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Commentary: Cell-free Stem Cell-Derived Extract Formulation for Treatment of Knee Osteoarthritis

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Osteoarthritis (OA) is the most pervasive joint disorder impacting over millions of people each year[1,2]. OA normally affects larger weight-bearing joints, with knees being most prevalent[1,2]. It is anticipated to affect over 67 million people by 2030[1,2]. Pathophysiology of OA is correlated with inflammation and decrease in vascularization in the articular cartilage degeneration[2]. This leads to considerable pain and diminished function[2]. Conventionally, OA is managed with immobilization, physical therapy, activity modification, pharmacological agents such as non-steroidal anti-inflammatory drugs (NSAIDs), and surgical interventions after traditional therapies have been futile[3]. These treatment modalities have deficiencies, often attempting to lessen pain instead of aiming on underlying pathology[4,5].

Over the last decade, a handful of molecular targets, such as, interleukin-1 (IL-1), transforming growth factor-β (TGF- β), matrix metalloproteinases (MMP), etc. have been recognized as mediators of OA[6]. Even though few of these targets are encouraging, they may well generate therapies with high risk-to-benefit ratio[6]. Thus, alternative safe and effective treatment modalities are required to address this unmet medical need.

Lately, there has been a significant surge in the use of biologics for regenerative medicine applications[7]. Biologics at present utilized in clinical practice include platelet rich plasma (PRP), lipoaspirate, bone marrow concentrate, and perinatal allogenic tissues including umbilical cord tissue, umbilical cord-derived Wharton's Jelly, cord blood, and amniotic tissue (amniotic membrane and fluid)[8]. The efficacy of these biologics is ascribed to the presence of stem cells, growth factors, cytokines and extracellular vesicles, including exosomes[8,9].

First-generation biologics, particularly whole stem cell products, have gained significant interest for clinical regenerative medicine applications and demonstrated potential therapeutic benefits[9]. Despite this, they are not without shortcomings, including creating a dependable source with a stable phenotype, genetic instability and chromosomal aberrations, intravenous administration associated toxicities caused by the physical trapping of the cells in the microvasculature of lungs, rejection by the host, formation of ectopic tissue, and tumorigenicity[9]. To address the limitations and harness the benefit of stem cells into a next generation biologics, it is vital to understand the mechanism of action of stem cells. The present literature posits that the mechanism of action for beneficial effects of stem cells does not arise from their ability to grow and differentiate

but is attributed to the secretion of bioactive molecules including growth factors, cytokines and exosomes[9]. As the current literature further demonstrates that these bioactive components of stem cells generate definite regenerative responses, we have accordingly pursued to establish whether a sub-cellular method to biologics can deliver similar benefits while circumventing the risk profile associated with whole stem cells. Endorsing this hypothesis, current studies have shown that stem cells-derived exosomes can act as a cell-free therapeutic substitute to whole cell therapy with excellent regenerative potential[10-12]. In addition to the advantages by means of risk removal, there may be additional therapeutic benefits of a cell-derived therapeutic methodology. For example, exosomes, given their smaller size, have the possibility to migrate to target organs efficiently, without getting trapped in the lung microvasculature[13,14]. Furthermore, a greater concentration of "active ingredients" can be dispensed directly to the patient, which may stimulate a better healing response than likely with whole stem cell treatments[9].

To meet the objectives of improving the risk profile and beneficial effects of regenerative medicine, our group formulated a novel cell-free stem cell-derived extract (CCM) from human progenitor endothelial stem cells (hPESCs). Our published preliminary study showed the presence of numerous growth factors, anti-inflammatory cytokines and extracellular vesicles including exosomes in this formulation[9]. This formulation, functionally, also substantially improved cell proliferation and stimulated stem cell migration[9]. From this study, we concluded that the presence of multiple factors within one formulation along with its ability to increase the rate of cell proliferation and migration, may have the potential in reducing inflammation and pain and enhancing tissue repair and regeneration. In addition to our study, several peer-reviewed published studies via *in vitro* and preclinical work also demonstrated the potential of exosomes (i.e., cell free therapies) in treating knee OA[15-17]. Despite this, there are no high level, peer-reviewed published clinical studies demonstrating the safety and efficacy of cell-free extract or exosomes for treatment of patients suffering with knee OA. To overcome this, we proposed a clinical trial[18] to evaluate the safety and efficacy of intraarticular injection of our novel cell-free stem cell-derived extract formulation for management of knee OA (Kellgren-Lawrence Grade 2 or 3 knee OA). We anticipate that the intraarticular injection of our formulation is safe, and patients will demonstrate improvement in pain, function, quality of life and overall satisfaction. We also anticipate that cartilage formation will improve over a period of 2 years compared to the baseline. In addition to our trial, as of March 03, 2022, there is only one more ongoing clinical trial registered on ClinicalTrials.gov for knee OA related to Cell-free extract or exosomes. Both trials are summarized in Table 1. In summary, positive outcomes from our proposed clinical trial[18] (NCT04971798) will lay the foundation for essential, prospective, larger, double-blinded, randomized controlled trials to further establish the safety and efficacy of our formulation to mitigate symptoms of knee OA, thereby, ultimately justifying its clinical use.

Table 1: Clinical trials registered on ClinicalTrials.gov till March 03, 2022 utilizing cell-free extract or exosomes for treatment of knee Osteoarthritis.

Study Identifier	Tissue Type	Study Phase; Estimated Enrollment (N)	Primary Outcome Measure(s)	Recruitment Status	Country
NCT04971798	human progenitor endothelial stem cells-derived extract formulation	Early Phase I; N=12	Treatment-emergent adverse effects as assessed by Comprehensive Metabolic Profile; Creatinine Levels; Liver Function Test; Complete Blood Count; C-Reactive Protein; Erythrocyte Sedimentation Rate; T, B and NK Cell Lymphocyte Subset; Serum IgG, IgA, IgM and IgE levels [Time Frame: 1 week, 6 weeks, 3 months, 6 months, 12 months]: To determine safety i.e., adverse events associated with intraarticular administration of CCM as assessed by Comprehensive Metabolic Profile; Creatinine Levels; Liver Function Test; Complete Blood Count; C-Reactive Protein; Erythrocyte Sedimentation Rate; T, B and NK Cell Lymphocyte Subset; Serum IgG, IgA, IgM and IgE levels[18].	Not yet recruiting	USA
NCT05060107	Allogenic mesenchymal stromal cells-derived exosomes	Phase I; N=10	Adverse Event [Time Frame: 12 months]: Occurrence of any adverse reactions within 12 months of treatment.	Not yet recruiting	Chile

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