated, not redox-silent**. It resists ascorbate and it resists the mild reductant dithiothreitol at concentrations used in protein purification. It does not resist glutathione, and the reduction that follows is genuine one-electron chemistry with radical intermediates — which may well be

the physiological point, since Cu(I) is the form cells import. A cell-free study in 2024 examining copper toxicity in mouse brain cells reached the same conclusion from the other direction: the complex still generates reactive oxygen species, though substantially less than free copper does, and the tripeptide has essentially no direct radical-scavenging activity of its own at the concentrations used in cell culture (Min et al., 2024). Its protection came from preventing copper-induced protein aggregation, not from mopping up radicals.



FIGURE 6 The redox claim, resolved by condition. Every entry is from cell-free solution chemistry; none of it is a measurement in tissue. What the chemistry establishes is that the complex’s redox behaviour is set by what is reducing it, which means the answer differs between the surface of the skin, the extracellular space and the inside of a cell.

09

Cut out of collagen

The most elegant fact about this molecule is where it comes from. The sequence Gly-His-Lys is not manufactured as a signal. It occurs inside larger proteins, and it is released when those proteins are cut up — which is exactly what happens when tissue is damaged and proteases are released at the wound. The injury generates its own repair signal out of the material that was injured. Molecules that work this way are called matrikines, and this is the textbook example.

Two source proteins are named in the literature. Both were checked against the reference protein database for this monograph rather than taken from review text, and both hold up — with additional detail the reviews do not carry.

PROTEIN	ACCESSION	LENGTH	GLY-HIS-LYS AT	NOTE
Collagen type I, α2 chain	P08123	1,366	943–945	a standard collagen Gly-X-Y triplet
SPARC / osteonectin	P09486	303	138–140	abundant wherever tissue is remodelling

real stratum-corneum concentrations into the speciation model, the authors calculate that **about 46 per cent of peptide-bound copper in skin would exist as the ternary complex** rather than the binary one (Bossak-Ahmad et al., 2020). Whatever is doing the work in a cream is, on that arithmetic, about half something the cell-culture experiments never tested.

PART THREE

What it does in cells and in animals

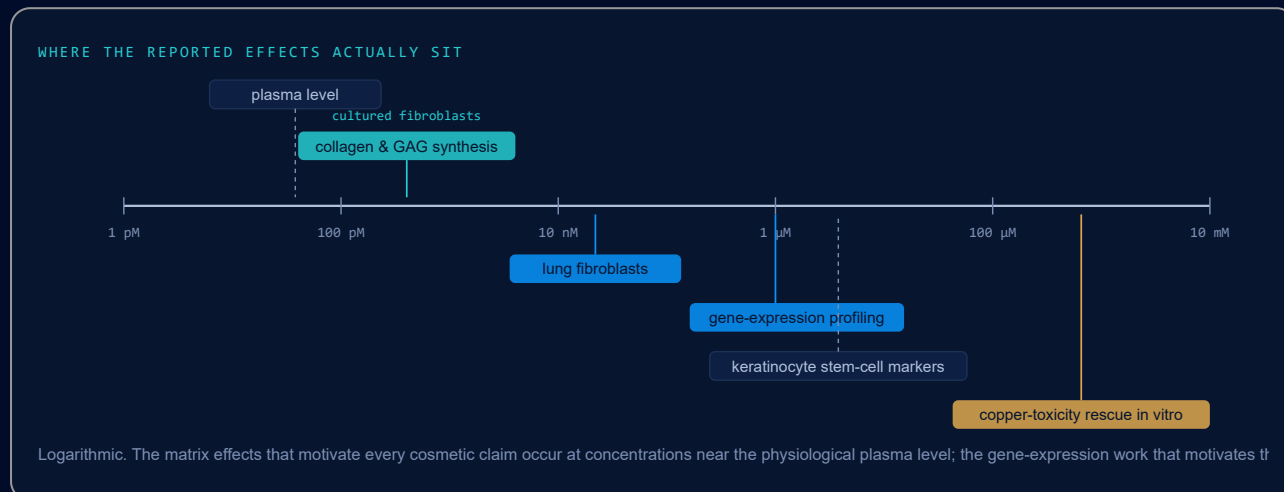


FIGURE 8 The concentration axis, which reconciles a good deal of apparent disagreement. Effects reported at one nanomolar and effects reported at one micromolar are separated by a factor of a thousand, and they are not evidence for the same proposition. All entries are cell-culture concentrations in the medium, not measured tissue concentrations.

10

The dermal matrix

The second substantial body of work on this compound did not come from the laboratory that discovered it. Through the late 1980s and the 1990s a group at Reims — François-Xavier Maquart, Jacques-Paul Borel, Anne Siméon, Yanusz Wegrowski and colleagues — worked out what the copper complex does to fibroblasts, and their results are the foundation of every cosmetic claim made for the molecule since.

The first paper set the concentration range that still defines the field. Collagen synthesis by cultured fibroblasts began to rise somewhere between 10^{-12} and 10^{-11} M, peaked at 10^{-9} M — one nanomolar — and did so without any change in cell number, so this was more collagen per cell rather than more cells (Maquart et al., 1988). Sulfated glycosaminoglycan synthesis followed the same shape, maximal at 10^{-9} to 10^{-8} M and falling back toward control at higher concentrations (Wegrowski et al., 1992). A dose-response that rises and then falls is characteristic of a signalling molecule rather than a nutrient, and it is worth noting how low these concentrations are: a nanomolar effect is two to three orders of magnitude below where most cosmetic actives are studied.

The Reims group then established what turned out to be the conceptually important result. The complex does not simply push matrix production upward. It raises the matrix metalloproteinases – the enzymes that *degrade* matrix – alongside their tissue inhibitors TIMP-1 and TIMP-2 (Siméon et al., 1999; Siméon et al., 2000a). Old material is cleared while new material is laid down. That is a description of turnover, and it is a materially different claim from “increases collagen”: a tissue that only accumulates collagen is a scar.

Within that turnover the changes are selective rather than uniform. Dermatan sulfate and chondroitin sulfate accumulate; hyaluronic acid does not. Decorin – the small proteoglycan that controls how thick a collagen fibril grows – goes up, while its relative biglycan goes down (Siméon et al., 2000b). Selectivity of that kind is hard to explain as a general stimulatory effect and is the best evidence in the literature that something specific is being signalled.

THE CONTROL THAT COMPLICATES THE STORY

In the experiment that established stimulation of MMP-2 by cultured dermal fibroblasts, the authors report that the effect was reproduced by **copper ions alone** and was **not** reproduced by the tripeptide without copper (Siméon et al., 2000a). For that endpoint the peptide is the delivery system and the copper is the active agent – which is consistent with everything in Part Two, and which sits awkwardly beside marketing that treats the peptide as the active ingredient.

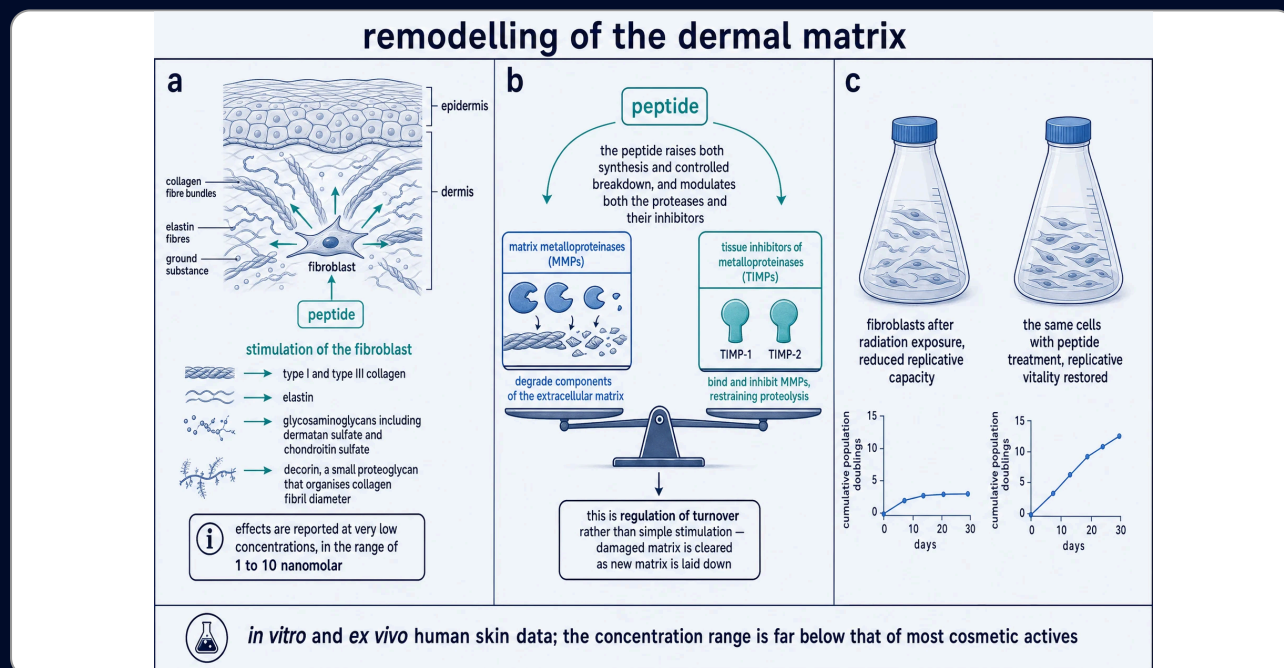


FIGURE 9 Remodelling of the dermal matrix in cultured human and rat fibroblasts and in rat wound tissue. The balance panel is the substantive point: both sides of matrix turnover move together. **NOTE ON PANEL (C).** The population-doubling curves are a schematic trace, not measured data – the underlying finding, that fibroblasts from patients who had received radiotherapy recovered replicative capacity on treatment, is reported in the corpus, but those specific values are not.

Wounds in living animals

The single strongest experiment in this literature is a 1993 study in the *Journal of Clinical Investigation*, and it deserves to be described properly because it is the one most often gestured at and least often read (Maquart et al., 1993).

Stainless-steel mesh cylinders were implanted under the skin of rats. Such a chamber fills with granulation tissue over weeks, and its contents can be removed and weighed and assayed — it converts wound healing into a measurable quantity of new tissue. Chambers received repeated injections of either saline or the copper complex at several concentrations. What came out of the treated chambers weighed more, and contained more DNA, more total protein, more collagen and more glycosaminoglycan, in a concentration-dependent way. The increase in collagen was twice the increase in non-collagen protein, so this was not simply more tissue. Messenger RNA for type I and type III collagen rose; messenger RNA for transforming growth factor β did not, which argues against the effect being mediated by the obvious fibrotic pathway. And a control tripeptide of similar size, glutamyl-histidyl-proline, had no significant effect.

That is a properly controlled in-vivo experiment with a specificity control, a dose-response and a mechanistic negative. It is a study in rats. Nothing in it is a statement about people.

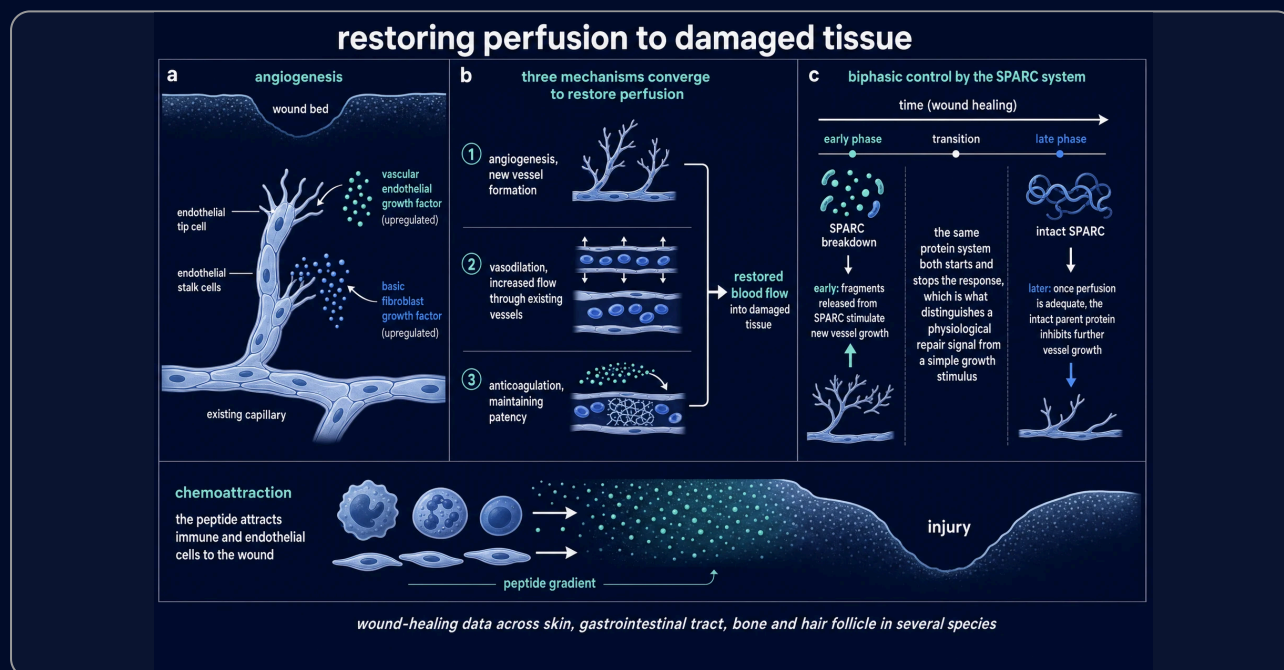


FIGURE 10 Restoring perfusion. Angiogenesis with raised vascular endothelial growth factor and basic fibroblast growth factor, and chemoattraction of repair cells along a concentration gradient, are both reported across the animal literature. The biphasic SPARC panel is a genuine and elegant idea: fragments released early promote vessel growth while the intact parent protein later restrains it. **ONE QUALIFICATION.** The anticoagulation arm of panel (b) traces to the discoverer's review articles rather than to a primary experiment in this corpus, and should be read as the weakest of the three mechanisms shown.

12

Lungs, and the first real target

The most active current research on this compound is not in skin. Since about 2016 several groups, largely in China and largely independent of one another and of the original laboratory, have tested it in models of lung injury. This body of work is the most methodologically modern in the field, and one paper in it produced something the previous forty years had not: a molecular target.

MODEL	SPECIES	DOSE AND ROUTE, AS REPORTED	PRINCIPAL RESULT
Endotoxin acute lung injury	mouse, C57BL/6	1 or 10 µg/g, intraperitoneal, ×3 over 3 d	reduced lung injury score, neutrophils, myeloperoxidase; blocked NF-κB p65 and p38 activation
Cigarette-smoke emphysema	mouse, C57BL/6J	0.2, 2 or 20 µg/g, intraperitoneal, alternate days, 12 wk	less alveolar enlargement at the two higher doses; Nrf2 up, Keap1 down; low dose ineffective on most endpoints
Bleomycin fibrosis (GHK, not GHK-Cu)	mouse, C57BL/6	2.6, 26 or 260 µg/mL/d, intraperitoneal, d4–21	less collagen deposition; TGF-β1/Smad2/3 suppressed dose-dependently
Silica-induced fibrosis	mouse; plus human observation	2 or 20 mg/kg, intraperitoneal	cytokines and hydroxyproline normalised; binds peroxiredoxin 6 directly
Smoke-induced muscle wasting	mouse, C57BL/6J	0.2 or 2 mg/kg, intraperitoneal, weekly, 7 wk	grip strength 175.5 g → 339.1 g at the higher dose; entirely SIRT1-dependent

The silicosis study is the one that matters most (Bian et al., 2024). Its authors did what almost nobody in this field had done: they went looking for what the molecule physically binds to. Using a biotinylated version of the complex as bait, followed by surface plasmon resonance to confirm the interaction and small interfering RNA to test whether it was necessary, they identified **peroxiredoxin 6** — an antioxidant enzyme — as a direct binding partner, and showed that silencing it abolished the complex’s protective effects on reactive oxygen species and mitochondrial function. After five decades of mechanism inferred from downstream consequences, that is the first identified molecular target with loss-of-function confirmation.

The same paper carries the most useful human data in the entire corpus, and it is observational rather than interventional. Plasma tripeptide was measured in fifteen patients with silicosis and eleven age-matched healthy controls: **35.67 ± 13.69 ng/mL against 105.50 ± 31.94 ng/mL**, $P < 0.0001$, falling further with clinical stage and correlating with both forced expiratory volume and diffusing capacity. A companion study of chronic obstructive pulmonary disease found the same shape: **70.27 ± 38.87 ng/mL against 133.0 ± 54.54 ng/mL** in healthy controls, correlating with muscle index, six-minute walk distance and quadriceps strength (Deng et al., 2023). Two independent cohorts, two chronic lung diseases, the same direction of effect. Whether the fall is a cause or a consequence of the disease is not established by either.

The muscle study is also notable for how completely it nailed down its mechanism. Molecular docking predicted binding to SIRT1; the complex raised SIRT1 expression and deacetylase activity dose-dependently; and a SIRT1 inhibitor abolished *every* protective effect — in cells and in mice, on cell viability, myotube diameter, signalling, mitochondrial markers, oxidative-stress markers, body weight, grip strength and muscle cross-sectional area. The authors note, correctly, that a pharmacological inhibitor is weaker evidence than a muscle-specific knockout, which they did not do.

A DISTINCTION THE REVIEWS BLUR

Two of the five lung studies above used the **uncomplexed peptide**, not the copper complex. The bleomycin-fibrosis authors say so explicitly and add that because they did not run the comparison, they cannot say whether the copper complex would have done better (Zhou et al., 2017). Later reviews nonetheless cite that work as evidence for GHK-Cu. Given the chemistry in Part Two — where at least one endpoint was reproduced by copper alone and not by the peptide alone — treating the two as interchangeable is not a small liberty.

13

Brain

A smaller and more recent literature has moved into the nervous system. In rats with experimentally induced intracerebral haemorrhage, the uncomplexed peptide given intraperitoneally before injury reduced brain water content and neurological deficit and cut the number of dying neurons, working through a microRNA that regulates vascular endothelial growth factor (Zhang et al., 2018). In mice carrying five familial Alzheimer's mutations, the copper complex given intranasally at 15 mg/kg three times a week for twelve weeks improved working memory, reduced amyloid plaque staining and lowered a neuroinflammation marker (Tucker et al., 2024).

Two cautions attach to that last result, and both matter. The 5xFAD experiment appears twice in the literature — once as a preprint and once as a journal article — from the same group with the same design and overlapping figures. It is one dataset, not two replications. And neither version

evaluated neuronal loss, which the authors state plainly as a gap.

A separate experiment in *normally* ageing mice — not a disease model — gave the complex intranasally at the same dose daily for eight weeks to animals aged twenty months (Tucker et al., 2023). Spatial-learning and working-memory measures improved in both sexes, and a marker of axonal damage fell in both sexes. But the effects were markedly sex-dependent at the four-week point, appearing in males before females, and one endpoint was flatly negative: the microglial marker IBA-1 did not shift, and the authors concluded in terms that deserve quoting for their unusual directness — microglia are not a robust target for this compound under those conditions.

A 2026 experiment compared routes head to head in aged mice, and found something genuinely odd. Intranasal delivery over eight weeks and intraperitoneal delivery over five days both produced some behavioural benefit, but their transcriptional signatures ran in *opposite* directions — intranasal treatment suppressed oxidative-phosphorylation gene sets while intraperitoneal treatment activated them. Whatever is happening, the route is not incidental to it. That work is a preprint and has not been peer reviewed (Mazzola et al., 2026).

THE ANIMAL AND CELL EVIDENCE, BY SYSTEM				
SYSTEM	SPECIES	STUDIES	MECHANISM PROPOSED	INDEPENDENT
Skin and dermal matrix	rat, human cells	many	matrix turnover, MMP/TIMP balance	yes — Reims
Wound repair	rat, rabbit	several	collagen and glycosaminoglycan gain	yes
Lung injury and fibrosis	mouse	five	NF-κB, Nrf2, TGF-β/Smad, PRDX6	yes
Skeletal muscle	mouse	one	SIRT1 — abolished by an inhibitor	yes
Brain	rat, mouse	four	p38 / miR-339-5p / VEGFA; plaque load	partly
Gut	mouse	one	SIRT1 / STAT3; barrier proteins	yes
Ligament	rat	one	none proposed	benefit transient
Human, interventional	—	three	two of the three were null — section 18	

FIGURE 11 The breadth of the animal and cell evidence against the narrowness of the human evidence, in one view. “Independent” means the work was done by a group with no authorship overlap with the laboratory that discovered the compound. Almost all of the recent mechanistic work qualifies, which is a real change from the literature of the 1990s and 2000s.

14

Gut, ligament, and the biomaterials turn

Beyond skin, lung and brain the evidence thins into single studies. In mice with chemically induced colitis, the complex by oral gavage for fourteen days improved disease activity, colon length and barrier proteins, acting through SIRT1 and STAT3; a knockdown experiment showed the barrier effect depended on STAT3 while the anti-inflammatory effect did not (Mao et al., 2025).

The ligament study is worth citing precisely because of what its own title concedes. Seventy-two rats underwent anterior cruciate ligament reconstruction and received weekly intra-articular injections for four weeks. At six weeks the treated knees were measurably less lax and one dose

group had stiffer grafts. At twelve weeks there was no significant difference in anything (Fu et al., 2015). The authors titled the paper to say the improvement was transient, and they were right to.

The largest recent growth area is not pharmacology at all but materials science: the tripeptide is being built into hydrogels, sponges, spicules and nanocarriers as one functional component among several. These are often good studies with proper factorial controls, and they consistently show the peptide-containing arm outperforming the arm without it. But they test a device, not a molecule, and their effect sizes belong to the construct.

15

The gene-expression claim

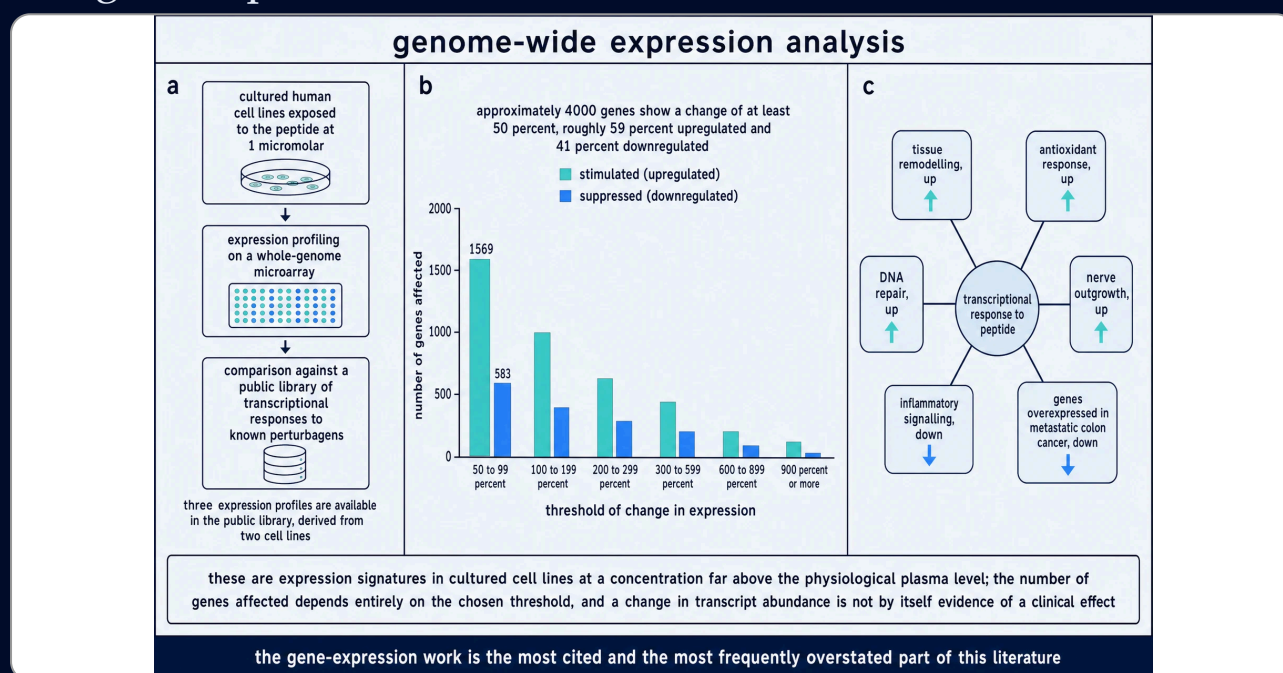


FIGURE 12 The gene-expression work and its caveat, which the plate states for itself. The headline figures are verified: 1 μ M, three Connectivity Map profiles from two cell lines, approximately four thousand genes at a 50 per cent threshold, 59 up to 41 down.

THE PER-BAND BAR HEIGHTS IN PANEL (B) ARE NOT TRACEABLE TO ANY SOURCE IN THIS CORPUS

, and they do not reconcile with the verified 59:41 split, so they should be read as illustrative of the shape of the distribution rather than as counts.

The most widely repeated statement about this molecule is that it changes the expression of about four thousand human genes, resetting them toward a healthier pattern. That claim is real, it is checkable, and it is systematically misunderstood.

Here is what was actually done. The Broad Institute's Connectivity Map is a public library of transcriptional responses: cultured cells are exposed to a compound and the resulting expression profile is stored, so that any new profile can be matched against the library. It contains three profiles for this tripeptide, all generated by exposing cells to **1 micromolar** compound — two in a prostate cancer line and one in a breast cancer line (Pickart et al., 2014). Re-analysing those

profiles, the authors calculated that 31.2 per cent of an estimated 13,424 genes changed by at least 50 per cent, split **59 per cent upward and 41 per cent downward** (Pickart & Margolina, 2018). Thirty-one per cent of 13,424 is about 4,190, which is where “four thousand genes” comes from.

Every one of those words is defensible. What they add up to is narrower than the headline. This is a threshold-dependent count of transcript changes, in two cancer cell lines, at a concentration a thousand-fold above the plasma level of the compound, from a database designed for compound-matching rather than for mechanism. Move the threshold and the count moves with it. A change in messenger RNA abundance is not by itself a change in protein, in cell behaviour, or in a person.

The same caution applies, with more force, to the study most often cited as showing that the compound reverses emphysema (Campbell et al., 2012). What that study did was profile lung tissue from six people with severe emphysema, derive a 127-gene signature of disease severity, and query it against the Connectivity Map — where this compound’s pre-existing cancer-cell-line profile came back as one of the strongest inverse matches. The authors then ran a single wet-lab follow-up: primary human lung fibroblasts, treated at 0.1 and 10 nanomolar, recovered their ability to contract a collagen gel. That is a real and interesting result. But **the compound was never given to a lung, an animal or a patient in that study**, and the authors themselves state that whether reversing the signature affects disease progression is unanswered.

The gap between “a database match plus a contraction assay” and “reverses emphysema” is the widest single gap in this molecule’s literature, and it is worth carrying into Part Four, where the human record is examined on its own terms.

PART FOUR

The human record

16

The peptide in human plasma

The claim that anchors the anti-ageing case is a simple one: the tripeptide’s concentration in human plasma falls with age, from about 200 ng/mL at twenty to about 80 ng/mL at sixty, and that decline tracks the loss of regenerative capacity.

Two things should be said about it. The first is that it is traceable, in this corpus, only to the discoverer’s own review articles — and the reviews are not internally consistent about it. One gives the ages as single values, twenty and sixty; another gives ranges, twenty to twenty-five and sixty to eighty, and specifies men (Pickart et al., 2012; Pickart et al., 2015). A third source repeats the figure citing those reviews rather than any measurement (Mavrych et al., 2026). There is also an arithmetical slip: one review equates 200 ng/mL with 10^{-7} M, but at a molecular mass of 340 Da, 200 ng/mL is closer to 6×10^{-7} M. None of this makes the figure wrong. It does mean it has never been independently confirmed as stated.

The second thing is that independent measurements now exist, and they tell a subtly different and rather more interesting story. Two Chinese groups, working on chronic lung disease, measured plasma tripeptide in healthy adults as a control condition:

SOURCE	POPULATION	N	PLASMA GHK, NG/ML
Pickart et al., reviews	age 20 (or 20–25)	not stated	~200
Pickart et al., reviews	age 60 (or 60–80)	not stated	~80
Bian et al., 2024	healthy, age-matched controls	11	105.50 ± 31.94
Bian et al., 2024	silicosis	15	35.67 ± 13.69
Deng et al., 2023	healthy controls	11	133.0 ± 54.54
Deng et al., 2023	chronic obstructive pulmonary disease	9	70.27 ± 38.87

The two independent healthy-control values, 105 and 133 ng/mL, sit below the quoted young-adult figure and above the quoted sixty-year-old figure — which is unsurprising for middle-aged control groups, and is at least compatible with the decline. What is much better established than the age relationship is the *disease* relationship. In both cohorts the concentration was roughly a third to a half lower in patients than in controls, and in both it correlated with objective measures of organ function rather than with symptoms. That is a reproducible finding from two independent groups in two different diseases, and it is stronger evidence than the age curve it is usually enlisted to support.

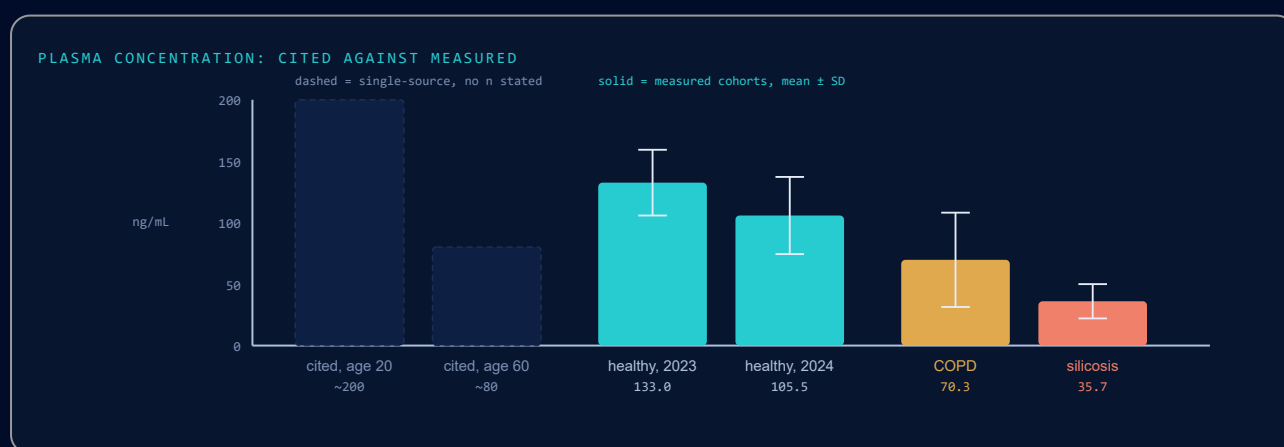


FIGURE 13 The cited age curve against the measured cohorts. The two dashed bars carry no sample size and no stated measurement method and trace to review articles by the compound’s discoverer; the four solid bars are means with standard deviations from two independent groups. The disease difference is much the better evidenced of the two claims this figure gets used to support.

It also does not establish direction. A peptide released by proteolysis of collagen and SPARC might reasonably fall when a tissue is scarred and no longer remodelling, in which case the low concentration is a readout of the disease rather than a contributor to it. Nothing in either study distinguishes those possibilities.

17

Does it get through skin?

Everything in Part Three happened in a dish or in an animal, at concentrations the experimenter chose. For the cosmetic use case — which is what almost all actual human exposure to this compound consists of — one question sits in front of all the others. When the complex is applied to skin, does any of it reach the living cells underneath, and at what concentration?

The literature's answer is not reassuring, and it is not consistent.

The most-cited dataset comes from a pair of companion papers, published in 2010 and 2011, using flow-through diffusion cells and human cadaver skin from three donors (Hostynek et al., 2010; Hostynek et al., 2011). Applied as a 0.68 per cent aqueous solution over 48 hours, copper crossed dermatomed skin to the extent of about 2 per cent of the applied dose, with substantially more retained in the tissue; through isolated stratum corneum alone, nearly 20 per cent crossed; and through isolated epidermis, **0.006 per cent** — the epidermis being by far the tighter barrier. Three features of that dataset need stating alongside the numbers. It tracked *elemental copper* by mass spectrometry, not the intact complex, and the authors themselves attribute much of the retained signal to the complex coming apart and the copper rebinding to endogenous ligands. It used a concentration of roughly 6,800 parts per million, against the 5 to 50 ppm typical of finished cosmetic products — a hundred- to thousand-fold difference. And the two papers disagree with each other about the dermal retention figure.

Against that, a separate experiment reported through a 2025 review found **no permeation of either peptide or copper at all** through intact human dermatomed skin over nine hours; measurable transport appeared only after the skin was pretreated with microneedles (reviewed in Mortazavi, 2025). For comparison, a conventional cosmetic peptide put through the same kind of assessment left 99.7 per cent of the applied dose in the surface wash, 0.22 per cent in the stratum corneum, 0.01 per cent in the viable epidermis and nothing at all in the dermis or receptor fluid (Bjerke et al., 2026).

Formulation work exists precisely because the base case is poor. Liposomes, ionic-liquid microemulsions, palmitoylation, arginine-rich carrier peptides and covalent conjugates have all been reported to improve delivery, with the better studies claiming roughly two- to five-fold gains over an aqueous control. Those are real improvements on a small number.

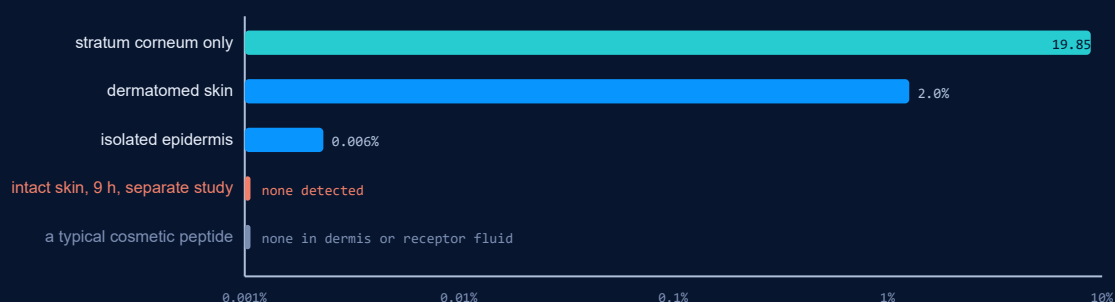
THE GAP THAT HAS NEVER BEEN CLOSED

The matrix effects in Part Three occur at one to ten nanomolar in culture medium. The penetration studies measure percentages of an applied dose at concentrations a

hundred to a thousand times higher than a real product uses, and they track copper rather than the complex. **No study in this corpus applies a cosmetically realistic dose and then reports the resulting concentration in living dermis in molar units.** The causal chain from the jar on the shelf to the nanomolar effect on a fibroblast is asserted everywhere and demonstrated nowhere. The 2025 review that examines this most carefully says so itself, noting the surprising absence of clinical studies for an ingredient in this wide commercial use.

WHAT REACHES THE OTHER SIDE OF SKIN

per cent of applied dose in receptor fluid, ex vivo diffusion cells — note the axis is logarithmic



The top three bars are one study at 0.68% — roughly 6,800 ppm, against the 5–50 ppm used in finished products — and they track elemental copper, not the intact complex.

FIGURE 14 Reported penetration, by skin layer and by study. The disagreement is the finding. It has not been reconciled in the literature, and the two sides differ in skin preparation, duration, analyte and concentration, any of which could account for it.

18

The trials that exist

Set aside the mechanism and ask what has been measured in people. The answer is a short list, and it is best read in order of what each study can actually support.

Randomised, controlled, clinical endpoint

Diabetic neuropathic foot ulcers, 1994. A multicentre, randomised, evaluator-blinded, placebo-controlled trial of the copper complex as Iamin Gel, on top of a standardised protocol of sharp debridement, pressure-relieving footwear and patient education. Median area closure was **98.5 per cent against 60.8 per cent** for vehicle ($P < 0.05$); closure was about three times faster; the effect was larger in ulcers over 100 mm²; and infection occurred in **7 per cent against 34 per cent** ($P < 0.05$) (Mulder et al., 1994). This is the best human result the compound has ever produced.

Venous stasis ulcers, 1992. A prospective, randomised, evaluator-blinded three-arm trial in 86 evaluable patients comparing a 0.4 per cent tripeptide-copper cream, 1 per cent silver sulfadiazine, and an inert vehicle. Silver sulfadiazine significantly reduced ulcer size against both

other arms. **There was no difference between the copper tripeptide cream and the placebo** (Bishop et al., 1992).

Skin after carbon-dioxide laser resurfacing, 2006. Thirteen patients randomised to a post-treatment regimen with or without the complex, assessed by computer analysis and blinded evaluators at twelve weeks. **No significant difference in resolution of redness, in wrinkles, or in overall skin quality.** The one endpoint that did differ was patient-reported satisfaction ($P = 0.04$) (Miller et al., 2006).

Randomised, but confounded by co-formulation

Male pattern hair loss, 2016. Forty-five men randomised to two doses of a complex of 5-aminolevulinic acid and the tripeptide, or placebo, daily for six months. Hair count rose by 52.6 and 71.5 in the two active groups against 9.6 in placebo ($P < 0.05$); hair length and thickness did not differ (Lee et al., 2016). The active agent is a two-component complex, so the tripeptide's own contribution cannot be separated.

EVERY HUMAN STUDY, BY WHAT IT CAN SUPPORT			
STUDY	n	DESIGN	RESULT
Diabetic foot ulcers, 1994	multi	RCT, blinded, vehicle	positive
Venous stasis ulcers, 1992	86	RCT, blinded, 3-arm	null vs placebo
The pivotal trial, 1994	511	pivotal, vehicle-controlled	failed, unpublished
CO ₂ laser resurfacing, 2006	13	randomised, blinded raters	null, objective
Pattern hair loss, 2016	45	RCT, but co-formulated	positive, confounded
Facial cream, 2002	71	conference abstract	not peer reviewed
Eye cream, 2002	41	conference abstract	not peer reviewed
Thigh skin, 1998	10	pilot, histology endpoint	biomarker only

Fifty-three years after discovery. The two studies with the strongest designs disagree, and the largest one was never published.

FIGURE 15 The human evidence in full. Neither the number of studies nor their size is the striking feature; it is that the compound has been in commercial use throughout, in products bought by many millions of people, on this.

Not peer-reviewed, and industry-connected

Three studies are cited far more often than any of the above, and they are the source of nearly every cosmetic claim: a facial cream applied for twelve weeks to 71 women with photoageing; an eye cream applied for twelve weeks to 41 women, reported as outperforming placebo and a vitamin K cream; and a thigh-skin application improving collagen production in 70 per cent of women treated against 50 per cent for vitamin C and 40 per cent for retinoic acid.

The first two are **conference abstracts from the 60th Annual Meeting of the American Academy of Dermatology, New Orleans, February 2002** (Leyden et al., 2002a; Leyden et al., 2002b). They have never been published as papers, carry no methods section a reader can evaluate, and include an author affiliated with the manufacturer whose product was tested. The third is a ten-participant pilot with a histological rather than clinical endpoint, published in a

journal not indexed by PubMed. A later randomised double-blind study reporting a 31.6 per cent reduction in wrinkle volume against an active comparator appeared in a journal published by a house widely regarded as predatory (Badenhorst et al., 2016).

TWO WIDELY CITED ITEMS THAT ARE NOT HUMAN TRIALS

A 2009 paper frequently offered online as clinical evidence for photoaged skin is an *in vitro* study of cultured keratinocytes and skin equivalents, with no human subjects and no clinical endpoint (Kang et al., 2009). And a 2010 randomised trial on décolleté photodamage sometimes attributed to this compound tested a **copper zinc malonate** complex, which is a different chemical entity.

19

What happened to the drug, and what is sold now

The most consequential fact about this molecule's human record is one that appears in no peer-reviewed paper.

Through the early 1990s ProCyt Corporation of Redmond, Washington developed the complex as a wound-healing drug under the name prezatide copper acetate, brand name Iamin, and pursued full approval from the US Food and Drug Administration. The 1994 diabetic-ulcer trial above was part of that programme. According to contemporaneous business reporting, a larger pivotal trial in **511 patients** completed in October 1994 and **failed to beat its control group**, though the compound was shown to be safe. ProCyt cut more than a third of its staff, abandoned the drug pathway, and refiled the same compound under the Class I medical device route, which requires considerably less evidence. Clearance to market Iamin Gel as a wound-care product was granted on 7 February 1996 — with the FDA expressly prohibiting the company from claiming that the product heals wounds (*The Seattle Times*, 7 February 1996).

That account rests on press reporting, not on a peer-reviewed publication or a primary regulatory document, and this monograph flags it as such. But the absence itself is evidence: a 511-patient pivotal trial in a compound with this much subsequent commercial life has no entry in the peer-reviewed literature. The largest human experiment ever conducted on this molecule is known only because a newspaper reported that it failed.

REGULATORY POSITION, AS OF AUGUST 2026

There is **no approved drug indication** for this compound in the United States, the European Union or elsewhere. It exists in commerce as a **cosmetic ingredient**, INCI name *copper tripeptide-1*, CAS 89030-95-5. The US Cosmetic Ingredient Review assessed it and concluded it is safe as used, at a typical use concentration reported by industry of **under 10 parts per million**. Two features of that assessment are worth knowing: the entity it names is the 2:1 species Cu^{2+}

[Gly-His-Lys]₂⁻, and its human-data section contains **no human testing of copper tripeptide-1 itself** — the human studies cited there are for related but different ingredients, and the compound-specific evidence is an in-vitro fibroblast assay and a rat wound-chamber study. A safety conclusion resting on very low use concentrations and on class-level data is a reasonable conclusion; it is not the same thing as a compound that has been tested in people.

Registered clinical research is, finally, beginning. A search of ClinicalTrials.gov returns no completed controlled trial of this compound with posted results. It returns one **Phase 2 trial that began recruiting in February 2026**: a 60-participant, vehicle-controlled study of a 0.1 per cent topical gel in a standardised punch-biopsy wound model, with time to re-epithelialisation as its primary endpoint (NCT07437586). It is the first properly registered, controlled, endpoint-driven trial in the compound's history.

Meanwhile the compound is sold in a third form that has no relationship to any of the evidence above. Vendors offer it as a lyophilised powder for reconstitution and injection, under research-use-only labelling. There is no approved injectable product, no human pharmacokinetic study of a parenteral route in this corpus, and no controlled trial of injected material at all. In April 2020 the FDA issued a warning letter to a compounding pharmacy that named this compound among some twenty peptides being made into sterile injectable products outside the conditions that exempt compounders from drug-approval requirements. The animal studies in Part Three used intraperitoneal, intra-articular, intranasal and oral routes at doses selected for rodents; none of them establishes anything about a human dose, and this document specifies none.

PART FIVE

Weighing it

	volume of published work	independent replication	clinical endpoint demonstrated	
cell culture and fibroblast studies				widely used as a topical cosmetic ingredient, where it has a long record of safe use
animal wound-healing models				copper complexes penetrate skin poorly, so formulation determines whether any of it reaches the dermis
ex vivo and in vivo human skin studies				injectable use is not approved in any jurisdiction and is not supported by controlled human trials
randomised controlled clinical trials with a clinical endpoint				no approved therapeutic indication anywhere

the largest single body of work originates from the laboratory that discovered the molecule a second substantial body of fibroblast and matrix work came from an independent French group the coordination chemistry has been characterised independently and is not in dispute the therapeutic claims and the gene-expression interpretation rest on a much narrower base than the chemistry does	separating what is established from what is proposed <table> <tr> <th>well established</th><th>proposed but not established</th></tr> <tr> <td>the coordination geometry and binding constant</td><td>clinical benefit in any named disease</td></tr> <tr> <td>copper redox silencing on binding</td><td>systemic anti-cancer activity</td></tr> <tr> <td>stimulation of matrix synthesis in cultured fibroblasts</td><td>reversal of ageing processes in humans</td></tr> <tr> <td>presence in plasma and decline with age</td><td>meaningful systemic exposure from topical application</td></tr> </table>	well established	proposed but not established	the coordination geometry and binding constant	clinical benefit in any named disease	copper redox silencing on binding	systemic anti-cancer activity	stimulation of matrix synthesis in cultured fibroblasts	reversal of ageing processes in humans	presence in plasma and decline with age	meaningful systemic exposure from topical application
well established	proposed but not established										
the coordination geometry and binding constant	clinical benefit in any named disease										
copper redox silencing on binding	systemic anti-cancer activity										
stimulation of matrix synthesis in cultured fibroblasts	reversal of ageing processes in humans										
presence in plasma and decline with age	meaningful systemic exposure from topical application										

FIGURE 16 The shape of the evidence. **ONE CORRECTION TO THE ARTWORK.** The bottom row of the upper-left matrix shows nothing at all under “randomised controlled trials with a clinical endpoint”. The right-hand cell is correct — no such trial has demonstrated a clinical endpoint — but the left-hand cell is not: three randomised controlled trials with clinical endpoints exist, described in section 18, and two of them were null. The distinction matters, because “untested” and “tested and failed” are different states and the second is the one this compound is in for two of its three trials.

20

Established, proposed, contradicted

Fifty-three years of work on a molecule of three residues has produced an evidence base with an unusual shape: extremely solid at the bottom, broad in the middle, and almost absent at the top.

CLAIM	STATUS	WHAT IT RESTS ON
Binds Cu(II) in a 3N square-planar sphere with a labile fourth site	Established	crystallography, EPR, NMR, potentiometry; multiple independent groups over 40 years
Affinity comparable to albumin’s N-terminal copper site	Established	equilibrium dialysis and calorimetry — with the caveat that low-molecular-weight carriers hold ~6% of plasma copper
Bound copper is redox-attenuated toward mild reductants	Established	inert to ascorbate and dithiothreitol; out-competes amyloid for copper
Bound copper is redox-silent	Contradicted	reduced by glutathione within minutes, catalytically; measurable oxidase activity in vitro
The sequence occurs in collagen α2(I) and SPARC and is released by proteolysis	Established	sequence verified at defined positions; the release mechanism is inferred, not directly observed in vivo
Stimulates matrix synthesis and turnover in cultured fibroblasts at 1–10 nM	Established	independent replication by the Reims group across a decade
Accelerates wound repair in rodents	Established	controlled wound-chamber studies with specificity controls
Protects lung and muscle in rodent injury models	Established	multiple independent 2016–2024 groups; one identified molecular target

CLAIM	STATUS	WHAT IT RESTS ON
Plasma concentration is reduced in chronic lung disease	Established	two independent cohorts, correlating with organ function
Plasma concentration falls from ~200 to ~80 ng/mL between 20 and 60	Single-source	the discoverer's reviews only; internally inconsistent; never independently confirmed as stated
Changes the expression of ~4,000 human genes	Established, and narrower than it sounds	two cancer cell lines at 1 μ M; threshold-dependent; transcript abundance only
Reverses the gene signature of emphysema	Misstated	a database match plus one fibroblast contraction assay; never given to a lung, animal or patient
Topical application delivers effective concentrations to living dermis	Not demonstrated	penetration studies conflict; none uses a realistic dose and reports a tissue concentration
Improves the appearance of ageing human skin	Weakly supported	the principal studies are 2002 conference abstracts; the one blinded trial with objective endpoints was null
Accelerates healing of diabetic foot ulcers	Contested	one strongly positive randomised trial in 1994; a 511-patient pivotal trial failed and was never published
Any systemic or injectable therapeutic effect in humans	Untested	no human pharmacokinetics, no controlled trial, no approved indication

Read down that middle column and a pattern emerges that is worth naming. Everything in the *established* rows is a measurement of the molecule itself — where the copper sits, how tightly it is held, what happens when a reductant reaches it, what a fibroblast does when it is added to the medium. Everything in the weak or contradicted rows is a claim about what the molecule does *to a person*. The dividing line is not between good and bad science. It is between questions that can be answered in a flask or a mouse and questions that require a clinical trial, and it falls exactly where the funding for clinical trials stops.

21

Why the evidence has this shape

It is tempting to read the pattern above as a scientific failure, and it is not one. The chemistry was done well, and the animal work of the last decade is better than the animal work of the first three. The gap is not where the science is weak. It is where the science stops, and the reason it stops there is structural rather than scientific.

Three forces point the same way. The molecule is a naturally occurring human peptide of three residues, first described in 1973, and is therefore very difficult to protect with composition-of-matter patents — which removes the mechanism that ordinarily pays for a Phase 3 programme. Its principal commercial market is cosmetic, and the regulatory route for a cosmetic ingredient requires safety data and no efficacy evidence whatsoever. And when the one serious attempt at drug approval was made, in the 1990s, the pivotal trial failed, which converted the compound from a drug candidate into a device and then into an ingredient.

The result is a molecule that has been in the hands of consumers for three decades, in products relying on published effects that were never tested in the form or at the dose in which those products deliver them. That is not fraud, and it is not a mystery. It is what happens when a compound's route to market does not require the evidence its marketing implies.

THE ONE ASYMMETRY WORTH NAMING

Almost every uncertainty in this document points the same direction. Where the chemistry is uncertain, it is uncertain about whether the complex is *more* reactive than claimed. Where the human evidence is uncertain, it is uncertain about whether there is any effect at all. There is no live question in this literature whose resolution would make the compound look better than the middle of its current range, and several whose resolution would make it look worse. A reader deciding how much weight to give the molecule should account for that asymmetry.

22

What would settle it

Four studies do not exist, and each of them would resolve something the present literature cannot.

A penetration study at a real dose, reporting a real concentration. Apply a finished product at its actual use concentration to human skin, and measure the concentration of the intact complex — not elemental copper — in viable epidermis and dermis, in molar units. If that number lands in the nanomolar range, the entire cosmetic literature acquires a foundation it has never had. If it does not, that is equally decisive, and equally worth knowing.

The wound trial, run again and reported either way. The 1994 diabetic-ulcer result was strong and the 1994 pivotal trial that followed it was not, and the field has been arguing past that fact for thirty years because the second one was never published. The Phase 2 trial that began recruiting in February 2026 is the first serious attempt to reopen the question.

Human pharmacokinetics for any systemic route. Material is being sold for injection with no published human data of any kind on what happens to it — how quickly it is cleared, whether the complex survives in plasma, where the copper ends up. Those are answerable questions and nobody has answered them.

A copper control, consistently applied. The single most informative control in this entire literature is the one that showed an effect being reproduced by copper ions alone and not by the peptide alone. Running that arm in every experiment would settle, endpoint by endpoint, how much of this molecule's biology belongs to the peptide and how much belongs to the metal it carries. On the evidence in Part Two, the answer may be uncomfortable for the peptide.

Until then, the honest summary is the one the chemistry supports. This is a real endogenous molecule, cut out of damaged collagen by the injury that damaged it, holding one atom of copper tightly enough to move it safely and loosely enough to give it up. What it does after that, in a person, at a dose anybody actually uses, is not known.

STANDING CONSTRAINT

This document describes published research on GHK-Cu. It does not recommend human use of the compound and specifies no dose, route or schedule for any person. Doses reported in these pages are the doses that published studies administered, given with the species, population and duration attached, and the great majority of them were administered to rodents by routes and at exposures that carry no implication for a human being. There is no approved therapeutic indication for this compound in any jurisdiction, and no injectable product has been approved anywhere. Nothing here is medical advice.

APPARATUS

References and method

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References

Generated from verified NCBI records rather than from recall. Author lists, journal names, volumes, pages and identifiers are read off the PubMed record for each citation, and the build refuses to run if any identifier fails to resolve. This series has twice shipped reference lists

drafted from memory in which identifiers pointed at real but unrelated papers, and once shipped a harvest in which a parsing error assigned each paper the identifiers of the last work it had itself cited.

The eleven entries at the end carry no PubMed record. Their presence is not an oversight: two of them are the conference abstracts that supply most of the cosmetic literature's human evidence, and one is a newspaper report that is the only located account of the largest clinical trial this compound has ever undergone.

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How this document was assembled

The corpus was built against project 05, the Therapeutic Peptide Research Library, extended by a PubMed and PubMed Central harvest. Both halves needed an identity gate before anything else, for a reason specific to this compound.

GHK is also the Goldman-Hodgkin-Katz equation. That abbreviation appears in most electrophysiology papers that compute a reversal potential or an ionic flux, and a case-insensitive substring search for “GHK” across a biomedical corpus returns a great many ion-channel papers that have nothing to do with a copper tripeptide. The matcher used here is therefore case-sensitive, bounded on both sides, and — for a bare GHK token — admits it only when subject-matter corroboration appears within 400 characters and no electrophysiology term appears in the same window. Unambiguous designations such as the systematic name or the residue string confirm on their own.

A local sweep opened every document-extension file in twenty stores and returned **530** matching assets. Classifying those by what they actually are is the step that matters, and it removes most of them: **280** are dated web snapshots of vendor product pages, **189** are vendor and affiliate blog copy collected as writing samples, **28** are the same handful of vendor product PDFs triplicated across three folders, and **8** are this project's own earlier internal write-ups. Only **25** were peer-reviewed scientific full texts. Reporting 530 as a corpus would have been a claim about coverage this document does not have.

Because the local snapshot held so little primary science, the pipeline queried NCBI directly by two routes. A PubMed harvest returned **256** relevant indexed records spanning 1973 to 2026. PubMed indexes titles, abstracts and MeSH terms only, so a second stage searched PubMed Central's *full text*, returning **1,150** matches. Stage 03 fetched the union.

The far-side screen then classified each fetched article by how substantively it uses the compound. **147** report their own experiments and name the compound inside a Methods section; **118** discuss it substantively without one. **143** mention it once or twice and were counted rather than read. **725** never name the tripeptide at all — they were returned by the broad "copper peptide" query term and are copper complexes of unrelated peptides. One was a Goldman-Hodgkin-Katz homograph and **17** had no body text deposited.

Merging the local and fetched sets *by PMCID* rather than adding them — 21 documents appear in both — gives the reading corpus this monograph is written from: **269 peer-reviewed scientific full texts, 1,781,143 words, roughly 3,562 printed-page equivalents**, together with the complete 256-record metadata layer.

STAGE	WHAT IT DOES	RESULT
01b	Targeted scan of the project's document stores, corroborated matcher	530 assets
01g	Classification by source kind, de-duplicated by content hash	25 scientific
02	PubMed E-utilities harvest	256 records
02b	PubMed Central full-text search	1,150 matches
03	Open-access full-text retrieval of the union	1,151 fetched
03c	Substantive-use screen and homograph rejection	265 kept
04	Keyed merge and inventory	269 unique
05	Reference list from verified NCBI records	68 citations
06	Assembly of this document	1 deliverable

Evidence handling

Findings are labelled by the kind of study that produced them, in the sentence that reports them. Randomised human trials, uncontrolled human studies, conference abstracts, animal experiments, cell and tissue measurements, cell-free solution chemistry and computational signature matches are different kinds of claim, and the difference is stated rather than left to the reader to infer. Animal and in-vitro findings are never phrased so as to imply a human outcome, and the species is named every time.

Three distinctions were held throughout because this literature routinely collapses them. The **free peptide against the copper complex**: several influential animal studies used uncomplexed GHK and said so, and at least one set of authors stated explicitly that they could not say whether the complex would have performed better. The **concentration** at which an effect was seen: matrix effects reported at one nanomolar and gene-expression profiles generated at one micromolar are separated by a factor of a thousand and are not evidence for the same proposition. And **what was actually done**: the most cited claim in the field — that this compound reverses the gene signature of emphysema — rests on a database match between two lists of genes plus one fibroblast contraction assay, and the compound was never given to a lung, an animal or a patient in that study.

Recency is weighted but not blindly. The 2020–2026 literature is the best in the field methodologically — it produced the first identified molecular target, the first independent plasma measurements, and the chemistry that qualifies the redox-silencing claim — and it is treated as current. Its regulatory and market statements are treated as current. Where a recent review restates an older claim without new data, the claim is traced back to the primary work and reported at the strength that primary work supports.

Where a number could be traced only to the laboratory that discovered the molecule, this document says so rather than laundering it through a citation. That applies to the plasma concentration decline, to the anticoagulation mechanism, and to the binding-constant comparison with albumin, whose usual presentation omits the same study's finding that low-molecular-weight carriers hold only about six per cent of plasma copper.

On the artwork. Eight illustration plates were commissioned for this monograph and every value, label and structure printed on them was checked against the evidence dossier. Nineteen values were confirmed; two were confirmed and improved with residue positions the plates did not carry; five were corrected or qualified in their captions; and one, an absorbance maximum, could not be verified either way and is printed nowhere in this document. **Two plates were withheld.** Both are chemical structure drawings, and in both the drawn skeleton is not this molecule — one adds a carbon to the glycine residue and prints a molecular formula wrong by two hydrogens, and the other draws a chelate whose donor atoms are five backbone atoms apart where the real complex closes a five-membered ring. A caption cannot repair either, because a reader reads the bonds. Both were replaced by authored figures carrying verified values. The plate-by-plate record is in the delivery bundle.



Compound Monograph No. 15 – GHK-Cu · compiled 2 August 2026

Corpus: 269 scientific full texts · 256 indexed records · 68 references

Source project 05 – Therapeutic Peptide Research Library

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