Wellbeing International Foundation

The Longevity Case

Cellular Maintenance and Healthy Ageing

Paper 10 in the CFT Advantage Series

WHITE PAPER

Wellbeing International Foundation

Abstract

One important feature of ageing is a progressive decline in the quality, coordination, and responsiveness of cellular signalling. Over decades the body's paracrine machinery, the chorus of growth factors, extracellular vesicles, and immunomodulatory peptides that cells use to speak to one another, becomes less coordinated. Tissues become less responsive, repair takes longer, and the low background of inflammation rises. Cell-Free Therapy (CFT) is designed to support aspects of that declining signalling environment with a concentrated, autologous, conditioned secretome derived from the patient's own cells. This paper sets out the biological basis for age-related paracrine decline, summarises the parabiosis literature on circulating youth factors (Conboy 2005, Loffredo 2013, Villeda 2011, Sinha and Katsimpardi 2014, Castellano 2017, Zhang 2023), positions CFT against the more speculative young-donor-plasma trend, and reviews the demographic and commercial shape of the longevity medicine market. Throughout, CFT is framed as cellular maintenance support, not as a treatment for disease and not as a reversal of ageing. The evidence is presented in full, including its limits.

Important Note on Evidence

The biological rationale for CFT in healthy ageing draws on robust pre-clinical work in paracrine signalling, parabiosis, and conditioned media, although direct evidence for CFT itself in human longevity outcomes remains limited. Randomised controlled trials of CFT for longevity outcomes do not yet exist; available human data are case-series, observational, and anecdotal. The discussion that follows treats those gaps as gaps, not as endorsements. Section 9 lays out the limitations explicitly so that physicians and clients can read the rest of the paper with appropriate calibration.

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1. Introduction: The Biology of Ageing

Ageing is not one process. It is a constellation of overlapping, compounding shifts: cellular regenerative capacity declines, mitochondria lose efficiency, senescent cells accumulate, the epigenome drifts, proteostasis fails, nutrient sensing is deregulated, and the metabolic envelope narrows. The hallmarks-of-ageing framework, codified by López-Otín and colleagues in 2013 and updated in 2023, lists twelve such axes (López-Otín et al. 2013, 2023). Among them, altered intercellular communication, the secreted language by which cells coordinate across tissues, has become a particularly active focus over the past fifteen years, because it appears to be both upstream of several other hallmarks and, at least in animal models, partially modifiable. Paracrine signalling is the strand this paper concentrates on; it is one strand among many.

A typical aged cell still carries most of its biosynthetic machinery. It can, in principle, produce growth factors, cytokines, microRNAs, and extracellular vesicles. What changes with age is the rate, the diversity, and the receptiveness of the surrounding tissue. The cell still speaks; the tissue is harder of hearing; and the signal-to-noise ratio of the background blood and interstitial environment falls. The result is tissues that respond more slowly to injury, recruit fewer repair cells, and slip more readily into a chronic, low-grade inflammatory state.

For most of the twentieth century, gerontologists focused on what was happening inside the cell: telomere shortening, DNA damage, oxidative stress. The parabiosis revolution of the 2000s and 2010s shifted attention to what was happening between cells, in the soluble environment that bathes them. CFT sits in that lineage. By concentrating an autologous, conditioned secretome and

returning it to the patient, CFT is designed to support aspects of the body's own paracrine capacity. It supports normal biological function. The functions in view are concrete: the paracrine signalling that underlies tissue repair, post-exercise recovery, angiogenesis, and the regulation of background inflammation, the processes the rest of this paper describes. It is positioned as an autologous biological preparation rather than a conventional pharmaceutical drug; it is not foreign donor material, and it does not promise to reverse ageing.

2. Age-Related Paracrine Decline

Three changes in the paracrine environment are particularly well characterised. Each is independently linked to phenotypes of ageing, and together they describe a system whose communication bandwidth has narrowed.

2a. Declining Growth Factor Secretion

Fibroblasts, endothelial cells, and tissue-resident progenitors all secrete progressively lower amounts of canonical growth factors with age. Hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1), and basic fibroblast growth factor (bFGF) are among the most studied. The drop reflects shifts in cellular metabolism, reduced translational throughput, transcriptional reprogramming, and accumulated cellular stress. Aged tissues, downstream, show impaired angiogenesis, slower epithelial closure after injury, and reduced post-exercise satellite cell activation in skeletal muscle.

2b. Diminished Extracellular Vesicle Output

Extracellular vesicles (EVs), including exosomes and microvesicles, ferry miRNAs, proteins, and lipids between tissues. They are a critical long-range arm of paracrine communication. With age, both the abundance and the cargo of circulating EVs change. The relative proportion of EVs carrying pro-inflammatory and senescence-associated cargo tends to rise, while EVs carrying regenerative cues tend to fall. These are population-level tendencies rather than uniform rules: EV subpopulations are heterogeneous and still incompletely characterised, and the direction described here is a general trend, not a fixed property of every fraction. The net effect is that the same vehicle now delivers a different message.

2c. Inflammageing and Altered Cytokine Profiles

Claudio Franceschi and colleagues coined the term 'inflammageing' to describe the chronic, low-grade rise in basal pro-inflammatory cytokines (TNF-alpha, IL-6, IL-8, MCP-1) that is a near-universal feature of human ageing. Two engines drive it: first, senescent cells, which secrete a characteristic inflammatory cocktail (the senescence-associated secretory phenotype, or SASP); and second, immune-cell remodelling, where myeloid skewing and thymic involution shift the balance towards

inflammation. Anti-inflammatory factors such as IL-10 and transforming growth factor beta do not always rise to compensate. Inflammageing is now considered a mechanistic driver of multiple age-related conditions, not a passive by-product of getting older (Franceschi et al. 2018).

3. Parabiosis: What Old and Young Blood Tell Us

Parabiosis is the surgical joining of two organisms so that they share a circulatory system. As an experimental tool it dates to the 1860s, but its modern, age-focused incarnation, heterochronic parabiosis, in which a young animal is joined to an old one, has produced some of the most striking evidence in the longevity literature. Rather than asking whether an aged cell is intrinsically broken, parabiosis asks whether it is responsive to a different milieu. The answers, repeatedly, have been yes.

3a. Conboy 2005: Reversing Muscle Ageing

Conboy and colleagues, working in Tom Rando's laboratory at Stanford, published the canonical heterochronic parabiosis paper in Nature in 2005. After two weeks of shared circulation, satellite cells in the aged mice (the resident stem cells of skeletal muscle) recovered a more youthful transcriptional profile and regained robust regenerative capacity. The authors traced part of the effect to restored Notch signalling. Aged liver showed parallel improvements via a separate molecular pathway (cEBP-alpha and cell cycle regulation). The implication was unambiguous: aged progenitor cells are not terminally exhausted; they are starved of permissive signals from their environment.

3b. Loffredo 2013: Cardiac Hypertrophy Regression

Loffredo, Steinhauser and colleagues, working with Richard Lee at Harvard, extended the paradigm to the heart. After four weeks of heterochronic parabiosis, age-related cardiac hypertrophy in old mice regressed substantially, with smaller cardiomyocytes and a more youthful expression profile. Using aptamer-based proteomics, the team identified growth differentiation factor 11 (GDF11) as a circulating factor whose levels drop with age and whose restoration recapitulated much of the parabiotic benefit (Loffredo et al. 2013).

3c. Villeda 2011: The Cognitive Cost of an Old Milieu

Villeda and colleagues in Tony Wyss-Coray's laboratory took the parabiosis model into the central nervous system. They showed that exposing a young mouse to old plasma decreased synaptic plasticity and impaired contextual learning, while exposing an old mouse to young plasma improved hippocampal neurogenesis and cognition. Among the negative factors they identified were CCL11

(eotaxin) and beta-2-microglobulin, both classically immune molecules. The work established that the systemic milieu can act on the brain in both directions, and that the brain is not a privileged compartment immune to circulating signals.

3d. Sinha and Katsimpardi 2014: Muscle, Brain, and the GDF11 Story

In 2014, two companion papers in Science, both linked to Amy Wagers' and Lee Rubin's groups, deepened the picture. Sinha and colleagues showed that restoring systemic GDF11 in old mice, either by parabiosis or by recombinant protein, improved muscle structure, satellite cell genomic integrity, and exercise capacity. Katsimpardi and colleagues, in the same issue, demonstrated vascular remodelling and neurogenesis in the aged mouse brain after exposure to young systemic factors, with a measurable rise in Sox2-positive neural stem cells.

3e. Castellano 2017: Human Cord Plasma and TIMP2

Castellano and colleagues, again in the Wyss-Coray group, took the work across species. They identified TIMP2, a tissue inhibitor of metalloproteinases enriched in human umbilical cord plasma, as a factor that, when administered to aged mice, improved hippocampal-dependent learning, memory, and synaptic plasticity. Crucially, depleting TIMP2 from cord plasma abolished the benefit, and neutralising TIMP2 in young mice impaired their normal cognitive performance. The Castellano paper is one of the cleanest demonstrations that a specific human-derived circulating factor can act on aged neural tissue in a defined, biologically interpretable way.

3f. The GDF11 Controversy and What It Teaches

The GDF11 story has not been simple. Subsequent work questioned the specificity of the original ELISA assays, suggested that some commercial antibodies cross-react with the closely related myostatin (GDF8), and raised the possibility that GDF11 may suppress, not promote, muscle regeneration in some contexts. The single-factor reductionist programme, in other words, has been harder to land than initial reports implied. This is not an indictment of the parabiosis literature; it is a useful cautionary note. Whatever drives the parabiotic effect is unlikely to be any single molecule. It is more likely a network: a coordinated shift in concentrations of dozens of growth factors, EVs, lipids, and immunomodulators acting in concert. This is precisely the property that a whole-secretome preparation has, and that a purified single-factor drug does not.

3g. From Parabiosis to Practice

Parabiosis is a research tool, not a clinical protocol. Mice in those experiments share a circulation continuously for weeks. CFT, by contrast, is delivered as periodic infusions of a concentrated autologous secretome. Whether the same network-level rejuvenation seen in mice translates to humans receiving intermittent, lower-volume infusions remains unproven. What parabiosis

establishes is the principle: aged tissues are responsive to circulating signals. CFT is designed to translate that principle into a clinically practical, autologous format, without donor material, without immune mismatch, and without the safety profile that comes with injecting another person's plasma.

4. The 'Young Blood' Trend and the Autologous Alternative

The parabiosis literature has not stayed in academic journals. It has spawned a category of consumer offerings, most visibly the young-donor-plasma startups, in which paying clients in their forties, fifties, or older receive infusions of plasma drawn from healthy young donors. The best-known of these, Ambrosia, charged eight thousand dollars for a litre of young plasma and twelve thousand for two. In 2019 the United States Food and Drug Administration issued a public warning, stating that there was no proven clinical benefit to such infusions for ageing, dementia, or neurodegenerative conditions, and noting the real risks of allergic, infectious, respiratory, and cardiovascular complications associated with plasma transfusion. Ambrosia paused operations the same week.

The young-donor-plasma model has three problems that CFT, by design, does not. First, the donor is somebody else, with a different MHC and HLA fingerprint, which carries the standard transfusion risks. Second, the product is whole plasma, an undefined and unstandardised mixture, with no characterisation of which factors are doing the work. Third, the supply depends on healthy young donors, which is neither scalable nor ethically neutral as an aspirational consumer product.

CFT inverts each of these. The donor is the patient. The product is the patient's own secretome, characterised in panel form before delivery against defined release criteria, with the full quality-control and batch-release detail (the assays, the release specification, and how batch consistency is handled) set out in Paper 02, From Blood Draw to Biology. And the supply scales with the client base, because each client is the source of their own preparation. Where young-donor plasma is a borrowed youth that the body must immunologically negotiate, CFT is the body's own biological vocabulary, concentrated and returned. The scientific proposition is cleaner: autologous, more defined, and more reproducible than donor-plasma approaches.

5. Environmental Conditioning and More Regenerative Secretory Profiles

One of the more useful findings to come out of the regenerative cell biology of the last decade is that aged cells are not statically aged. When mesenchymal stromal cells, fibroblasts, or bone marrow stromal cells from older donors are placed under carefully controlled environmental

conditions, their secretory profile shifts. Reduced oxygen tension, three-dimensional culture environments, and other defined conditions can push secreted factors back towards a more pro-regenerative, less pro-inflammatory composition. The conditioned medium produced by those cells, the fluid in which they have been kept, becomes enriched in the kinds of factors that aged tissues are missing.

This is the operational principle of CFT. Autologous cells obtained from a blood draw are exposed to controlled environmental conditions that influence their secretory output, and the resulting cell-free secretome, growth factors, cytokines, extracellular vesicles, and other bioactive molecules, is collected, characterised, and returned to the patient. The preparation is not presented as a drug. It does not rely on donor material. It supplements the body's own communication system using the body's own outputs. The in vivo durability of any single dose, and the extent to which in vitro profile shifts translate to in vivo benefit in humans, remain open questions, treated honestly in Section 9.

6. Cell Banking: Preserving a Younger Starting Point

The case for cell banking set out here is a hypothesis-driven concept, not an evidence-backed conclusion. No study has yet shown that cells or secretomes banked decades earlier produce superior clinical outcomes, and the rationale below should be read in that light. If aged cells in culture can be coaxed back towards a younger profile, then cells that were already young when banked, and that have been cryopreserved without the wear of subsequent decades of in vivo stress, may retain a more favourable starting point. The biological time-capsule logic of cell banking flows from this. A draw taken at thirty-five and banked for future use may provide source material with a more favourable biological starting point than cells collected decades later, provided viability, phenotype, secretory profile, and release characteristics are preserved and validated after storage.

This approach is the subject of a separate paper in this series (Paper 08, Bank Once, Treat Many). The two papers are complementary: this one frames the longevity case for paracrine supplementation; that one details the scientific and operational rationale for prospective banking. For the purposes of the longevity argument, the relevant point is that the starting biology of the source material matters, and a single early-life draw enables a multi-decade programme of supplementation.

7. The Longevity Medicine Market

The longevity medicine category sits inside a clear public-health trajectory. The World Health Organization estimates that the global population aged sixty and over will reach 2.1 billion by 2050, approximately double the 2020 figure, with the proportion of the world population over sixty rising

from 12 per cent to 22 per cent over that period (World Health Organization). The number of people aged eighty and older is expected to triple between 2020 and 2050. Independent industry research consistently puts the global longevity market in the tens of billions of US dollars and growing in the high single digits, but the demographic substrate, not the market estimate, is the durable point: a rapidly enlarging cohort of older adults who are increasingly oriented towards healthspan rather than lifespan alone.

WIF's target client profile, an educated, health-conscious individual in their forties, fifties, or older who is investing actively in their own physiology, sits inside that demographic. Crucially, CFT is positioned as cellular maintenance support, not as a longevity miracle. The commercial case is not the scientific case, but it explains why disciplined communication matters: the category has a long history of overpromising, and the offers that survive will be the ones that underclaim and overdeliver.

8. Implications for Physicians and Clients

For the physician, the argument is straightforward. The biological case for paracrine supplementation in ageing is strong, the parabiosis literature is robust, and the autologous route avoids the immunological and ethical pitfalls of donor-plasma alternatives. Where the literature is thin, in this case the human RCT data on CFT itself for longevity endpoints, the appropriate response is to communicate that thinness honestly to clients and to position CFT inside a holistic programme of exercise, sleep, nutrition, and stress management.

For the client, the message is simpler still. CFT is not a treatment for ageing. There is no accepted clinical treatment that reverses human ageing as a whole. CFT is a way of supporting the biological maintenance systems that the body already runs, using the client's own cellular signals, concentrated and returned by the client's own physician. The reasonable expectation is incremental support of recovery, function, and resilience within a physician-led programme. In WIF's current model, this is delivered on a periodic cadence of infusions spaced across the year, against a backdrop of the lifestyle fundamentals (exercise, sleep, nutrition, stress management) that everyone already knows but that few sustain. Optimal frequency for longevity-oriented use remains an area for further evidence generation.

9. Current Evidence and Limitations

This assessment has three parts. First, what the evidence supports. Animal parabiosis data are well-replicated and span muscle, heart, brain, and vasculature. In vitro and animal studies of conditioned media show anti-inflammatory, pro-angiogenic, and pro-mitotic effects consistent with the paracrine model. Case reports and observational series of CFT recipients describe subjective improvements in energy, recovery, and general wellbeing. These reports are uncontrolled, with no

comparator group or systematic follow-up, and are noted here as observations rather than as evidence of efficacy.

Second, what the evidence does not yet support. There are no published randomised controlled trials of CFT for longevity outcomes. Most human data on CFT specifically remain observational, with the well-known confounders of placebo response, regression to the mean, and concurrent lifestyle improvement. Translation from highly controlled mouse studies to genetically and behaviourally diverse human populations is non-trivial in any biology, and longevity biology is no exception.

Third, the open questions. The full identity of the network of circulating youth factors is not characterised. The durability of secretome supplementation between infusions is not yet quantified in humans. The long-term safety of cells banked for multiple decades, while biologically reassuring, lacks the multi-decade follow-up that ultimate confidence will require. None of these are reasons not to act; all of them are reasons to act with appropriate framing. It bears repeating that paracrine decline is one hallmark of ageing among many; CFT is directed at that signalling strand specifically, and is not presented as acting on genomic, epigenetic, mitochondrial, or other independent drivers of ageing.

WIF's position on this is unambiguous. CFT supports normal biological function. It is not intended to diagnose, treat, cure, or prevent any disease, including the diseases of ageing. Communication with clients must reflect that. Long-term credibility with physicians, clients, and regulators is a function of consistent under-claiming.

10. Conclusion

Ageing is, in significant part, a story about declining cellular communication. The body's cells continue to produce the molecules that tissues need, but in smaller quantities, with shifted compositions, and against a noisier inflammatory background. Parabiosis research has established, across multiple organ systems, that aged tissues remain responsive to a more favourable milieu. The challenge has always been how to deliver that milieu safely, ethically, and at scale.

Cell-Free Therapy is one such approach. By concentrating an autologous, conditioned secretome and returning it to the patient, CFT is designed to support one of the systems that age affects: the paracrine signalling that coordinates tissue maintenance. It avoids the donor mismatch, regulatory ambiguity, and ethical fragility of young-donor plasma. It is delivered through the patient's own physician, on a periodic cadence, inside a holistic programme of healthy ageing.

The longevity medicine market is large, growing, and increasingly discerning. Offers that match the biology and respect the limits of the evidence will earn the long position. CFT, framed as cellular maintenance support, is consistent with that discipline. Future priorities for WIF and its physician partners are clear: rigorous clinical evidence, mechanistic characterisation of the secretome, and

continued underclaiming on the marketing side. The biological rationale is substantial; the discipline of communication around it is what will make the category durable.

11. References

1. Conboy, I. M., Conboy, M. J., Wagers, A. J., Girma, E. R., Weissman, I. L., & Rando, T. A. (2005). Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature, 433(7028), 760–764. [Link]

2. Villeda, S. A., Luo, J., Mosher, K. I., Zou, B., Britschgi, M., Bieri, G., et al. (2011). The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature, 477(7362), 90–94. [Link]

3. Loffredo, F. S., Steinhauser, M. L., Jay, S. M., Gannon, J., Pancoast, J. R., Yalamanchi, P., et al. (2013). Growth differentiation factor 11 is a circulating factor that reverses age-related cardiac hypertrophy. Cell, 153(4), 828–839. [Link]

4. Sinha, M., Jang, Y. C., Oh, J., Khong, D., Wu, E. Y., Manohar, R., et al. (2014). Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. Science, 344(6184), 649–652. [Link]

5. Katsimpardi, L., Litterman, N. K., Schein, P. A., Miller, C. M., Loffredo, F. S., Wojtkiewicz, G. R., et al. (2014). Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. Science, 344(6184), 630–634. [Link]

6. Castellano, J. M., Mosher, K. I., Abbey, R. J., McBride, A. A., James, M. L., Berdnik, D., et al. (2017). Human umbilical cord plasma proteins revitalize hippocampal function in aged mice. Nature, 544(7651), 488–492. [Link]

7. Franceschi, C., Garagnani, P., Parini, P., Giuliani, C., & Santoro, A. (2018). Inflammageing: a new immune-metabolic viewpoint for age-related diseases. Nature Reviews Endocrinology, 14(10), 576–590. [Link]

8. United States Food and Drug Administration. (2019). Important information about young donor plasma infusions for profit. FDA Statement, 19 February 2019. [Link]

9. Baker, D. J., & van Deursen, J. M. (2020). Senescent cells: since Hayflick. Seminars in Cell & Developmental Biology, 100, 8–16. [Link]

10. Tabula Muris Consortium. (2020). A single-cell transcriptomic atlas characterizes ageing tissues in the mouse. Nature, 583(7817), 590–595. [Link]

11. López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2023). Hallmarks of aging: An expanding universe. Cell, 186(2), 243–278. [Link]

12. Zhang, B., Lee, D. E., Trapp, A., Tyshkovskiy, A., Lu, A. T., Bareja, A., et al. (2023). Multi-omic rejuvenation and lifespan extension on exposure to youthful circulation. Nature Aging, 3(8), 948–964. [Link]

13. Industry research firms covering the longevity medicine market in 2024 and 2025 include Mordor Intelligence, Market Research Future, and Emergen Research. Their estimates are commercial in nature and are cited only for directional sizing; the public-health and demographic framing in this paper rests on World Health Organization and United Nations data.

14. World Health Organization. (2025). Ageing and health. Fact sheet, 1 October 2025. [Link]

15. United Nations, Department of Economic and Social Affairs, Population Division. (2022). World Population Prospects 2022. [Link]

Disclaimer: Individual results vary. Cell-Free Therapy is not intended to diagnose, treat, cure, or prevent any disease, including age-related conditions. 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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