LONGEVERON™ LEDGER
CELL-BASED THERAPIES

UPDATES IN CELL THERAPY AND HEALTHY AGING

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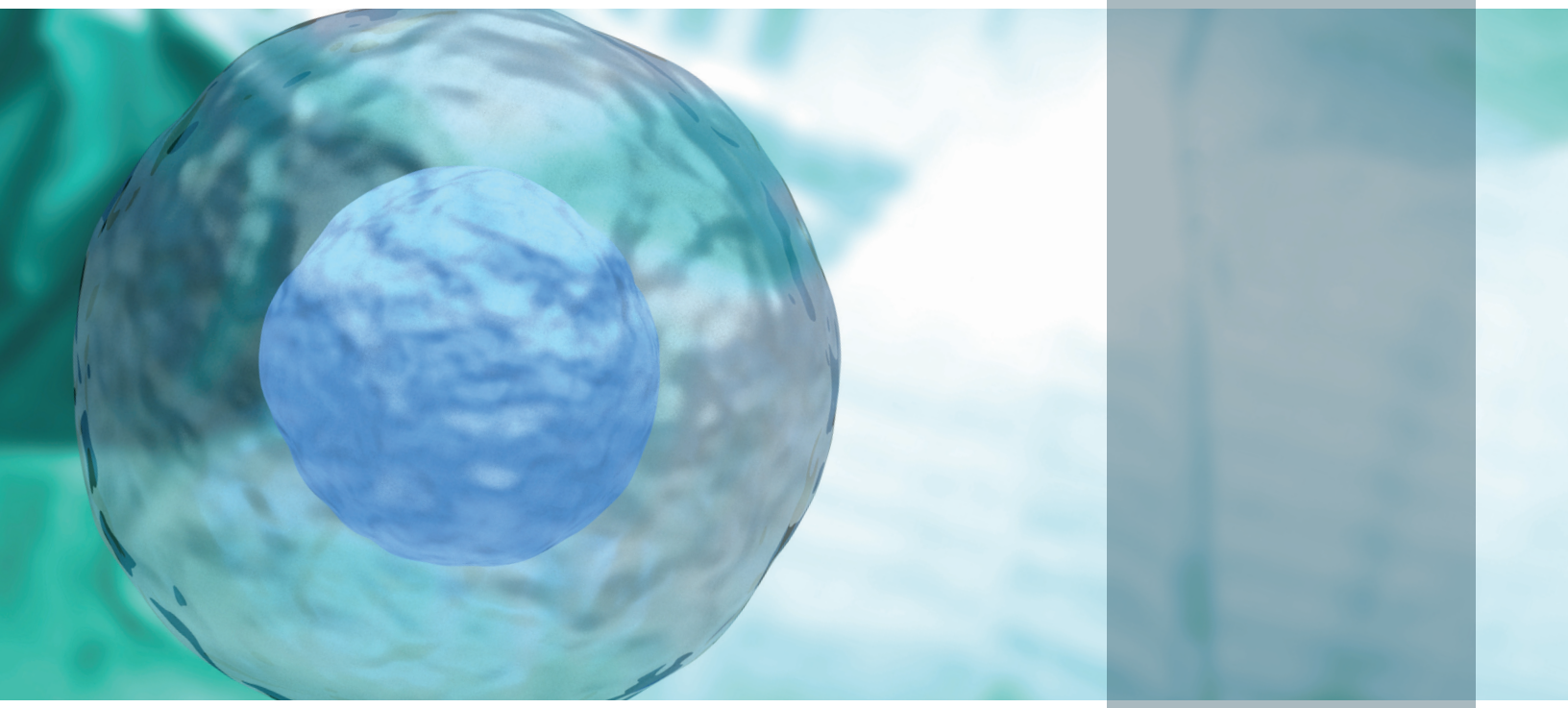
Longeveron Inc.



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Treatments for Alzheimer's Disease and Related Dementias – Longeveron Announces Positive Results of Phase I Clinical Study of Lomecel-B Cell Therapy for Alzheimer's Disease

Fifty million people worldwide currently have dementia, which is a progressive decline in cognitive functioning that can interfere with daily activities, and eventually lead to a loss of independence and death over the course of years. The most common form of dementia is Alzheimer's disease. Scientists have found abnormal proteins in the brain of patients with Alzheimer's disease. These abnormal proteins deposit in the brain tissue itself and can interfere with the normal functioning of the brain. Some early signs of Alzheimer's disease may include: memory loss; confusion about time and places; impaired problem solving and planning abilities; difficulty with speaking, writing clearly and completing familiar tasks; impaired ability to understand visual images and spatial relationships; and mood or personality changes. In the US alone, approximately 5.4 million people suffer from Alzheimer's disease, and this number is projected to increase to 14 million by 2050 according to the Alzheimer's Association, a leading non-profit organization for dementia research. The cost of care for these patients is already stressing healthcare systems, not to mention the enormous toll it takes on families and care-givers.

There is thus an urgent need for effective treatments for Alzheimer's disease and related dementias. However, there are **currently no approved medications** that can **slow-down**, stop, or reverse the **progression of Alzheimer's disease**. Only five medications have received FDA approval for Alzheimer's disease, and none significantly alter the course of disease progression. Three of these (donepezil, galantamine and rivastigmine) fall into a class of drugs called "cholinesterase inhibitors," and another, memantine, is in a class of drugs called "NMDA receptor antagonists." All four of these work by altering the communication between the cells of the brain (these are called neurons). The fifth medication is a combination of two of these drugs (donepezil and memantine).

With the exception of the above five drugs (which do not appear to ameliorate disease progression), we have witnessed decades of failed attempts to develop small molecule drugs for treating Alzheimer's disease. At Longeveron, we hope that an alternative approach using regenerative medicine may provide a much needed solution for combating this devastating disease. Medicinal Signaling Cells (MSCs) have numerous mechanisms of action that may potentially impact the complex pathology associated with Alzheimer's disease. Beyond the hallmarks of the abnormal proteins, which can deposit in areas of the brain or "plaques", Alzheimer's disease is also characterized by inflammation in the brain (referred to as "neuroinflammation"), poor functioning of the blood vessels of the brain ("neurovasculature dysfunction"), and degeneration of brain cells ("neurodegeneration"), among other features. MSCs can potentially have an effect on all of these aspects of Alzheimer's disease, and preclinical studies support this conclusion [1-9]. Using mouse models of Alzheimer's disease, MSCs decreased inflammation in the brain, promoted break-down and clearance of the abnormal proteins deposited in the brain, promoted new nerve cell formation ("neurogenesis"), and improved the cognitive/behavioral performance of the mice. In addition when MSCs were given to younger animals they prevented the development of the abnormalities in the brains.

Longeveron recently completed a Phase 1 clinical trial to evaluate the safety and gain preliminary information about the potential efficacy of its MSC product, called Lomecel-B (formerly referred to as Longeveron Mesenchymal Stem Cells, or LMSCs), for Alzheimer's disease. This randomized, placebo-controlled study was funded in part by the Alzheimer's Association. A total of 33 subjects with mild Alzheimer's disease participated in this Phase 1 study. Each subject was randomly assigned to a group and received a single infusion of low-dose or high-dose Lomecel-B, or placebo in a double-blinded manner (meaning that neither the subjects nor clinical staff knew which intervention each subject received). This Phase I trial met its primary safety endpoint, which paves the way for future trials in subjects with Alzheimer's disease. Importantly, several pre-specified secondary efficacy endpoints and biomarker results support potential benefit from Lomecel-B. The study results provide support for the theory that Lomecel-B can potentially reduce Alzheimer's disease associated brain inflammation, improve function of blood vessels in the brain, reduce brain damage due to Alzheimer's disease progression, and promote regenerative responses. Key findings from new and previously disclosed data:

- Lomecel-B infusion was well-tolerated in this trial, with no treatment-related serious adverse events observed throughout the 1-year follow-up, including no indications of amyloid-related imaging abnormalities (ARIA) as assessed by magnetic resonance imaging (MRI);
- The average Mini Mental State Exam (MMSE) score, which is a measure of cognitive function declined

more slowly in the low-dose Lomecel-B group compared to the placebo group. At 13 weeks after infusion, the low-dose Lomecel-B group MMSE score was higher (better) compared to placebo (difference of 2.69 ± 1.39 points; p=0.0182; 2-sided 95% CI 0.51 – 4.97);

- At 26 weeks post-infusion, patients in the low-dose Lomecel-B arm showed a significantly higher (better) average score on the Quality of Life in Alzheimer Disease (QOL-AD) compared to placebo (difference of 3.85 ± 1.943 points; p=0.0444; 2-sided 95% CI 0.13 – 9.12);
- At 26 weeks post-infusion, the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL), a measure of competence in basic and instrumental activities of daily living, was significantly higher (better) in the low-dose Lomecel-B group compared to placebo (difference of 6.95 ± 3.46 points; p=0.0118; 95% CI 1.99 – 13.94);

Biomarkers:

- Subjects receiving Lomecel-B had significantly increased serum levels of several provascular biomarkers (VEGF, IL4, and IL-6) relative to the placebo group post-infusion.
- There was a significant increase in D-dimer in the high-dose, but not low-dose, Lomecel-B arm versus placebo;
- Subjects receiving Lomecel-B had significantly increased serum levels of several anti-inflammatory cytokines (sIL-2Rα, IL-4, IL-10 and IL-12) relative to the placebo group postinfusion;
- There were no significant changes in the Lomecel-B arms versus the change in placebo for any of neuronal-related biomarkers examined;
- MRIs showed a significant increase in change in left hippocampus volume in the high-dose Lomecel-B arm versus the change in placebo group at Week 13 (p=0.0311). By Week 26, the difference was no longer significant. The low dose Lomecel-B arm showed no significant difference versus placebo.

The complete trial results are currently being prepared for publication in a peer-review journal, and results detailed above are posted in a press release on the company's website, www.longeveron.com. Longeveron plans to use proceeds from its IPO to start a larger Phase II trial in the second half of this year.



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LONGEVERON'S U.S. CLINICAL TRIALS UPDATE

Longeveron is conducting several clinical trials under FDA oversight to evaluate the clinical effects of Longeveron's Lomecel-B product. Lomecel-B is an allogeneic, bone marrow-derived medicinal signaling cell (MSC) product manufactured under current Good Manufacturing Practices (cGMP) in Longeveron's cell processing facility in Miami, Florida. Longeveron currently has one clinical study ongoing, four completed and in the data collection and/or analysis phase, and three more studies expected to begin in 2021. These multi-center trials range from Alzheimer's disease to Aging Frailty and other chronic disease indications. If you or someone you know may be interested in learning more about the trials, details can be found by typing "Longeveron" in the search bar on www.ClinicalTrials.gov.

Completed – Phase 2b Clinical Study of Lomecel-B for Aging Frailty Subjects

We have completed our Phase 2b clinical study of a Lomecel-B infusion for Aging Frailty subjects. The multicenter study was conducted at various hospitals and clinics, primarily in South Florida, including the Miami VA Healthcare System, and was supported in part by a Small Business Administration (SBIR) grant from the NIH's National Institute on Aging (NIA). It is anticipated that the top-line trial results will be announced in the 3rd quarter of 2021. One-hundred-and-forty-nine trial subjects were randomized to receive a single peripheral intravenous infusion of Lomecel-B at different doses (25 million, 50 million, 100 million or 200 million cells), or placebo, followed by a 1-year observation period to evaluate safety and efficacy. The primary objective of the study is to assess the effect of Lomecel-B on exercise tolerance and endurance via the six-minute walk test. Additional endpoints include gait speed, grip strength, assessments for risk and fear of falling, depression, sexual function, cognition, various patient reported outcomes and activities of daily living, and blood-based biomarkers.

Completed – Phase 1 Clinical Study of Lomecel-B for Alzheimer's Disease Subjects

We have also completed our Phase 1 Alzheimer's disease (AD) trial designed to examine the safety of Lomecel-B on people in the early stages of AD (mild AD). The results showed that Lomecel-B was safe and well-tolerated in this study. Full results are currently being analyzed and a manuscript describing the methods, results and conclusions are expected to be submitted for potential publication in a peer-reviewed journal.

Completed – Phase 1 First-In-Human Clinical Study of Lomecel-B in Hypoplastic Left Heart Syndrome Subjects

We have also completed our Phase 1 first-in-human clinical study of Lomecel-B in Hypoplastic Left Heart Syndrome (HLHS), a rare pediatric cardiac condition. The study of 10 trial subject babies was conducted by a consortium of leading pediatric cardiac surgeons at centers that included the University of Maryland Medical Center, University of Cincinnati/Children's Hospital Medical Center and University of Utah Primary Children's Hospital, and was supported in part by a Maryland Stem Cell Research Fund (MSCRF) TEDCO Grant. This study was designed to assess safety and tolerability of intramyocardial injection of Lomecel-B administered to 10 babies with HLHS during the Stage 2 bidirectional cavopulmonary anastomosis (BDCPA, or "Glenn procedure") surgery. HLHS is a rare congenital heart defect that effects approximately 1,000 babies per year in the U.S. Babies with HLHS are born with an underdeveloped left ventricle, which impairs the heart's ability to pump adequate amounts of blood throughout the body. Without a three-staged reconstructive surgery, the condition is often fatal. Even with surgery, HLHS is still associated with high mortality. The Phase 1 safety results have enabled Longeveron to advance its HLHS program into a Phase 2 multi-center randomized, double-blind, placebo-controlled trial, which is scheduled to begin in the third quarter of 2021. The Phase 2 trial, which will study approximately 35 patients nationwide, is being funded by a grant from the National Institute of Health's National Heart, Lung, and Blood Institute (NHLBI).

All Longeveron clinical trials in the United States referenced in this Longeveron Ledger have been listed in ClinicalTrials.gov and have been conducted under an FDA Investigational New Drug Application (IND).



Completed – Phase 1/2 Clinical Study of Lomecel-B for Immune Response and the Influenza Vaccine Subjects

We have completed a Phase 1/2 multicenter, randomized, double-blind placebo-controlled trial designed to assess whether a Lomecel-B infusion can improve the immune response in frail, elderly patients receiving the influenza vaccine. Frailty is associated with poor response to influenza vaccination and higher rates of flu due to weakened immune systems. Top line data from this trial are expected in the third quarter of 2021.

Enrolling – Phase 1 Clinical Study of Lomecel-B for Covid-19 and Acute Respiratory Distress Syndrome Subjects

We are enrolling subjects in our Phase 1 RECOVER Trial which is evaluating Lomecel-B infusions on Acute Respiratory Distress Syndrome (ARDS) due to COVID-19. The RECOVER Trial is a double-blind, randomized, placebo-controlled study designed to evaluate the safety and gain preliminary information about the potential efficacy of up to three intravenous administrations of Lomecel-B. The primary measures of efficacy are functional lung recovery, recovery from infection, inflammatory status, immune status, and lung imaging. The RECOVER Trial received a prestigious TEDCO award from the Maryland Stem Cell Research Fund (MSCRF). Participating clinical centers include the Miami VA Health System, University of Maryland Medical Center and Wake Forest University Hospital.

LONGEVERON'S FOREIGN TRIALS/ REGISTRY UPDATE

NASSAU, BAHAMAS

Enrolling – Single-Arm Treatment Registries of Lomecel-B

In 2017, Longeveron received approval from the National Stem Cell Ethics Committee (NSCEC) under the Bahamian Ministry of Health to have single-arm experimental Treatment Registries (i.e. there are no placebo or other treatment groups so every participant receives Lomecel-B) in Nassau, Bahamas, for the following conditions:

- **Aging Frailty (ages 50-95);**
- **Frailty for reasons other than aging (ages 18-95) (e.g. from autoimmune issues, chronic Lyme Disease, Chronic Fatigue Syndrome);**
- **Musculoskeletal Injury Due to Overuse or Athletics (ages 18-95);**
- **Alzheimer's Disease/Cognitive Impairment (ages 50-unlimited);**
- **Osteoarthritis (ages 18-95). [Current travel rules/restrictions into Nassau:**

Every traveler must receive a negative Covid-19 RT-PCR and an approved Travel Visa from the Bahamian Ministry of Tourism website travel.gov.bs]

TOKYO, JAPAN

Approved – Phase 2 Clinical Study of Lomecel-B for Aging Frailty Subjects

A Phase 2, investigator-sponsored clinical trial has been approved by Japan's Pharmaceutical and Medical Devices agency (PMDA) intended to evaluate the safety and efficacy of Lomecel-B infusion in Japanese Aging Frailty subjects. The planned study is a 45-subject randomized, double-blind, placebo-controlled trial, and it is anticipated that the clinical sites will be Juntendo University Hospital and the National Center for Geriatrics and Gerontology (NCGG). This trial is expected to initiate in 2021.

How Does Longeveron Get Its Bone Marrow & Make Its Product?

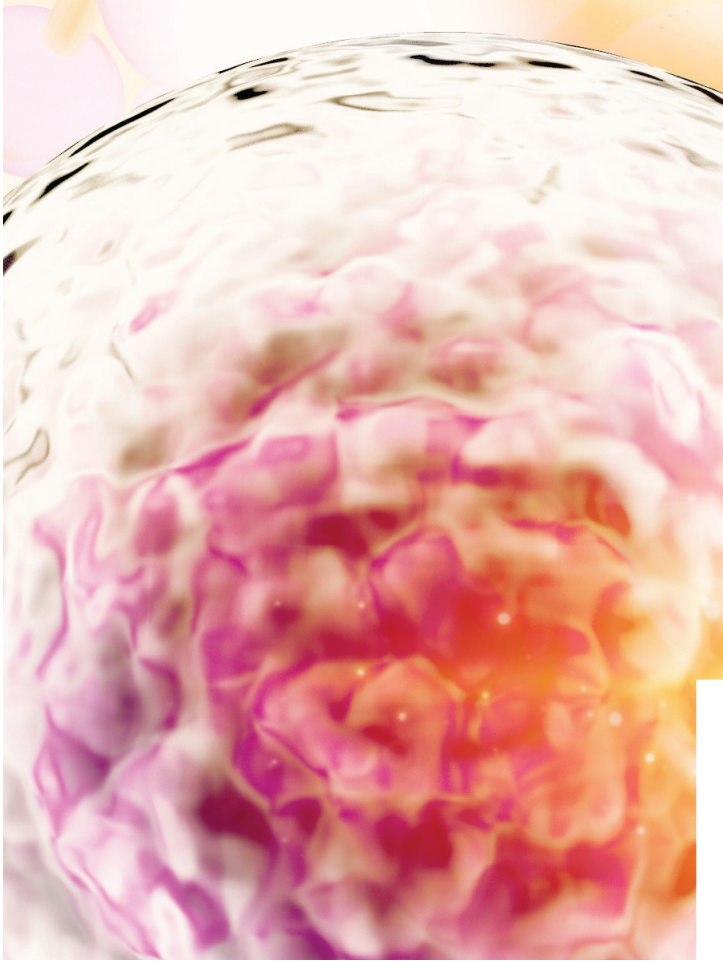
Longeveron's Lomecel-B is an allogeneic (i.e. derived from a donor rather than from one's own body) medicinal signaling cell (MSC) isolated from donor bone marrow extractions. Bone marrow is the soft, spongy tissue inside bones. It is a reservoir for certain types of stem cells, including those that give rise to blood cells (hematopoietic stem cells), as well as the MSCs used to make Lomecel-B.

Why use MSCs? MSCs have a number of unique properties that make them highly attractive for their potential role in aging-related conditions and other disorders. For example, MSCs have the unique property that they do not need to be tissue-type matched, such as would be necessary for a heart or other organ transplant. MSCs express undetectable levels of a protein called major histocompatibility complex class II (MHC-II), and low levels of MHC-I, which is why MSCs can be transplanted into a host without triggering a harmful rejection response [1, 2]. As such, MSCs that are derived from a single donor can be transplanted into unrelated patients, which is referred to as "allogeneic" use.

Like all cells of the body, MSCs are subject to the damaging effects of aging, and can become severely diminished in both total numbers and function with age. The MSCs used for Lomecel-B are sourced from young, healthy adults. This is an important consideration in the context of impacting aging-related conditions since the cells of Lomecel-B are of a relatively young phenotype and less exposed to detrimental effects of the aging process [3].

How does Longeveron pick donors? Longeveron carefully chooses donors who are extensively screened and tested for eligibility under a strict screening protocol that adheres to FDA Code of Federal Regulation (CFR) 21 Part 1271 Subpart C Donor Eligibility requirements. Potential donors undergo a comprehensive medical history and extensive laboratory testing to rule out metabolic disorders and diseases such as: bleeding and autoimmune disorders; heart, lung, or liver disease; neurological disorders; and high-risk of contracting/transmitting communicable disease. In addition, donors are tested for numerous infectious diseases and illicit drug use (and of course, must be free of any of these). This testing occurs at several times prior to collecting bone marrow from the donor.

After the donors pass the screening tests and are determined to be eligible donors, there is a bone marrow extraction procedure. This simple procedure takes just minutes and requires local anesthesia and a syringe to extract marrow from the hip bone. Longeveron isolates MSCs from the fresh donated marrow, and are collected and grown in cell culture at Longeveron's laboratory and



manufacturing facility in Miami, Florida. The MSC cell results in a high purity product which must pass rigorous pre-defined characteristic criteria to ensure that each product adheres to the standards established by Longeveron. Once this process is complete, Lomecel-B is stored in our –196°C deep freezers until needed, at which point the product is thawed and prepared for infusion or injection. The entire production and administration process is conducted according to Longeveron's Chemistry, Manufacturing and Controls documents filed with the US FDA in our approved Investigational New Drug applications.

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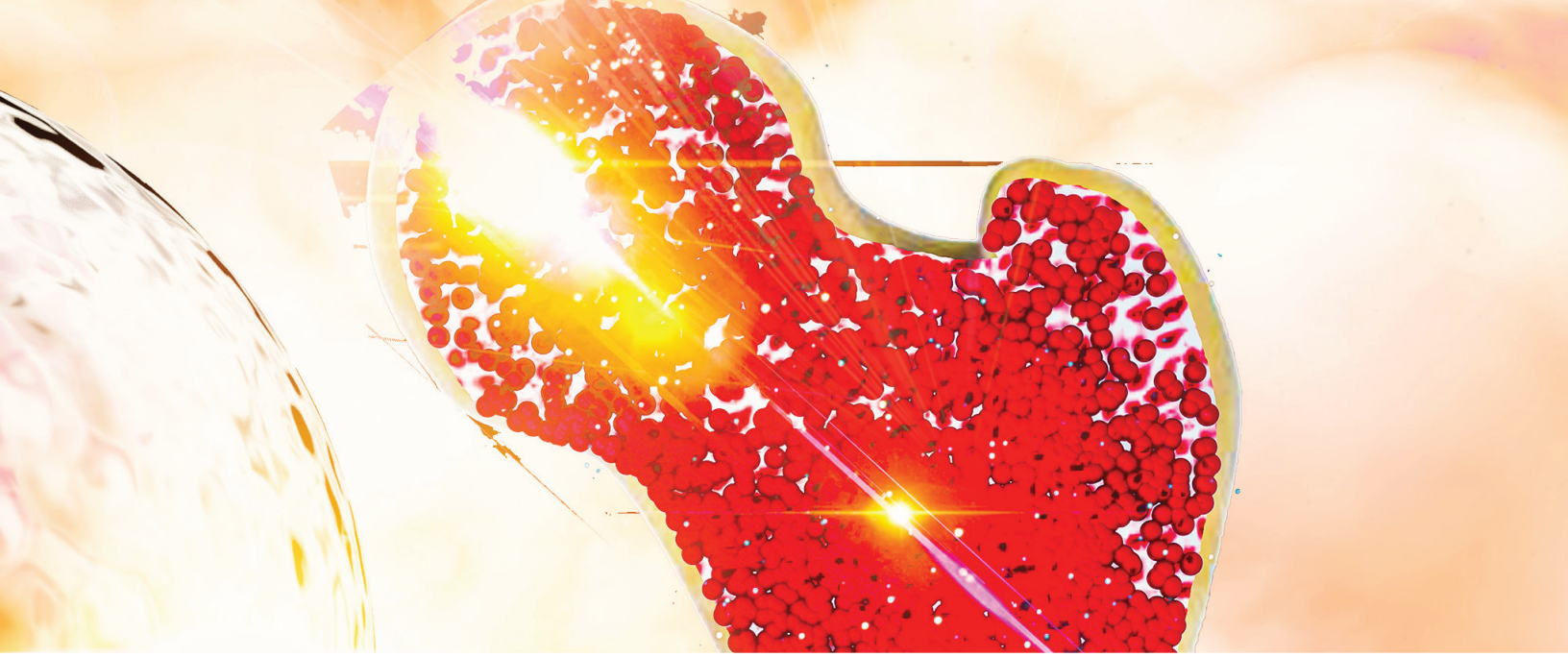

Medicinal Signaling Cells – Possible Benefits for Spinal Cord Injury & Stroke

The potential of Medicinal Signaling Cells (MSCs) to impact traumatic neurological injury was recently demonstrated in a publication out of Sapporo Medical University School of Medicine and Yale University School of Medicine by Dr. Osamu Honmou, Dr. Jeffery D. Kocsis, and colleagues[1]. They reported results from a Phase 2 clinical study using MSCs in subjects with spinal cord injury. Spinal cord injury can lead to paralysis, in which the connections between the brain and part or most of the rest of the body become permanently severed, resulting in loss of both sensation and ability to move muscles. There are currently very limited options (and not very successful options) to help prevent paralysis from occurring after spinal cord injury, and to date there are no therapies that can reverse paralysis.

The study included 13 subjects with acute spinal cord injury. Each received a single intravenous infusion of MSCs at approximately 40 days after the spinal cord injury, along with receiving the regular standard of care. At six months after administration of the MSCs, 12 of the 13 subjects (92.3 %) showed improvement as assessed by the commonly used American Spinal Injury Association (ASIA) impairment scale and the International Standards for Neurological and Functional Classification of Spinal Cord (ISCSCI-92). All subjects also showed improvement in activities of daily living at six months after administration (assessed using the Spinal Cord Independence Measure, or SCIM). And just as impressively, the five patients who had a more moderate injury (Grade C on the ASIA scale) all showed improvement at just one day after MSC administration. Importantly, no MSC-related safety concerns were reported.

In the study, the team used “autologous” MSCs, meaning the cells were sourced from the same subject to whom they were given. The cells were then culture expanded (meaning grown outside of the body to increase their numbers). This process of cellular expansion takes about a month to complete, so as a consequence, subjects in that study were unable to receive the MSCs until approximately 26 to 54 days after the spinal cord injury. This cellular expansion process is similar to how Longeveron’s Lomecel-B product is made, but since Longeveron’s Lomecel-B is an “allogeneic” product (meaning the cells come from a donor so this cellular expansion can be done in advance), it could be available and used immediately as an “off-the-shelf” product for spinal cord injury patients if approved by the FDA.

As an interesting note, this same collaborative team had also previously reported encouraging findings using autologous MSCs for addressing stroke[2], which is a condition where a blood clot can prevent blood flow to a portion of the brain. If not rapidly treated, a stroke can permanently cause cell death of the affected portion of the brain and lifelong debilitating consequences. Like the spinal cord injury study, the stroke study was not placebo-controlled. Nevertheless, there were indications of potential neurological improvement that suggest promise of this approach for this neurological condition, and by extension, perhaps more broadly for neurological conditions in general.

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About Longeveron

Longeveron is a clinical stage biotechnology company developing cellular therapies for specific aging-related and life-threatening conditions. The Company's lead investigational product is the LOMECEL-B™ cell-based therapy product ("Lomecel-B"), which is derived from culture-expanded medicinal signaling cells (MSCs) that are sourced from bone marrow of young, healthy adult donors. Longeveron believes that by using the same cells that promote tissue repair, organ maintenance, and immune system function, it can develop safe and effective therapies for some of the most difficult disorders associated with the aging process and other medical disorders. Longeveron is currently sponsoring Phase 1 and 2 clinical trials in the following indications: Aging Frailty, Alzheimer's disease, the Metabolic Syndrome, Acute Respiratory Distress Syndrome (ARDS), and hypoplastic left heart syndrome (HLHS). The Company's mission is to advance Lomecel-B and other cell-based product candidates into pivotal Phase 3 trials, with the goal of achieving regulatory approvals, subsequent commercialization and broad use by the healthcare community. Additional information about the Company is available at **www.longeveron.com**.

Longeveron Announces Pricing of an Upsized $26.6 Million Initial Public Offering & NASDAQ Listing

Longeveron Inc. (NASDAQ:**LGVN**) recently became a publicly-traded company via an underwritten initial public offering of the sale of 2,660,000 shares of common stock at a price of $10.00 per share and raised in the aggregate gross proceeds of $26,600,000 (prior to underwriting discounts, commissions, and other offering expenses). In addition, an additional 250,000 shares were purchased at the public offering price in connection with an overallotment option provided to the underwriters, thus raising for Longeveron an additional $2,500,000 (less the underwriting discounts and commissions).

Trading of Longeveron's common stock on the Nasdaq Capital Market under the symbol "LGVN" began on February 12, 2021. Kingswood Capital Markets, a division of Benchmark Investments, Inc., acted as sole book-runner for the offering, and Alexander Capital L.P. acted as co-manager. Buchanan Ingersoll & Rooney PC acted as counsel for Longeveron, and Nelson Mullins Riley & Scarborough LLP acted as counsel to the underwriters.

This newsletter shall not constitute an offer to sell or the solicitation of an offer to buy any of the securities described herein, nor shall there be any sale of these securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

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