Review

Mitochondria-targeted therapy in anti-aging medicine: A review

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Abstract

Background: Mitochondrial dysfunction associated with aging is a major contributor to cellular senescence and systemic decline in metabolism. The core concept behind mitochondria-targeted anti-aging therapy is to restore cellular health by replacing damaged mitochondria with healthy, fully functional ones. However, directly transplanting isolated mitochondria is challenging as they degrade rapidly outside the protective environment of a cell. Large extracellular vesicles (microvesicles [MVs]) may provide a protected, cell-like microenvironment that helps preserve mitochondrial integrity during extracellular transport. According to published data, such MVs can facilitate intercellular transfer of mitochondria and biomolecules involved in regulating mitochondrial functional activity. Following internalization, the transferred mitochondria integrate into the metabolic pathways of the recipient cell. They produce adenosine triphosphate, help rebalance mitochondrial dynamics, stimulate the removal of defective mitochondria from the cell (mitophagy), and generate new, functionally competent mitochondria (mitogenesis). **Objective**: The review evaluates the potential of MV-mediated mitochondrial transfer as a viable and immunologically adaptable strategy for restoring mitochondrial function and inhibiting cellular aging. Mitochondria-containing MVs (M-MVs), isolated from cells of young donors or tumor cell lines, can serve as transport vehicles for the intercellular transfer of mitochondria. The functional activity of transferred mitochondria can be prolonged through both non-pharmacological (intermittent hypoxia, physical exercise, caloric restriction, antioxidant nutrition) and pharmacological interventions (rapamycin, metformin, resveratrol, and others), which support mitophagy and mitogenesis. **Conclusion**: MV-mediated mitochondrial transfer can establish a physiologically grounded platform for conducting complex therapy aimed at preventing and treating diseases associated with cellular aging.

Keyword: Cellular senescence, Extracellular microvesicle, Mitochondrial transplantation, Mitochondrial dynamics, Mitophagy, Mitogenesis

1. Introduction

Adenosine triphosphate (ATP) generation by oxidative phosphorylation (OXPHOS) involves electron transfer through complexes I–IV of the mitochondrial electron transport chain, followed by ATP synthesis by complex V. Electron transport establishes an electrochemical gradient that ATP synthase uses to produce ATP, carbon dioxide, and water.[1] OXPHOS is remarkably efficient, generating approximately 36 ATP molecules per glucose molecule, compared with only two ATP molecules from glycolysis.[2] However, OXPHOS inevitably produces reactive oxygen species (ROS) as byproducts, primarily via complexes I and III of the electron transport chain. These ROS are normally neutralized by endogenous antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase, glutaredoxins, thioredoxins, and catalases.[3]

Anaerobic unicellular organisms do not use OXPHOS for ATP synthesis. They meet their energy needs through glycolysis and therefore do not generate significant amounts of ROS. The evolutionary acquisition of mitochondria—originally free-living α-proteobacteria—proved to be a pivotal event that enabled the evolutionary transition from unicellular to multicellular organisms. However, this transition also established a mechanism for oxidative cellular damage and

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programmed cell death.[4] Overall, the shift from cellular immortality to cellular death can be viewed as a transition from a glycolytic, low-energy mode of existence to a high-energy, mitochondria-driven development that gave rise to complex life forms.

Cellular senescence determines the aging of a multicellular organism. Senescent cells (SnCs) gradually accumulate in tissues, and their accumulation contributes to the development of chronic diseases. Therefore, the development of strategies aimed at countering cellular senescence remains a central focus of numerous biomedical studies.

It is widely recognized that mitochondrial dysfunction is a key trigger of cellular senescence.[5] Impaired mitochondrial function leads to metabolic imbalance, resulting in decreased ATP production and increased generation of ROS. Elevated ROS levels cause cumulative oxidative damage to nucleic acids, lipids, and proteins.[6]

Mitochondrial DNA (mtDNA) lacks protective histones and has a minimal repair capacity. Consequently, mtDNA is the first to accumulate oxidative damage, which disrupts its replication and transcription.[7] ROS also cause detrimental effects on mitochondrial dynamics and mitogenesis.[8] This self-reinforcing cycle that accelerates mitochondrial aging is referred to as the "mitochondrial vicious cycle."[9]

With age, the balance between ROS production and antioxidant defense shifts toward oxidative overload, causing the proportion of defective mitochondria to gradually and irreversibly increase.[10] SnCs attempt to compensate for mitochondrial inefficiency by enhancing glycolysis, but this metabolic shift is insufficient to meet their energy demands.[6] The resulting energy deficit may contribute to the development of the senescence-associated secretory phenotype (SASP), promoting inflammation and impaired tissue function.[11]

Given that age-related mitochondrial damage is largely irreversible, replacing defective mitochondria with new ones represents the most rational therapeutic strategy. This article discusses the microvesicle (MV)-mediated transfer of functional mitochondria into SnCs as a method for bioenergetic rejuvenation and lifespan extension of cells. It also examines complementary non-pharmacological and pharmacological approaches to sustaining mitochondrial function and decelerating organismal aging.

2. Microvesicle transfer of mitochondria in anti-aging therapy

Mitochondria play a central role in maintaining cellular homeostasis by regulating energy production, redox balance, apoptosis, and immune modulation. Intercellular mitochondrial transfer is an adaptive process that mitigates the detrimental effects of cellular damage and energy deficits. The exchange of mitochondria between neighboring cells can occur via tunneling nanotubes (TNTs), structures formed from F-actin.[12] TNTs establish transient dynamic networks that facilitate the intercellular exchange of bioenergetic and signaling components. This exchange enables cells to respond more effectively to stress induced by infection or injury.[13] Notably, it has been demonstrated that the transfer of mitochondria from mesenchymal stem cells to damaged cardiomyocytes via TNTs improves cardiac function and enhances the bioenergetic and angiogenic potential of endothelial cells.[14,15]

Once released into the extracellular environment, mitochondria rapidly lose viability—typically within minutes—which is why the distant transfer of "naked" mitochondria does not play a significant role in intercellular bioenergetic exchange. However, nature has devised a transport mechanism to move mitochondria through the extracellular space by encapsulating them within MVs.[15] Extracellular vesicles are phospholipid bilayer-enclosed particles. They are secreted by virtually all cell types and are broadly classified into two main subtypes based on their biogenesis: exosomes and MVs. Exosomes are formed through the inward budding of endosomal membranes, whereas MVs are generated via the outward budding of the plasma membrane. Exosomes range in size from 50–150 nm, while MVs vary from 100 to 1,000 nm.

Cellular activation and apoptosis are potent triggers for the formation and secretion of these vesicles, whose primary functions include the transport of biomolecules and their protection from enzymatic degradation and other extracellular stresses.[16]

MVs, unlike exosomes, are capable of transporting mitochondria.[17] In turn, mitochondria help maintain the structural integrity of MVs and preserve their negative surface charge.[18] Compared to liposomes, MVs exhibit a longer circulatory half-life and more favorable biodistribution.[19] The migration pattern of MVs is determined by their surface receptor profile, while the reduced pH characteristic of inflammatory sites facilitates their fusion with recipient cells.[20,21]

MV-mediated mitochondrial transplantation is an innovative therapeutic strategy based on the premise that healthy mitochondria isolated from donor cells can replace defective mitochondria in recipient cells, thereby enhancing the energetic capacity and stress resilience of these cells.[22] This strategy represents a pathogenesis-targeted approach for treating both primary mitochondrial disorders and conditions associated with age-related mitochondrial insufficiency.

Through continuous fusion and fission, mitochondria

dynamically adjust their morphology, mass, and intracellular distribution. This phenomenon is known as mitochondrial dynamics. This mechanism enables cells to either repair or remove dysfunctional mitochondria, thereby maintaining ATP production.[23] Fused and fragmented mitochondria can differ in transport chain activity; fused mitochondria are predominantly engaged in active ATP synthesis, whereas fragmented ones primarily generate ROS.[24] ATP produced by transplanted mitochondria can support all energy-dependent cellular processes, enhance mitochondrial dynamics, and stimulate both mitophagy and mitogenesis. As schematically illustrated in Figure 1, donor mitochondria can fuse with the endogenous mitochondrial network, thereby boosting ATP synthesis and reducing ROS production.[24] Theoretically, this effect should initiate a cascade of events leading to the long-term restoration of the bioenergetic potential of recipient cells.

The regenerative capacity of mitochondria-containing MVs (M-MVs) has been previously demonstrated in various experimental models. After a stroke, astrocytes deliver mitochondria to neurons via CD38-dependent mechanisms, thereby protecting neurons from hypoxic damage. Donor mitochondria enhanced the bioenergetics of recipient cells by modulating mitochondrial dynamics and stimulating mitophagy and mitogenesis.[25] Intramyocardial injection of M-MVs derived from pluripotent stem cells improved post-infarction cardiac function.[26] M-MVs obtained from mesenchymal stem cells increased ATP production in alveolar type II epithelial cells and improved the survival of mice after acute lung injury induced by lipopolysaccharide.[27] Additionally, M-MVs promoted the regeneration of damaged nervous tissue[17] and protected myocytes from oxidative damage.[28] Recent studies have shown that platelet-derived MVs can transport functional mitochondria into the vascular endothelium and accelerate wound healing.[29] In early-phase clinical trials, mitochondrial transplantation improved myocardial function after ischemia and demonstrated its safety and technical feasibility.[30,31] Thus, MV-mediated mitochondrial transplantation represents a highly promising medical technology aimed at restoring cellular bioenergetics, reducing oxidative stress, and enhancing the organism's resilience to stress factors.

Allogeneic mitochondrial transplantation has demonstrated its therapeutic efficacy in both animals and humans. Unlike allogeneic immune cells, allogeneic M-MVs do not exhibit alloreactivity.[32] Given the broad tissue specificity of mitochondria, M-MVs derived from the blood of young healthy donors could potentially be used in the treatment of various mitochondrial and age-related diseases.

Mitochondria-containing MVs derived from tumors represent a novel and intriguing subject of research in the field of anti-aging therapy. Proliferating tumor cells provide the cytoplasmic space and building materials necessary for active mitogenesis. It has been shown that cancer cells deprived of mtDNA completely lose their proliferative and tumorigenic potential. This indicates that tumor cells are compelled to maintain intracellular conditions favorable for mitochondrial renewal and the preservation of their functional activity.[33] In experimental models of Parkinson's disease and liver injury, donor mitochondria isolated from hepatocellular carcinoma HepG2 cells reduced oxidative stress, increased ATP production in recipient cells, and improved tissue and locomotor parameters in the organism.[34,35]

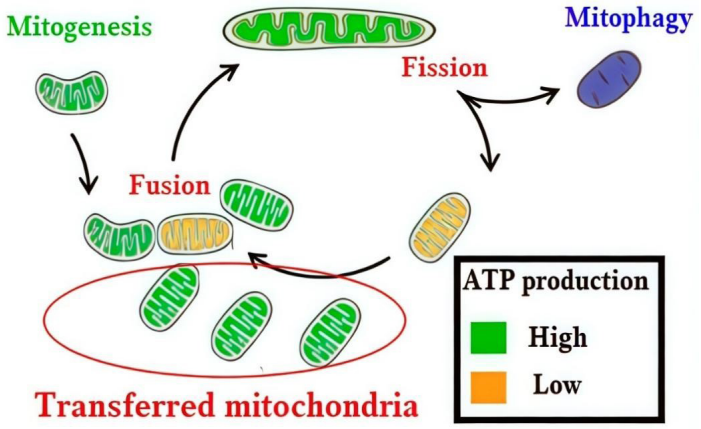

Figure 1. The role of donor mitochondria in restoring cellular bioenergetics. Transplanted mitochondria produce adenosine triphosphate (ATP) and stimulate ATP-dependent processes in the recipient cell, including mitophagy and mitogenesis. A portion of donor mitochondria fuses with the endogenous mitochondrial network, thereby enhancing ATP production and reducing ROS generation. Created with Above Illustrator 2025. Partially adapted from Zhang *et al*.[32]

Tumor and normal tissues utilize overlapping molecular pathways that regulate their regeneration.[36] In addition to mitochondria, tumor-derived MVs contain various signaling molecules (microRNAs, mRNAs, and growth factors) capable of stimulating tissue and organ regeneration. In a mouse model of kidney injury, tumor-derived MVs, regardless of their origin (L929 sarcoma, LLC carcinoma, B16 melanoma), exerted a pronounced nephroprotective effect.[37,38] Notably, tumor-derived MVs improved kidney function in models of both chronic and acute kidney injury,[37] providing the energetic support necessary for rapid functional recovery of the organ. It should be noted, however, that the direct contribution of microvesicular mitochondria to the regenerative processes in the aforementioned experiments was not investigated.

The use of tumor-derived MVs raises justifiable concerns due to their oncogenic risk. It has been previously shown that such MVs can promote tumor growth.[39] Importantly, however, these MVs do not contain mutagenic material. They appear to be capable of accelerating the growth of existing cancer cells

rather than inducing *de novo* carcinogenesis. In a previous study, a six-month observation of mice that received tumor-derived MVs revealed no visible signs of tumor growth.[38] Nevertheless, the safety of repeated administration of tumor-derived MVs requires further meticulous investigation.

Another potential source of transplantable M-MVs could be the organs of young healthy animals. It should be borne in mind that xenogeneic mitochondria are highly immunogenic, and that normal human antibodies, including those targeting galactosyl epitopes, can rapidly eliminate xenogeneic M-MVs via phagocytic mechanisms.[40] To overcome this immunological barrier, xenogeneic mitochondria must undergo "humanization," aimed at replacing immunogenic xenogeneic proteins with non-immunogenic human counterparts. This "humanization" process is thought to occur through the progressive exchange and modification of mitochondrial membrane proteins over several cell culture passages, enhancing compatibility with human cellular machinery. Only 13 mitochondrial proteins are encoded by mtDNA, while over 1,100 are encoded by nuclear genes.[12] As mitochondria are passaged in human cells, along with the replacement of xenogeneic proteins with human analogs, remodeling of the outer mitochondrial membrane lipids may occur, adapting mitochondrial metabolism to the human environment.[41,42] After "humanization," mitochondria can be encapsulated in MVs and transplanted into humans. Such an approach opens a conceptually elegant path toward scalable production of M-MVs and their broad medical application. Undoubtedly, this approach remains hypothetical at present and requires thorough experimental investigation.

3. Non-pharmacological and pharmacological prolongation of mitochondrial functional activity

Mitochondrial transfer into recipient cells is a short-term intervention. Nevertheless, the transferred organelles can trigger a cascade of events that improve cellular bioenergetics.[43] It is evident that measures supporting the enhanced energy metabolism are necessary to achieve a long-term effect. In this regard, preference should be given to natural interventions to which the organism is evolutionarily adapted and that do not pose a risk of serious side effects.

Hypoxia is an inducer of glycolytic activity in eukaryotic cells. Under hypoxic conditions, hypoxia-inducible factor 1-alpha triggers an energy shift from OXPHOS to glycolysis. This transition stimulates B-cell lymphoma 2 protein family/adenovirus E1B 19 kDa-interacting protein 3-mediated mitophagy, which selectively removes defective mitochondria, thereby reducing intracellular production of ROS. Hypoxia also enhances the production of erythropoietin and other pro-angiogenic factors.[44] During reoxygenation, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) is activated, which, along with nuclear respiratory factor 1, stimulates mitochondrial biogenesis. The replenished population of functional mitochondria enables cells to sustain ATP production even under conditions of oxygen deprivation.[44,45] As illustrated in Figure 2, exercise-induced hypoxia is accompanied by transient hyperoxia, which enhances the activity of antioxidant enzymes, thereby strengthening the body's antioxidant defense.[45,46]

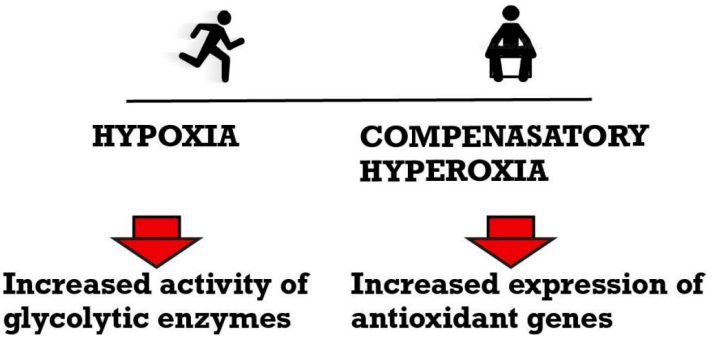

Figure 2. Hypoxia accompanied by transient hyperoxia enhances cellular protection against oxidative stress. Adapted from Seledtsov *et al*.[45]

It is important to note that hypoxia/hyperoxia-induced expression of antioxidant genes persists in cells after a hypoxic episode, providing long-lasting adaptive antioxidant effects.[47] Currently, hypoxia has become a widely accepted method for athletic training and a non-pharmacological strategy for disease prevention and treatment.[46]

The effects of hypoxia and physical exercise overlap with those of calorie-restricted nutrition. Both exercise and fasting activate AMP-activated serine/threonine protein kinase and PGC-1α, with B-cell lymphoma 2 protein family serving as a key regulator of these processes.[48]

Age-related increase in ROS production in the body underscores the importance of antioxidant nutrition and vitamin supplementation as part of a comprehensive anti-aging strategy. In this regard, fat-soluble vitamins (D, A, E) offer an advantage over water-soluble vitamins, as they can be stored in adipose tissue and maintain their physiological levels in the blood for extended periods. It has been shown that vitamin E (α-tocopherol) directly protects mitochondrial membranes from lipid peroxidation, while vitamin D regulates mitochondrial biogenesis through the vitamin D receptor–PGC-1α axis.[49,50]

It has been established that SnCs activate anti-apoptotic pathways and thereby ensure their survival despite extensive DNA and intracellular organelle damage. SnCs develop a SASP, characterized by increased production of pro-inflammatory cytokines, chemokines, proteases, and bioactive lipids. The observed changes in SnC metabolism

are considered promising targets for drug therapy.[51,52]

Drugs used in anti-aging therapy are divided into two categories: senolytics, which induce senolysis, selectively eliminating SnCs, and senomorphics, which induce senostasis, suppressing the pathological expression of SASP components. Senolytics (e.g., dasatinib, fisetin, navitoclax) induce apoptosis in SnCs by acting on key enzymes, including p53, p21, B-cell lymphoma 2 protein family proteins, protein kinase B, phosphoinositide 3-kinase, and forkhead box O4, that counteract the development of apoptosis.[51] In contrast, senomorphics (e.g., metformin, rapamycin) prolong the lifespan of SnCs, normalize their metabolism, and attenuate SASP production by inhibiting nuclear factor kappa B, mechanistic target of rapamycin, interleukin1α, p38 mitogen-activated protein kinase, and related signaling pathways.[51]

The therapeutic application of senolytics is significantly limited by the variability in the sensitivity of SnCs to their action, which stems from the heterogeneity in the expression of anti-apoptotic molecules among these cells. Furthermore, senolytics are likely to accelerate the growth, differentiation, and, consequently, the aging of the young cells that replace the eliminated SnCs. It also cannot be ruled out that while senolytics may not affect young cells under physiological conditions, they could reduce their adaptive potential under stressful or pathological conditions.[52] Although experimental studies demonstrated the ability of senolytics to extend the lifespan of short-lived organisms, translating this effect to humans remains highly contentious. Senolytics may be reasonably employed for short-term interventions—for instance, to interrupt a chronic pathological process—whereas their long-term use appears questionable.

Unlike senolytics, senomorphics directly or indirectly support mitochondrial functional activity. Among the most studied senomorphics are rapamycin and metformin. Rapamycin (sirolimus) is an antifungal macrolide originally isolated from *Streptomyces hygroscopicus*. Its anti-aging effects are primarily associated with inhibition of mechanistic target of rapamycin, suppression of nuclear factor kappa B, reduced phosphorylation of S6K and 4E-BP, and activation of nuclear factor erythroid 2-related factor 2.[51,53,54]

Metformin is a synthetic biguanide and is widely used as a medication for treating type 2 diabetes.[55] The mechanism of action of metformin involves activation of AMP-activated serine/threonine protein kinase, inhibition of mitochondrial complex I, and increased expression of PGC-1α.[56,57] A similar mechanism of action on cellular metabolism is exhibited by 5-aminoimidazole-4-carboxamide ribonucleoside[58] and berberine, a natural alkaloid found in plants such as goldenseal and barberry.[59]

Nicotinamide adenine dinucleotide (NAD^+) precursors (nicotinamide riboside and nicotinamide mononucleotide) are able to maintain NAD^+ levels in cells and enhance DNA repair activity.[60] It has been shown that sustained restoration of NAD^+ levels enhances sirtuin family of enzymes-dependent mitophagy, stabilizes mitochondrial dynamics, and reduces the severity of chronic inflammation, both in preclinical models and early human studies.[61,62]

Senomorphic compounds such as resveratrol, quercetin, and urolithin A stimulate mitophagy via the PTEN-induced kinase 1/Parkin pathway, which is involved in the detection and removal of damaged mitochondria.[63-65]

Theoretically, senomorphics may also include 3-(2,2,2-trimethylhydrazinium) propionate (meldonium, mildronate) and trimetazidine dihydrochloride (Preductal)—drugs widely used in treating cardiovascular diseases. These medications, through different mechanisms, inhibit the entry of fatty acids into mitochondria, enhance glycolysis, and reduce mitochondrial production of ROS.[66,67]

Pharmacological anti-aging therapy should likely be based on long-term intermittent use of medications with periodic rotation during treatment. Such therapy should not result in drug dependence or resistance. Combining drugs with different mechanisms of action should be aimed at achieving a combined or synergistic therapeutic effect and reducing the overall drug burden. As an example, a possible comprehensive drug therapy regimen aimed at maintaining mitochondrial health is presented in Table 1.

Table 1. Comprehensive drug-based prevention and treatment of age-related disorders

Days	Medication during the day
0, 1	Metformin 1,000 mg × 1; urolithin A 3,000 mg × 2
2–4	Metformin 500 mg × 1; urolithin A 3,000 mg × 1
5, 6	Berberine 500 mg × 4; spermidine 20 mg × 2
7–9	Berberine 500 mg × 2; spermidine 20 mg × 1
10, 11	Metformin 1,000 mg × 1; resveratrol 1,200 mg × 2
12–14	Metformin 500 mg × 1; resveratrol 1,200 mg × 1
15, 16	Berberine 500 mg × 4; quercetin 500 mg × 2
17–19	Berberine 500 mg × 2; quercetin 500 mg × 1
20, 21	Nicotinamide riboside 500 mg × 2; trimetazidine 80 mg × 2
22–24	Nicotinamide riboside 500 mg × 1; trimetazidine 80 mg × 1
25, 26	Nicotinamide riboside 500 mg × 1; meldonium 250 mg × 4
27–29	Nicotinamide riboside 500 mg × 1; meldonium 250 mg × 2

Note: Day 0 represents the start of the treatment course.

For meaningful results, such therapy courses should be

conducted regularly over an extended period. Temporary breaks between courses can vary widely from several days to several months.

The presented approach, like any other strategy for the prevention and treatment of age-related disorders, cannot yet be considered a clinical recommendation, as it is primarily based on experimental data that require clinical validation.

4. Conclusion

In addition to their fundamental role in energy metabolism, mitochondria are involved in numerous cellular processes that ensure cell viability and shape their adaptive potential. Mitochondrial dysfunction underlies a broad spectrum of age-related pathologies. Therefore, there is an acute need to develop new strategies aimed at improving mitochondrial health and sustaining their functional activity. In this context, extracellular MVs have emerged as a promising mechanism, as they can contain functional mitochondria and facilitate their transfer between cells. The presence of mitochondria in MVs has been demonstrated using flow cytometry, quantitative polymerase chain reaction, Western blot, and transmission electron microscopy.[68] Compared to pharmacological and genetic anti-aging interventions, MV-based approaches offer several distinct advantages, as they: (i) enable direct mitochondrial replacement and can rapidly restore energetic function in recipient cells; (ii) can provide sustained bioenergetic improvement by influencing mitochondrial dynamics, as well as mitophagy and mitogenesis; (iii) can be effectively combined with nonpharmacological and pharmacological interventions. Overall, comprehensive mitochondrial therapy, which includes MV-mediated mitochondrial transplantation, has the potential to bring about a paradigm shift in anti-aging medicine—from symptomatic treatment to bioenergetic restoration of cells. Undoubtedly, translating such therapy into medical practice will require thorough preclinical validation and subsequent controlled clinical trials to validate its safety and therapeutic efficacy.

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The author declares no conflict of interest.

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