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The Whole Secretome Advantage

Why the Full Cocktail Outperforms Single-Factor Approaches

Paper 06 in the CFT Advantage Series

WHITE PAPER

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Abstract

Many contemporary regenerative biologics isolate a single component for the sake of mechanistic clarity: a recombinant growth factor, a purified exosome preparation, or a platelet concentrate. This paper sets out the biological case for delivering a complete cell-derived secretome instead. Tissue repair is a coordinated, multi-phase response in which extracellular vesicles, soluble growth factors, cytokines, lipid mediators, and matrix-modulating proteins act in concert. Single-factor approaches face four recurring limitations: short pharmacokinetic half-lives, missing signalling context, an inability to address pathway redundancy, and the need for higher exposure to elicit a cellular response. Cell-Free Therapy (CFT) preserves the broader secretome composition that the donor cells release under controlled conditioning, and it does so from autologous starting material. The paper compares whole-secretome preparations against three single-component alternatives, summarises what is and is not yet established about combinatorial effects, and closes with a practical framework for physicians evaluating these categories. Direct head-to-head clinical comparisons remain limited; the argument for whole-secretome preparations rests on the underlying biology of repair rather than on settled comparative-efficacy data.

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1. Introduction: A Single Instrument or the Whole Orchestra

A single violin, played with technique and care, is music. A full orchestra is different in kind, not just in volume. Strings, woodwinds, brass, and percussion do not simply add their lines together; they layer, accent, anticipate, and answer one another in a score that no single instrument could carry. In regenerative biology, the question of single instrument or whole orchestra is more than a metaphor. It frames a real choice in product design: deliver one purified molecule with a clean mechanistic story, or deliver the broader cell-derived preparation that biology itself uses for repair.

Reductionism has been the dominant design principle in modern biomedicine. Identify a single pathway, isolate a single ligand or vesicle population, control its dose, and study its effect. The approach has produced extraordinary drugs, but it has also produced a recurring pattern of disappointment in regenerative settings: pre-clinical promise for an isolated factor that does not translate, or translates only modestly, in clinical work (Annex, 2013; Carmeliet and Jain, 2011). Tissue repair is not a single-pathway phenomenon. It involves coordinated immune-cell recruitment, matched modulation of inflammation, angiogenesis, extracellular matrix remodelling, and the reactivation of resident progenitor populations (Eming, Martin, and Tomic-Canic, 2014).

This paper makes the biological case for whole-secretome preparations and examines three single-component alternatives that physicians and patients encounter routinely: recombinant growth factors, purified exosome products, and platelet-rich plasma. It then sets out where Cell-Free Therapy (CFT) sits in this landscape, what is reasonably claimed for whole-secretome approaches, and what remains an open question. The argument is not that single-factor biologics have no role; in narrowly defined indications, they do. The argument is that for the broad goals of supporting tissue function, a preparation that preserves the cell's native repertoire of signals is biologically better matched to the task than any one of those signals delivered alone.

2. Why Multi-Factor Signalling Is the Native Language of Repair

2a. Robustness, Specificity, and Temporal Coordination

Cells do not signal to one another with single molecules. When a fibroblast encounters tissue injury, it does not release only VEGF, only TGF-β, or only IL-6. It releases a set of soluble factors and extracellular vesicles in a regulated temporal and spatial pattern (Vizoso et al., 2017; Gnecchi et al., 2008). This multi-component release pattern carries three properties that a single molecule cannot reproduce.

First, robustness. If any one molecule is blocked, neutralised by an antibody, or rapidly degraded, parallel signals remain to drive the required biological response. Angiogenesis, for example, has multiple upstream triggers: hypoxia, VEGF, FGF, hepatocyte growth factor, angiopoietins, and matrix-bound cues (Carmeliet and Jain, 2011). A clinical preparation that contains many of these concurrently is more likely to engage a viable repair pathway in any given tissue context than a single recombinant ligand.

Second, specificity. The same growth factor can mean different things to a cell depending on what other signals accompany it. VEGF in the presence of complementary angiopoietin and matrix cues drives organised vessel formation; VEGF without that context can produce leaky, disorganised vasculature (Carmeliet and Jain, 2011). The cell does not interpret a ligand in isolation, it interprets a signature.

Third, temporal coordination. Tissue repair proceeds through phases: haemostasis, inflammation, proliferation, and remodelling. Each phase requires a different signalling profile, and what is helpful in one phase can be counterproductive in another (Eming, Martin, and Tomic-Canic, 2014). The cell-derived secretome carries factors relevant to multiple phases, and the tissue context determines which subset is engaged at any given moment.

2b. Phase-Dependent Composition of the Repair Response

Wound-healing biology offers the cleanest illustration. Initial haemostasis and early inflammation depend on platelet-derived signals and pro-inflammatory cytokines. The proliferative phase depends on growth factors that drive fibroblast and endothelial recruitment, including VEGF, FGF, PDGF, and HGF. Remodelling depends on matrix metalloproteinases, their tissue inhibitors, and TGF-β isoforms that influence collagen organisation. A preparation that supplies factors relevant to several phases provides the tissue with options; the local cellular environment selects which option to engage (Eming, Martin, and Tomic-Canic, 2014).

This is not a claim that whole-secretome preparations magically synchronise with a particular wound's biology. It is a more modest claim: that a compositionally rich preparation supplies more of the inputs the local cellular machinery is built to read.

3. Cooperation Between EVs and Soluble Factors

3a. EV-Delivered Cargo and Its Soluble Context

Extracellular vesicles are one of several routes by which cells exchange signals (Yáñez-Mó et al., 2015; Raposo and Stoorvogel, 2013). EVs carry microRNAs, mRNAs, proteins, lipids, and metabolites; their cargo can be delivered to recipient cells through fusion, endocytosis, or receptor-mediated uptake (Kalluri and LeBleu, 2020). EVs do not, however, act in isolation in physiological signalling. They are released alongside soluble proteins, lipids, and metabolites, and the receiving cell experiences both inputs in parallel (Vizoso et al., 2017).

This co-delivery has practical consequences. The activity of an EV-delivered microRNA in a recipient cell depends on the state of the pathways that the microRNA targets, which is in turn modulated by the soluble cytokine and growth-factor environment around the cell. Soluble factors, for their part, can be presented and concentrated through co-occurrence with vesicle traffic, and EV-bound proteins extend the signalling half-life of factors that would otherwise be cleared rapidly from

circulation (Phinney and Pittenger, 2017). Treating EVs and soluble factors as two independent drug categories misses the way the cell encounters them in vivo.

3b. What Direct Comparative Evidence Does and Does Not Show

It is important to be precise about what the literature presently establishes. The biology of multi-component signalling is well documented. What is less well documented is the direct, head-to-head clinical comparison of a whole-secretome preparation against its purified components in matched human indications. Pre-clinical work in cardiac, renal, and musculoskeletal models consistently shows that mesenchymal-cell secretome and EV preparations carry regenerative activity (Phinney and Pittenger, 2017; Vizoso et al., 2017). Clinical work in humans, with rare exceptions, has not yet directly contrasted whole-secretome against single-component arms in adequately powered, well-controlled studies.

The honest position, therefore, is this: the case for whole-secretome over isolated components is grounded in the biology of how cells signal during repair, supported by pre-clinical comparative work, and not yet confirmed by definitive head-to-head clinical trials. Where the paper later refers to advantages of multi-component preparations, that wording carries this caveat.

4. Single-Factor Approaches: Where They Fall Short

4a. Recombinant Growth Factors

Recombinant growth factors have been the most extensively studied single-component biologics in regenerative medicine. They are easy to define, manufacture, characterise, and patent. The clinical record across cardiovascular and limb-ischaemia indications is, by general acknowledgement, modest. Single-factor angiogenic strategies, including VEGF and FGF monotherapy in critical limb ischaemia, have not consistently translated the robust pre-clinical signal into clinical benefit (Annex, 2013; Carmeliet and Jain, 2011).

Several factors contribute. Recombinant growth factors generally have short circulating half-lives in vivo, providing only a brief window of exposure after each administration. Single ligands miss the modulatory context that the receiving cell requires to interpret the signal correctly: a pure VEGF exposure can produce disorganised vasculature absent the supporting cues that normally accompany it. Higher local concentrations are sometimes used to overcome these limitations; concentrations above the physiological range can drive off-target binding, increase the risk of unintended effects, and shift the dose-response in unhelpful directions (Carmeliet and Jain, 2011).

None of this means recombinant growth factors are without value. In specific, narrowly defined applications (for example, certain bone-defect indications where local biology is tractable), recombinant proteins can be effective. The lesson is more limited: that the single-factor strategy carries built-in constraints in tissue contexts where repair depends on signalling networks rather than on one upstream input.

4b. Purified Exosome Preparations

Purified exosome products have emerged as a distinct commercial category in regenerative medicine. They are typically isolated from cell-culture media or tissue lysates, scaled up, and marketed as a more defined alternative to crude secretome preparations. The intention to standardise is reasonable; the reductionist trade-off it implies is the harder question.

By design, a purified exosome preparation excludes the soluble fraction of the secretome. Estimates of the soluble-versus-vesicular split vary by source tissue and conditioning protocol, but a substantial portion of the bioactive material in cell-derived secretome typically sits outside vesicles (Vizoso et al., 2017). Removing that fraction removes the soluble-context signal that, as discussed above, the cell uses to interpret EV cargo.

Purified exosome preparations also face practical heterogeneity issues. Different isolation methods (ultracentrifugation, size-exclusion chromatography, tangential-flow filtration, immunoaffinity capture, polymer-based precipitation) yield preparations with different size distributions, purity profiles, and co-isolated contaminants (Willms et al., 2018; Welsh et al., 2024). Reporting standards have improved with MISEV2018 and MISEV2023, but methodological consistency across laboratories and across commercial suppliers remains a work in progress (Théry et al., 2018; Welsh et al., 2024). Two products labelled as exosome preparations may be biologically very different.

None of this argues that EVs are irrelevant. They are a real and important component of cell-derived signalling. The argument is that a preparation containing only the EV fraction loses the soluble context that the cell evolved to read alongside vesicle cargo.

4c. Platelet-Rich Plasma

Platelet-rich plasma (PRP) is the regenerative product physicians encounter most often in day-to-day practice, particularly in musculoskeletal medicine. It is autologous, broadly available, and prepared at the point of care. Its biological premise is to concentrate the platelet-derived growth factors released on activation: PDGF, TGF-β, VEGF, EGF, and others (Andia and Maffulli, 2013).

Two characteristics distinguish PRP from a cell-derived whole-secretome preparation. First, PRP's active payload is platelet-derived rather than white-cell or stem-cell-derived. The factor profile reflects platelet biology, which overlaps with but does not duplicate the broader secretory output of leukocytes, mesenchymal cells, or other secretome-relevant populations. Second, preparation methods (centrifugation protocol, leukocyte content, platelet concentration, activation method) vary substantially across commercial systems and operators, producing meaningful biological variation in the final product (Andia and Maffulli, 2013; Filardo et al., 2018).

Clinical evidence for PRP is mixed and indication-specific. Meta-analyses in knee osteoarthritis suggest PRP may offer modest, mainly short-term symptomatic benefit relative to hyaluronic acid in some patient subgroups, with effect sizes that depend on preparation protocol and outcome measure (Filardo et al., 2018). For tendinopathy, rotator-cuff disease, and lateral epicondylitis, evidence is similarly mixed (Andia and Maffulli, 2013). Whole-secretome preparations have a

different premise: rather than concentrating one cell's release products from blood, they collect the broader paracrine output of conditioning-stimulated cells, including but not limited to platelet-derived factors. The two should not be treated as interchangeable.

5. CFT's Composition: A Characterised Multi-Component Preparation

Cell-Free Therapy is prepared from a peripheral blood draw of approximately 150 mL. The white-blood-cell fraction is isolated and conditioned (it is not expanded in long-term culture, nor enzymatically reprogrammed) and the cell-free output of that conditioning step is recovered, characterised, and stored. The resulting preparation contains extracellular vesicles in a range of sizes, soluble proteins including growth factors and cytokines, lipid mediators, and other small molecules released as part of the cell's physiological response to the conditioning environment.

Internal batch characterisation indicates the presence of multiple growth factors and signalling proteins associated with tissue repair, including members of the VEGF, FGF, PDGF, and HGF families, alongside immunomodulatory cytokines and EV-associated cargo. Specific ranges and identities depend on donor biology, conditioning conditions, and assay platform; representative ranges are reported in CFT-internal batch records and the Quality Over Quantity paper of this series. The composition is consistent with the broader profile of cell-derived secretomes documented in the literature (Vizoso et al., 2017; Phinney and Pittenger, 2017; Gnecchi et al., 2008).

Two design choices follow from this. Each preparation is autologous, which removes donor-mismatch immune considerations and aligns the EV surface signature with the recipient. And each preparation retains the soluble fraction alongside the vesicular fraction, so the whole-secretome rationale discussed in Sections 2 and 3 is preserved by the manufacturing route rather than reconstructed afterwards from purified components.

What this paper does not claim

This paper does not claim that CFT, or any other whole-secretome preparation, treats, prevents, cures, or mitigates any specific disease. It does not claim that whole-secretome superiority over single-component biologics has been established by definitive head-to-head clinical trials in humans; the case rests on the biology of multi-component signalling and on supporting pre-clinical comparative work. The discussion of recombinant growth factors, purified exosomes, and platelet-rich plasma identifies categorical limitations of those approaches in defined contexts; it does not deny that each has appropriate clinical applications. References to internal CFT characterisation are representative ranges, not regulatory release specifications.

6. Implications for Physicians

For physicians evaluating regenerative biologics, the practical question is rarely whether any one preparation is universally better than another. It is whether the chosen preparation is matched to

the indication and to the biology the clinician is trying to support. A few principles fall out of the discussion above.

Match the preparation to the biology of the goal. Where the goal is supporting a multi-phase repair process (broad musculoskeletal recovery, for example), a multi-component preparation is biologically better matched than any single-factor product. Where the goal is a narrowly defined, single-pathway intervention with a well-characterised target, a recombinant factor in a regulated indication may be appropriate.

Ask compositional questions, not just particle-count or platelet-count questions. For exosome products, ask which isolation method was used, what fraction of the total secretome bioactivity is captured, and how product-to-product reproducibility is monitored. For PRP, ask about platelet concentration, leukocyte content, activation protocol, and how those choices are matched to the clinical indication. For whole-secretome preparations, ask about donor source (autologous versus allogeneic), conditioning method, and the characterisation profile available for the specific batch.

Do not equate manufacturing definition with biological completeness. A purified, well-defined product can be exactly the right answer in some indications and the wrong answer in others; a less precisely defined multi-component preparation can be the right answer where the biology of repair is multi-pathway. The decision is clinical, not just biochemical.

Frame patient conversations carefully. Whole-secretome and single-component categories carry different evidence bases and different regulatory standings across jurisdictions. The most useful framing for patients is to describe what each category is, what it can reasonably be expected to do, and what remains to be confirmed by further clinical work.

7. Limitations and Open Questions

Several open questions remain in this area. The most important is the lack of large, well-controlled, head-to-head trials directly comparing whole-secretome preparations against their purified components in matched indications. Until such trials accumulate, the case for whole-secretome over isolated components rests primarily on biological plausibility and on pre-clinical comparative work, not on top-line clinical superiority data.

Composition standardisation is a related challenge. The same starting material processed under different conditioning protocols can yield preparations with meaningfully different compositions. This is less problematic when each preparation is characterised, batch-controlled, and documented; it is more problematic when broad claims about whole-secretome products in general are made on the basis of one specific manufacturing process. Comparisons across preparations should be made carefully.

Characterisation methods are also still maturing. EV size and concentration measurements depend on instrument and method (Welsh et al., 2024); soluble growth-factor and cytokine measurements

depend on assay format, platform, and the choice of multiplex panel. Reported ranges should always be read with the method in mind.

Finally, the biology itself is incomplete. The relative contribution of EV cargo, soluble factors, and lipid or metabolite components to specific outcomes in specific tissues is not fully resolved. Future work that addresses these contributions in matched human indications will sharpen the design choices that follow.

8. Conclusion: Returning to the Orchestra

The reductionist instinct is powerful, and in many areas of medicine it has been the right one. Identify a target, isolate a molecule, dose it precisely, study what happens. In regenerative biology, however, the underlying problem the cell is solving is not amenable to a single-target answer. Tissue repair is a multi-phase, multi-pathway process driven by a coordinated, multi-component signal.

A whole-secretome preparation is biologically better matched to that task than any single component delivered alone. Recombinant growth factors miss the modulatory context the cell needs to interpret a signal; purified exosomes miss the soluble fraction that accompanies vesicle traffic in vivo; platelet-rich plasma concentrates one cell type's release products and varies meaningfully with preparation method. CFT is designed to preserve the broader cell-derived signal that biology itself uses for repair, drawn from the patient's own cells, characterised batch by batch, and delivered as a complete preparation rather than a reconstruction.

The orchestra metaphor is not, in the end, only a metaphor. A single instrument is music. A coordinated ensemble is something else, and the biology of tissue repair has been written for the ensemble. Whole-secretome preparations are an attempt to deliver, intact, the kind of signal the cell was built to read.

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Disclaimer: Individual results vary. Cell-Free Therapy is not intended to diagnose, treat, cure, or prevent any disease. The information in this paper is provided for educational purposes and does not constitute medical advice. CFT supports the body's normal biological function through autologous, cell-free biological preparations.

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Prepared with the guidance of, and reviewed under, the Scientific & Medical Advisory Committee.

June 2026