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REVIEW ARTICLE

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Allogeneic mesenchymal stem cell therapy: A regenerative medicine approach to geroscience

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Abstract

Extraordinary advances in medicine and public health have contributed to increasing life expectancy worldwide. However, health span—"healthy aging"—has paradoxically lagged to parallel this increase. Consequently, aging-associated illnesses, such as Alzheimer's disease and aging frailty, are having a growing impact on patients, their families, and entire health-care systems. Typically, such disorders have been treated as isolated disease entities. However, the inextricable links between aging-associated disorders and the aging process itself have become increasingly recognized, leading to formation of the field of geroscience. The geroscience concept is that treating the aging process itself should lead to treatment and prevention of aging-related disorders. However, the aging process is complex, dictated by highly interrelated pleiotropic processes. As such, therapeutics with pleiotropic mechanisms of action (either alone, or as part of combinatorial strategies) will be required for preventing and treating both aging and related disorders. Mesenchymal stem cells (MSCs) have multiple mechanisms of action that make these highly promising geroscience therapeutic candidates. These cells have a high safety profile for clinical use, are amenable to allogeneic use since tissue-type matching is not required, and can have sustained activity after transplantation. Herein, we review preclinical and clinical data supporting the utility of allogeneic MSCs as a geroscience therapeutic candidate.

KEYWORDS
geroscience, mesenchymal stem cell, regenerative medicine

1 | INTRODUCTION

The interdisciplinary field of geroscience is aimed at understanding the relationship between the biology of aging and aging-related disorders. The central tenant, the "geroscience hypothesis," is both simple and profound: targeting aging will delay the emergence, and diminish the severity, of many chronic diseases because the major underlying risk factor for these diseases is aging.[1]

The aging process is complex, resulting from the integration of numerous physiological processes—or maybe more precisely, pathophysiological underpinnings.[2] Viewed from a pathophysiological framework, aging can be considered a pleiotropic and treatable disease.[3,4] In the context of geroscience, a pleiotropic approach is thus essential to treating aging-related disorders and improving the health span to match the ever-increasing life expectancy. As a potential therapeutic, mesenchymal stem cells (MSCs) represent

important candidates for meeting many of the requisites as a pleiotropic intervention (Table 1).

The geroscience potential of MSCs resides in their intrinsic properties.[5-15] MSCs have powerful anti-inflammatory properties and home to sites of injury and inflammation, and are thus ideal candidates for treating aging-related inflammation (also referred to as "inflammaging"[16]). MSCs: secrete numerous bioactive molecules that stimulate endogenous stem cell recruitment, proliferation, and differentiation; inhibit apoptosis and fibrosis; can, to an extent, differentiate in vivo to contribute to repair and regeneration; have the potential to improve immune function; and promote neovascularization. MSCs can also regulate host stem cell niches through paracrine activity and cell-cell interactions to promote intrinsic repair and regenerative responses.[17-20]

Mesenchymal stem cells possess important immunoprivileged/immunoevasive properties, thereby rendering them safe for allogenic use. This results from MSCs having undetectable levels of major histocompatibility complex (MHC) class II molecules, and low-level MHC class I expression.[19,21] Even xenogeneic grafts of human MSCs into immunocompetent rodent, dog, goat, baboon, and swine do not evoke anti-allograft response.[11] Thus, MSCs have the potential to be an "off-the-shelf" therapy that is immediately available and accessible to broad patient populations.

TABLE 1 Geroscience application of allogeneic MSCs

Pillars of aging[3]	Hallmarks of aging[4]	Potential benefits of MSCs
Inflammation	—	Inhibit pro-inflammatory pathways Stimulate anti-inflammatory pathways
Stem cell and regeneration impairment	Stem cell exhaustion Cellular senescence	Replenish exhausted MSCs Promote intrinsic regenerative and repair responses Reduce cellular senescence
Stress maladaptation	Altered intercellular communication	Potential to renormalize stress response
Epigenetics alterations	Epigenetics alterations	Unknown
Macromolecular damage	Genomic instability Telomere attrition	Reduce DNA damage Reduce oxidative stress
Metabolic dysfunction	Nutrient sensing dysregulation Mitochondrial dysfunction	Mitochondrial exchange Reduce oxidative stress
Proteostasis dysfunction	Proteostasis dysfunction	Potential to stimulate proteostatic responses

Abbreviation: MSCs, mesenchymal stem cells.

Allogeneic MSCs have a demonstrated high clinical safety profile,[19,20,22] and benefits from a single infusion of MSCs can persist for months.[17,18,20,23-25] Furthermore, multiple dosing is well-tolerated, and human MSCs can persist for over a month in immunocompetent hosts, thereby helping to explain their sustained beneficial effects.[17,18,20,22-26] MSCs have also been shown to not undergo malignant transformation after transplantation into patients.[25] A comprehensive meta-analysis of 36 clinical studies entailing 1024 volunteers (either healthy or with a clinical condition) supports the concept that MSC treatment has an exceptionally high safety profile.[20]

Since MSCs can be used as an allogeneic treatment, they can be sourced from young healthy donors. Such sourced MSCs can provide significantly higher potency over similarly prepared autologous MSCs.[14,27-30] This likely is due to the fact that autologous MSCs, being used in the context of treating aging, can be impaired by advanced age and/or patient comorbidity.[31,32] Relative to young and middle-aged adults, MSCs from elderly adults appear to have reduced regenerative potential, as indicated by diminished proliferative capacity, diminished differentiation potential, increased senescence, increased expression of DNA-break repair genes, altered DNA-methylation and gene-expression patterns, impaired migration, altered expression of microRNAs and cell-surface markers, and diminished anti-inflammatory activity.[33-41]

2 | PRECLINICAL EVIDENCE DEMONSTRATING THE POTENTIAL OF ALLOGENEIC MSCS TO IMPROVE HEALTH SPAN AND LIFE EXPECTANCY

Preclinical studies support the efficacy of allogeneic MSCs as a geroscience-directed therapeutic. In one of the earliest studies to examine this, mice aged 18-24 months were transplanted with allogeneic bone marrow stem cells (which contain a mixture of MSCs and other stem cell types).[42] Those mice transplanted with stem cells from young donor mice (1-2 months old) had a 16% increase in average life expectancy, and a substantial decline in age-related bone density deterioration. Such benefits were not imbued using MSCs sourced from old donors (from 20-24 month-old mice). A caveat to this study is that all animals underwent X-irradiation (500 cGy) prior to transplantation of the stem cells, which would appear confounding in terms of relating the results to an understanding of treating the aging process. Nevertheless, the results are encouraging and provide rationale for further study.

In more direct experiments to evaluate the potential of allogeneic MCSs for aging, transplantation of young normal mouse MSCs into premature-aging-model mice (*Bmi-1*-defiicient) were performed using a multi-dosing paradigm.[43] The transplanted MSCs promoted growth in the treated mice, which was not seen with vehicle control, and led to significant improvements in life span (>100% increase over

untreated mice). This was accompanied by migration of the MSCs to multiple organs and differentiation into multiple cell types, and inhibition of cellular senescence normally seen in the *Bmi-1*-defiicient mice. Moreover, bone osteogenesis was improved and bone adipogenesis reduced, with concomitant reduction in osteoporosis. Immune status also improved. Furthermore, oxidative stress and DNA damage in multiple organs were broadly reduced. Cumulatively, these results suggest the pleiotropic potential of allogeneic MSCs to treat aging and aging-associated diseases.

In yet another study, 18-month-old mice were given single or multiple intravenous infusions (four infusions at 2-week intervals) of human MSCs.[44] The treated mice showed significant improvements in locomotion, and behavioral/cognitive performance improved as assessed via passive avoidance and the Morris water maze. Impressively, these improvements approached those of normal young mice (8-weeks old). Furthermore, treated mice showed improved hippocampal cell count.

Reproductive potential of old female mice could also be significantly improved after receiving regular transplants of MSCs derived from young mice.[45] Impressively, offspring survival also improved. It is interesting to note that these results were more profound when MSCs derived from young female mice were used, compared to male donor mice. In another murine study, allogeneic transplant of MSCs reversed aging-associated dysregulation of the gastrointestinal immune system.[15] In these studies, aged mice (>18 months old) that received transplanted MSCs showed improved levels of mucosal secretory IgA and plasma IgG antibody production that restored nearly to levels seen in young mice. These were accompanied by increased Th1- and Th2-type cytokine responses by $CD4^+$ T cells. Also, a Sprague-Dawley rat that was treated every 2 weeks with human MSCs starting at 6 months old was reported to have lived past 44 months old—a 22% increase over the life-expectancy of 36 months.[46]

Together, these and other[47,48] preclinical findings suggest the geroscience potential of allogeneic MSCs to positively improve multiple aspects of aging.

3 | CLINICAL EVALUATION OF ALLOGENEIC MSCS FOR AGING-RELATED INDICATIONS

There are currently over 250 clinical trials for use of allogeneic MSCs reported on https://clinicaltrials.gov (as of August 8, 2019). Given the pleiotropic mechanisms of action of these cells, it is not surprising that the vast majority of these trials are for aging-related conditions (eg, the metabolic syndrome, cardiac indications, osteoarthritis, autoimmune disorders, and type II diabetes). Three of these studies are for aging frailty (accession numbers NCT02065245, NCT02982915, and NCT03169231), which can be considered an extreme form of unsuccessful aging.

Aging frailty is a biologically driven decline in function and reserves across multiple physiologic systems that appears independent of the chronological aging process.[49,50] The biological basis of aging frailty appears multifaceted and includes an aging-related chronic systemic inflammatory state known as "inflammaging."[5,7,8,11-13] This loss of physiological control over inflammation appears resultant from an imbalance between the levels of pro- and anti-inflammatory cytokines, as well as diminished capacity to restore equilibrium once an inflammatory stimulus has subsided. The ultimate result is elevated serum levels of pro-inflammatory cytokines and diminished serum levels of anti-inflammatory cytokines (eg, tumor necrosis factor [TNF]-α and interleukin-10, respectively).

Subjects with aging frailty are exceptionally compromised in their ability to cope with everyday or acute stressors. This leads to increased vulnerability to disease and injury (eg, increased adverse clinical outcomes, such as falls, fractures, infections, hospitalizations, institutionalizations, and mortality).[13,51] As a result of aging frailty, normally small insults (eg, minor infection, minor surgery, tolerance for a new drug) result in dramatic and disproportionately severe adverse consequences, frequently leading to a spiral of decline. From a clinical standpoint, aging frailty is characterized by weakness, weight loss, slowness, and low activity, as well as chronic inflammation as described above. A conservative estimate for the prevalence of aging frailty is 10% of those aged 65 years and older.[52,53] And this prevalence will continue to increase with changing demographics towards a more elderly population. Given the important consequences, leading geriatric researchers, including Linda Fried, John Morley, Kenneth Rockwood, and Jeremy Walston, have recommended that everyone aged 70 years and older should be evaluated for frailty using the simple, validated frailty assessment tools available.[54]

The first-in-human clinical study using allogeneic MSCs as an intervention for aging frailty was recently completed, called the "CRATUS study" ("AllogeneiC Human Mesenchymal Stem Cells [hMSC] in Patients With Aging FRAilTy Via IntravenoUS Delivery"; NCT02065245).[26,55,56] CRATUS was a safety study consisting of two phases in which subjects with aging frailty were intravenously infused with either allogeneic MSCs or placebo. Phase 1 was an open-label dose-escalation study in which each subject was given a single dose of 20 million MSCs, 100 million MSCs, or 200 million MSCs. The treatments were found to be safe and well-tolerated at all dosages (eg, there were no reported adverse events or serious adverse events related to the cells, and no observed immunoreactions against the product as assessed by anti-human leukocyte antigen [anti-HLA] antibody production). Despite the trial only being powered for safety, there were also statistically significant improvements in several key measures of effect. These included decreased inflammatory status, such as a significant decrease in TNF-α; and improved physical functioning, as assessed by the 6-minute walk test and spirometry. These phase 1 measures were then prospectively tested in a small placebo-controlled, randomized, double-blinded phase 2 trial. The cells were again found to be safe and led to similar significant improvements in key effect measures of aging frailty.

Combined, the phase 1/2 results of the CRATUS study can be summarized as follows: (a) allogeneic MSCs were safe and well-tolerated when administered to aging frailty subjects; (b) allogeneic MSC treatment led to statistically significant improvements in key measures of aging frailty, including decreasing inflammation and improving physical performance; and (c) none of the evaluated safety or effect measures showed

worsening. While not significant, there also appeared to be a trending decrease overall in incidents of serious adverse events with MSC treatment relative to placebo. Based on the promising results of CRATUS, a larger phase 2b study is now being conducted (NCT03169231). This trial consists of five treatment arms (25 million, 50 million, 100 million, or 200 million allogeneic MSCs, or placebo), is powered for effect based on the 6-minute walk test, and is currently enrolling. A second related study to evaluate the potential of allogeneic MSCs to improve immune status in subjects with aging frailty is also being conducted (NCT02982915).

4 | CONCLUSION

Worldwide demographics continue to shift towards populations with increased life expectancy. Consequently, the importance of achieving a health span that parallels those changes has become paramount. A geroscience approach offers promise towards achieving these goals, by treating the aging process itself. Given the complex and multifactorial nature of the biology aging, a multimodal approach is required. As presented herein, there is strong evidence suggesting the high potential of allogeneic MSCs as a geroscience therapeutic due to their pleiotropic mechanisms of action. Animal models have shown that allogeneic MSCs can successfully treat many aspects of the aging process, and lead to significant improvements in life expectancy with accompanying increases in health span. Clinical evaluation from early stage trials supports the promise of allogeneic MSCs to successfully treat aging frailty. Ultimately, this regenerative medicine approach could be extended to examine whether MSC can be used to prevent aging frailty and for treating aging in general. Given the high safety profile of allogeneic MSCs, these studies would appear to be the imminent next steps.

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CONFLICTS OF INTEREST

All authors are affiliated with Longeveron LLC, either as full-time employees or consultants. Dr. Hare reported having a patent for cardiac cell-based therapy. He holds equity in Vestion Inc. and maintains a professional relationship with Vestion Inc. as a consultant and member of the Board of Directors and Scientific Advisory Board. Dr. Joshua Hare is the Chief Scientific Officer, a compensated consultant and advisory board member for Longeveron and holds equity in Longeveron. He is also the co-inventor of intellectual property licensed to Longeveron.

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