THE COMPOUND

a sunday briefing

The Skin & Hair Peptide Stack

Topical vs. systemic — and what the literature actually shows.

for the operator who reads before they pin

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Nothing in this document is a recommendation to administer, prescribe, or self-administer any compound.

Topical vs systemic, seven compounds, four evidence tiers, no doses.

By The Compound — the Sunday briefing on peptides for founder-operators.

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Disclosure: The operator who publishes The Compound also owns heroxbio.com, an RUO peptide vendor. Full FTC disclosure on the About page.

What this is

A working reference on the seven compounds that show up most often in skin, hair, and aesthetic-aging conversations. Mechanism, half-life where the literature is clean, the named author you should search, and what the community reports.

It is not a protocol. It is not a sales sheet. There are no doses anywhere in this document. Doses live behind the email gate, in cited issue summaries, where they belong.

We use a four-tier evidence framework throughout:

• **Tier 1.** Randomized controlled trials in humans.

• **Tier 2.** Open-label human studies, case series, registry data.

• **Tier 3.** Animal models and mechanistic in-vitro work.

• **Tier 4.** Operator n=1 and anonymized community reports.

Each compound below is tagged with the tier its strongest evidence sits in. Most peptides in this lane live at Tier 3 systemically and Tier 1 or Tier 2 topically. That asymmetry is the entire story of this document.

Topical vs systemic — and the regulatory split

The single most important frame for the skin and hair lane is that the same molecule sits in two completely different regulatory and evidence buckets depending on how it is delivered.

GHK-Cu is the cleanest example. As a topical cosmetic ingredient — a serum or cream applied to the skin — copper tripeptide has been on shelves at Sephora, in dermatologist offices, and in clinical-skincare lines for more than two decades. The FDA regulates it as a cosmetic. The published cosmetic literature on topical GHK-Cu is Tier 1 in places: small randomized trials, controlled split-face studies, gene-expression work in human skin biopsies. Pickart and colleagues built the foundational corpus over forty years. You can buy a copper-peptide serum at a drugstore tonight.

The same molecule, in injectable form, sits in a different regulatory universe. Injected GHK-Cu in humans is a research compound — sold for research use only by RUO vendors — and the human evidence base is thin. Most of what we know about systemic GHK-Cu effects comes from animal models and from the gene-expression work Pickart's group has published. The community reports exist. The Tier 1 human data does not.

This pattern repeats across the lane. Topical melanotan analogs sit in cosmetic-adjacent grey markets. Injected melanotan II is RUO. Topical thymosin beta-4 fragments appear in some dermatology research. Injected TB-500 is RUO. The molecule is the same. The evidence tier, the regulatory status, and the risk profile are not.

Three implications follow from this split:

First, evidence claims do not transfer between routes. A randomized trial of a topical copper-peptide serum is not evidence for what an injected version does systemically. The mechanism may be related. The pharmacokinetics, the exposure, the off-target risk — those are different problems.

Second, most retail topical products are dramatically under-dosed compared to the concentrations used in published research. We get to that further down. The serum on the shelf and the serum in the trial are usually not the same product.

Third, the founder-biohacker community has assembled a working picture by combining topical literature, injected animal data, and Tier 4 n=1. The Compound's job is to map that picture honestly — to mark which claims sit on Tier 1 and which sit on Tier 4 — so you can decide what you actually believe.

We do not collapse the tiers. We do not pretend the cosmetic literature is the systemic literature. And we do not pretend Tier 4 is nothing — it is the least-controlled tier, but it is also where the earliest signal lives in a class of molecules that the formal trial machinery has not yet caught up to.

The seven compounds in the skin and hair lane

1. GHK-Cu

Glycyl-L-histidyl-L-lysine, copper-bound. The flagship.

What it is. A naturally occurring tripeptide with high copper-binding affinity. The cornerstone compound in the skin and hair lane.

Mechanism. GHK forms a complex with copper(II) ions and acts as a copper chaperone — a molecule that delivers a metal ion to specific cellular destinations. Downstream effects in published work include modulation of gene expression related to extracellular matrix remodeling, antioxidant response, and wound repair. Pickart and Margolina's 2018 review documents over 4,000 genes whose expression is modulated by GHK in human cells.

Half-life. Short in plasma — minutes — though tissue residence and copper-delivery effects appear to outlast plasma clearance.

Evidence tier. Topical: Tier 1 in places. Systemic injected: Tier 3.

Primary literature. Pickart and Margolina, 2018 (International Journal of Molecular Sciences). Pickart's broader corpus across four decades on PubMed under "GHK copper peptide." Cosmetic dermatology trials on copper-peptide serums in the 2000s and 2010s.

What the community reports. Skin texture changes commonly reported within four to eight weeks of consistent topical use at research-grade concentrations. Hair density anecdotes are noisier and confounded by every other thing the same users are doing. Injection-route reports often pair GHK-Cu with TB-500 in recovery stacks rather than in pure skin-and-hair stacks.

What we don't know. Systemic effects of injected GHK-Cu in humans are under-characterized. Copper accumulation risk at sustained injected exposure has not been well studied. The dose-response relationship outside topical applications is unclear.

2. PT-141 (Bremelanotide)

Melanocortin receptor agonist. Adjacent, not central.

What it is. A synthetic peptide that activates melanocortin receptors, primarily MC4R. FDA-approved as Vyleesi for hypoactive sexual desire disorder in premenopausal women. Appears in the skin and hair conversation because of its melanocortin-system relationship to melanotan II — same receptor family, different selectivity profile.

Mechanism. PT-141 acts on central melanocortin receptors in the hypothalamus to modulate sexual arousal pathways. Its relationship to skin pigmentation is much weaker than melanotan II's because PT-141 is more selective for MC4R than MC1R. Skin and hair effects are not the primary indication.

Half-life. Approximately 2 hours after subcutaneous administration in published pharmacokinetic work.

Evidence tier. Tier 1 for the approved indication. Tier 4 for any skin or hair adjacent claim.

Primary literature. Kingsberg et al., 2019 (Obstetrics & Gynecology) — RECONNECT trial of bremelanotide for HSDD. Diamond et al., 2006 on early bremelanotide development. The melanocortin-receptor literature broadly under King and colleagues.

What the community reports. Sexual-arousal effects are the dominant report. Flushing and nausea common. Skin pigmentation is rare at doses used for the approved indication; this is not melanotan II in disguise.

What we don't know. We are flagging PT-141 here because of its melanocortin-system adjacency to compounds that do affect skin pigmentation, not because there is a meaningful skin-and-hair use case. The regulatory observation is that PT-141 is FDA-approved for one indication and is not a skin-or-hair

compound. We are not making a recommendation to administer it.

3. Epitalon

Khavinson tetrapeptide. Longevity-adjacent. Thin Western evidence.

What it is. A synthetic tetrapeptide (Ala-Glu-Asp-Gly) developed by Vladimir Khavinson and the St. Petersburg Institute of Bioregulation and Gerontology. Marketed in the community as a telomere-and-pineal compound.

Mechanism. Russian-language and translated work attributes epitalon's effects to telomerase induction and pineal gland regulation, with downstream effects on melatonin rhythm and gene expression. The mechanistic claims rest heavily on Khavinson's group's own work; independent Western replication is limited.

Half-life. Reported as short — under an hour — in available pharmacokinetic notes. The dosing rationale in the community treats it as a pulse compound rather than steady-state, which the half-life supports.

Evidence tier. Tier 2 in the Russian literature. Tier 3 to Tier 4 in the Western literature. The asymmetry is striking and a reader should weigh it.

Primary literature. Khavinson and colleagues across the 1990s, 2000s, and 2010s — the foundational corpus, much of it published in Russian-language journals with English abstracts. Khavinson, 2002 (Bulletin of Experimental Biology and Medicine) is one of the more-cited entry points. Anisimov and colleagues on bioregulator peptides in animal models.

What the community reports. Subjective sleep changes are the most consistent report. Skin-quality changes appear in longer cycles. The anti-aging claims are louder than the data supports — that is the gap.

What we don't know. Most of what a Western reader would want to know. Independent RCTs in Western populations are sparse. Long-term safety data is thin. The telomerase-induction claims have not been robustly replicated outside Khavinson's group.

4. Thymosin Beta-4 / TB-500

Actin-binding peptide. Skin remodeling angle.

What it is. A synthetic peptide based on a region of thymosin beta-4, an actin-binding protein. In the skin and hair lane it shows up for tissue-remodeling reasons distinct from its joint-and-recovery use.

Mechanism. TB-4 binds G-actin, the monomer form of the cytoskeletal protein actin, and is implicated in cell migration, angiogenesis, and tissue repair. The skin-relevant work focuses on dermal remodeling and wound-healing endpoints. The hair-relevant work is thinner but exists in early-stage models.

Half-life. Reported in the multi-day range for the parent thymosin beta-4 in some pharmacokinetic work. The synthetic TB-500 fragment's exact half-life in humans is less cleanly characterized.

Evidence tier. Tier 2 for thymosin beta-4 in dry eye and wound-healing trials. Tier 3 for TB-500 fragment in skin and hair endpoints.

Primary literature. Goldstein et al. — foundational papers on thymosin beta-4 biology. RegeneRx clinical trials on thymosin beta-4 (the parent peptide, not the TB-500 fragment) for dry eye and wound healing. Search "thymosin beta-4 wound healing" on PubMed for the corpus.

What the community reports. Skin-quality changes are reported but slower-building than with topical GHK-Cu. The fragment-vs-full-protein question is rarely engaged in community discussion; most users do not distinguish TB-500 from TB-4.

What we don't know. Whether the TB-500 fragment recapitulates full TB-4 activity in humans is not well characterized. Most published work is on the full protein, not the fragment that vendors sell. Skin-specific dose-response in humans is essentially uncharacterized.

5. Hair-specific topicals — Thymuskin and copper-peptide serums

The retail hair lane and the formulation gap.

What it is. A class of topical hair products formulated around thymic peptides (Thymuskin, the thymus-peptide-based shampoo and serum line developed in Germany) and copper tripeptide (a wide range of copper-peptide hair serums and scalp formulations). These are commercial cosmetic products, not RUO research compounds.

Mechanism. Thymuskin's thymus-peptide formulation is proposed to modulate hair-follicle inflammatory signaling. Copper-peptide hair serums are proposed to extend the anagen (growth) phase of the hair-follicle cycle and to modulate the perifollicular extracellular matrix. The mechanism in both cases is plausible at the bench level. The formulation question is whether what is in the bottle delivers what the bench work uses.

Half-life. Not the right framing for a topical formulation. The relevant pharmacokinetic question is residence time on the scalp and penetration past the stratum corneum, both of which are formulation-dependent.

Evidence tier. Tier 2 for Thymuskin in some open-label scalp studies sponsored by the manufacturer. Tier 3 for copper-peptide hair serums in most of the available work.

Primary literature. Thymuskin manufacturer-sponsored studies in the 1990s and 2000s. The Pickart corpus on copper peptides applied to hair-follicle work. Search "copper peptide hair follicle" on PubMed for the published bench work.

What the community reports. Density and shedding-rate changes reported in the four-to-six-month range with consistent use. Confounded heavily by minoxidil, finasteride, microneedling, and dietary changes that the same users are usually doing in parallel. Disentangling the contribution of any one component is hard from community data.

What we don't know. Whether retail-grade copper-peptide hair serums deliver concentrations consistent with the published bench work. The next section is about this exact problem.

6. Melanotan II

MC1R/MC4R agonist. Sunless tanning. Cardiovascular caveat.

What it is. A synthetic non-selective melanocortin receptor agonist. The community's sunless-tanning peptide. Sold by RUO vendors, not approved by any major regulator for any indication.

Mechanism. Melanotan II activates MC1R receptors on melanocytes, driving melanin synthesis and skin darkening. It also activates MC3R, MC4R, and MC5R, which is why the side-effect profile includes nausea, appetite suppression, sexual-arousal changes, and — the load-bearing caveat — cardiovascular effects including blood pressure changes and reports of arrhythmia in case literature.

Half-life. Approximately 30 minutes after subcutaneous administration in available pharmacokinetic work. Pigmentation effects accumulate over weeks despite the short plasma half-life because the effect is on melanocyte signaling, not steady-state drug exposure.

Evidence tier. Tier 3 to Tier 4. There are no large human RCTs on melanotan II. Case reports of adverse events are the most-cited human literature.

Primary literature. Hadley and colleagues — original melanotan development work in the 1980s at the University of Arizona. Case reports across the 2000s and 2010s on adverse events including melanocytic lesion changes and cardiovascular events. Search "melanotan II adverse" on PubMed for the case literature.

What the community reports. Pigmentation effect is real and dose-related. Nausea on early doses near-universal. Existing nevi (moles) darkening is commonly reported and is a flagged dermatologic concern. The cardiovascular caveat is the one most community discussions under-weight relative to its case-report support.

What we don't know. Long-term safety in any population. Whether the melanocytic-lesion changes reported in case literature represent a meaningful melanoma risk at population scale. The exact contribution of MC4R activation to the cardiovascular side-effect profile.

7. Cerebrolysin

Cognitive-aging adjacency. Briefly.

What it is. A peptide preparation derived from porcine brain tissue, used as an investigational neurotrophic agent. Not a skin-and-hair compound. Included here only because the cognitive-aging conversation overlaps heavily with the aesthetic-aging cohort, and both lanes interact in the founder-operator stack.

Mechanism. Cerebrolysin's proposed mechanism involves neurotrophic factor mimicry and modulation of neuronal survival pathways. The mechanism literature is dense and this is not the document for it.

Half-life. Variable across the peptide-fraction components. Not a single-half-life compound.

Evidence tier. Tier 1 to Tier 2 in stroke and cognitive-impairment trials, primarily in European and Asian populations. Not characterized for aesthetic or skin endpoints.

Primary literature. Chen et al., Cochrane reviews on cerebrolysin in acute ischemic stroke. Bornstein and colleagues on vascular dementia trials.

What the community reports. Cognitive-clarity reports in long-time users. Not relevant to the skin and hair lane.

What we don't know. Whether anything cerebrolysin does has aesthetic-aging implications. We are flagging it as adjacent because the cohort overlaps, not because the literature supports a skin-and-hair use case. A future Compound issue covers cerebrolysin in its own lane.

What the Reddit-and-Instagram corpus actually says

Tier 4 is its own evidence layer if you read it honestly. We do not pretend it is Tier 1. We also do not pretend it is nothing.

The crossover threads between r/Peptides and r/SkincareAddiction are where most of the topical-versus-injected debate plays out in real time. The dominant pattern: experienced users separate the topical and systemic conversations cleanly, while newer users frequently conflate them. The most-cited topical brands rotate but the most-cited active ingredient is GHK-Cu by a wide margin, with retinoids and tretinoin as the cosmetic-pharma comparators.

The Instagram corpus on Epitalon is dominated by Nathalie Niddam's interviews and the broader bioregulator-peptide community downstream of her work. The voice is more enthusiastic than the published Western evidence supports. Read the interviews for the mechanism story; do not read them for the dose. Khavinson's own publications are the primary source.

Hair-specific community reporting is the noisiest of the four. The reason is confounding. Users running copper-peptide serums are almost always also running minoxidil, often finasteride, and frequently microneedling. The signal-to-noise on copper-peptide hair-density claims in community data is therefore low, and the n=1 reports are most useful as hypothesis generators rather than as evidence.

The melanotan II community is the most internally divided. The hardcore tanning users dismiss the cardiovascular caveat. The more-cautious users treat it as the load-bearing risk. The case-report literature sides with the cautious users, and we do too.

Across all four communities, the meta-pattern is the one that motivated this newsletter: the picture is assembled by reading six sources and synthesizing. The Compound's job is to do the synthesis once a week so you do not have to.

Topical formulation realities

The single most useful piece of working knowledge in the topical lane is that most retail copper-peptide serums are dramatically under-dosed compared to the concentrations used in published research.

The bench work on GHK-Cu in skin remodeling and gene-expression endpoints typically uses concentrations in the high-microgram-per-milliliter to low-milligram-per-milliliter range, applied in well-characterized vehicles. The retail products on dermatology shelves and at mass-market beauty retailers vary across multiple orders of magnitude in actual peptide concentration, vehicle composition, and formulation stability. Copper peptides oxidize. The vehicle matters. The container matters. The formulation date matters.

Three formulation realities every reader should hold:

• **Concentration.** The label rarely tells you the actual concentration of the active. "Contains GHK-Cu" is not a concentration claim. Brands that publish their concentration (a small minority) are doing the reader a service.

• **Vehicle and penetration.** Peptides are large, polar molecules that do not cross the stratum corneum efficiently. The vehicle — the carrier formulation — determines whether any of the labeled active gets to the dermal layer where the published mechanisms operate. Most retail vehicles are not optimized for peptide penetration.

• **Stability.** Copper peptides degrade. A bottle that has been open for six months on a bathroom counter is not the same product as a freshly made batch. Published research uses fresh, controlled preparations.

The takeaway is not "all topicals are scams." It is that the gap between the bench and the bottle is large, and a reader who wants to evaluate a topical product against the published research has to look at concentration, vehicle, and stability before drawing any conclusion about expected effect.

What the Brief covers next

Coming Sundays in The Compound:

• The dosing summaries for each of these compounds, behind the email gate, with cited issue references.

• A formulation-grade comparison of the most-discussed retail copper-peptide serums against published research concentrations.

• The Khavinson bioregulator corpus translated for Western readers — what replicates, what does not, what is still open.

• The melanotan II cardiovascular case-report review — every published case, summarized and tier-tagged.

• Hair-stack synthesis: how the community combines copper peptides, minoxidil, finasteride, and microneedling, and where the evidence actually supports the combinations.

The Sunday briefing is where the dosing, the cited summaries, and the working stack discussions live. This document is the public-archive map of the lane.

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