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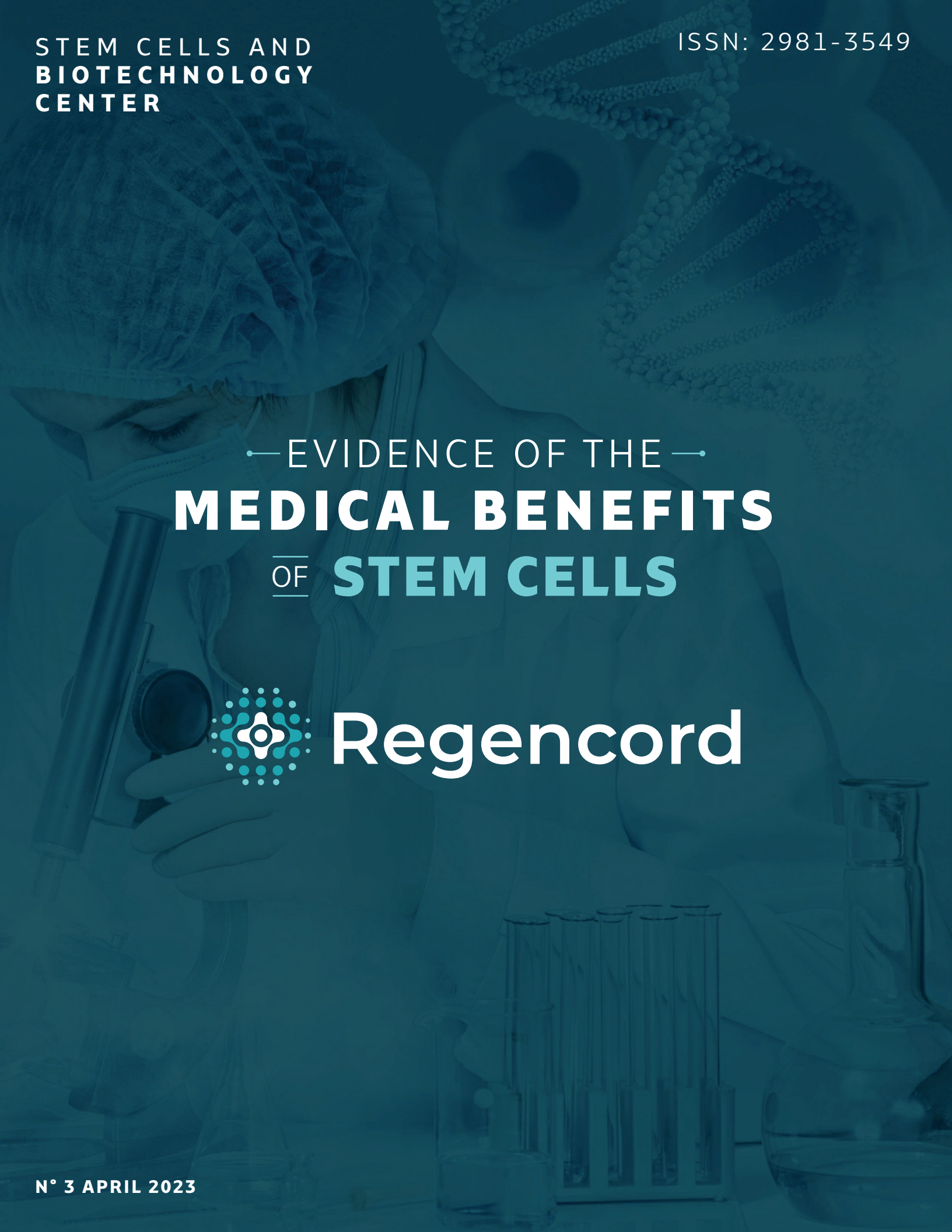

EVIDENCE OF THE MEDICAL BENEFITS OF STEM CELLS

Regencord

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INTRODUCTION

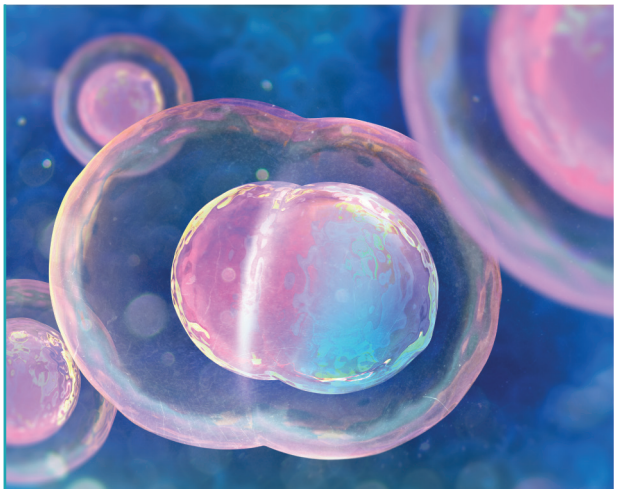
> ***"The regenerative medicine revolution is upon us. Like iron and steel to the industrial revolution, like the microchip to the tech revolution, stem cells will be the driving force of this next revolution."***

Cade Hildreth, founder of BioInformant, a stem cell industry research firm. Citado por: Tony Robbins, Peter Diamandis and Robert Hariri. Life Force; Simon and Schuster, 2022.

> ***"Stem cells seem to hold major promise for contemporary medicine, one which could almost be more significant than a discovery of DNA"***

Kurpisz M. New Technologies Based on Stem Cell-Therapies in Regenerative Medicine and Reproductive Biology. Cells. 2022 Dec 26;12(1):95.

Stem cells are distributed throughout all body tissues and accompany us throughout life. Although they lose vitality as we age or become ill, they hold unique characteristics that give them immense therapeutic potential. First, stem cells can multiply indefinitely, preserving their stemness. Second, under adequate stimuli, they can differentiate into mature cells of different organs (for example, into brain, heart, and liver cells). Third, stem cells can distribute themselves throughout the body in a targeted manner, in response to biochemical signals from diseased tissues.



The main breakthrough in the development of the "Regenerative Medicine" was to isolate stem cells from a person, culture them *in vitro*, expand them and, transfer them to the original donor (autologous transplantation), or to another individual (allogeneic transplantation), to provide the benefits of their therapeutic properties. Thus, it led to the large-scale production and to the availability of stem cells in the amounts required for different uses in which these cells have been demonstrating their usefulness.

Autologous stem cells tend to be used less and less for therapeutic purposes, not only because the patient's disease itself can weaken his own cells, but because, as age progresses, stem cells also age. An alarming finding is that senescence of stem cells can lead them to acquire anti-regenerative properties (for example, inducing cell death). On the other hand, among the exogenous sources of stem cells, those from fetal tissues, in particular from the umbilical cord wall, they stand out for being a good source of "universal donor" cells (do not generate rejection), high proliferation capacity, wide differentiation potential, long-term preservation of biological properties, availability in large quantities from non-invasive sources and without the ethical-legal

drawbacks of other sources.

HOW DO STEM CELLS ACT?

These cells perform their therapeutic functions through four basic mechanisms:

1. Stem cells differentiate into the corresponding cells of the diseased organ and thus replace the injured or dead native cells.

2. They directly transfer to local cells, which are in the process of aging and death, intracellular organelles (such as mitochondria, which are the cell's source of energy production). Revitalizing the diseased native cells and restore the biological balance.

3. Once they reach the diseased organ, stem cells can release hundreds of molecules that have the biological activity necessary to correct the damage (for example, inflammation, oxidation, or cell death).

4. Through direct cell–to–cell communication, stem cells make other cells to modify their harmful behavior (for example, pro-inflammatory white blood cells switch to an anti-inflammatory phenotype).

The aforementioned mechanisms of action explain the amazing regenerative, anti-inflammatory and immune-regulatory properties of these cells.

The wide margin of safety and the promising potential of stem cells suggest that we are on the verge of a new therapeutic paradigm. However, it should be acknowledged that, in many cases, clinical evidence is still limited, and it is necessary to overcome several obstacles before stem cells are implemented as official treatment protocols. It is also important to highlight that this booklet does not intend to make an exhaustive review of the evidence available on the clinical uses of stem cells but rather to briefly cite the clinical conditions in which there is an acceptable level of evidence of the safety/efficacy of stem cells, with the respective literature support.

Finally, as science and technology advance continuously, it is relevant to mention the stem cell-derived extracellular vesicles (EVs), which are loaded with biologically active molecules and, according to current scientific evidence, have practically all the therapeutic virtues of these cells, but with important advantages, such as their small size that allows them to easily reach the injured area and to escape destruction by the immune system; not inducing an immune response in the patient, have no tumorigenic activity (tumor formation), as they are not living organisms that self-replicate and, finally, be stable particles easily modifiable and storable for long periods. For the aforementioned reasons, many authors consider that EV-based therapy constitutes the “second generation” of regenerative medicine.

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OSTEOARTICULAR DISEASES AND PAIN

Osteoarticular disorders, such as osteoarthritis, tendon injuries, herniated discs, and osteoarticular degenerations of the spine, are among the most studied disorders in regenerative medicine, which is currently considered as a safe and cost-effective option, capable of regenerating tissues and repairing damage.

OSTEOARTHRITIS

Articular cartilage has very little self-repair potential, mainly due to its poor vascularization and shortage of stem cells. The little tissue that is regenerated may not have the same biochemical and biomechanical properties as native cartilage. Therefore, a focal cartilage lesion can spread uncontrollably until joint replacement is required.

Conventional treatments for osteoarthritis, based on physical therapy, analgesics, and anti-inflammatory drugs, show only modest clinical benefits, with a high incidence of side effects caused by drugs or surgery; while dozens of clinical studies and meta-analyses, including thousands of patients, show that intra-articular application of stem cells, results in an important recovery of cartilage and clinical (pain and functional limitation), imaging, arthroscopic and quality of life parameters. In fact, some researchers consider that this may be the treatment of osteoarthritis with the best cost-effectiveness ratio, especially of joints in which these cells can be applied locally (1-15).

TENDON INJURIES

There is no agreement on the treatment of acute traumatic tendinopathies, although 20 to 30% of sports injuries involve tendons. On the other hand, chronic tendinopathies, such as tendon degeneration, are repetitive stress injuries that subject the tendon to excessive stress or overload, causing microscopic alterations that weaken the mechanical properties of the tendon. Traditionally, treatment for acute or chronic tendinopathies included analgesics, anti-inflammatory drugs, physical therapy, and, if conservative treatment is not sufficient, surgery. Frequently, when non-surgical treatment is unsatisfactory, infiltration with glucocorticoids at site of injury is performed. However, its effectiveness is transient and with the disadvantage that these drugs eventually alter the metabolism of the tendon, weakening it and increasing the risk of ruptures. In contrast, most of the published clinical studies show that the intralesional application of stem cells, with or without growth factors, improves pain, joint performance, and structural defects of the injured tendon (16-23).

INTERVERTEBRAL DISC DEGENERATION

The intervertebral disc prevents the vertebrae from coming together and damps the compressive forces on the spine. Degeneration of the intervertebral disc is accompanied by the loss of vitality of its stem cells, resulting in disc deformation and instability, which can cause local pain or even painful, disabling nerve injury. Treatment options for disc degeneration include palliative treatment based on medications, physical therapy, and often require surgery, which can lead to biomechanical problems and accelerated degeneration of the adjacent segments. The intradiscal application of stem cells is a safe procedure that is minimally invasive, with long-lasting beneficial effects, which does not require surgery or hospitalization, and compares favorably with results obtained with surgical interventions, such as spinal fusion or disc replacement, at much lower costs (24- 36).

SPINAL AND LOWER BACK PAIN

Apart from the disc, all the other structures that constitute the anatomy of the spine (muscles, intervertebral joints, nerve roots, sacroiliac joints, etc.) are capable of causing pain in the area involved or to radiate to the lower extremity (37). In these cases, benefits of local infiltration of stem cells have already been demonstrated in controlled clinical trials, a higher risk/benefit ratio than other conventional alternatives (38,39).

PAIN

Every day, accumulating evidence show the benefits of stem cells to treat neuropathic pain, indicating that this may be a new approach for the treatment of a condition that deteriorates patient's quality of life and for which conventional medicine has little to offer. Moreover, it has been shown that, at injury sites, stem cells inhibit the production of pain-causing substances, while releasing analgesic substances, correcting the imbalance between chemical pain mediators and analgesics, thus constituting a new strategy for the treatment of pain caused by a wide variety of diseases (40-44). It is relevant to notice that there is some evidence regarding intractable pain, in which stem cells potentiate the analgesic effect of opioids (45,46).

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CARDIOVASCULAR DISEASES

Ischemic heart disease (angina, infarction) and cardiomyopathy (heart failure) are among the leading causes of morbidity and mortality worldwide despite the significant advances achieved in technology, surgery, and cardiovascular pharmacology. Paracrine and regenerative actions of stem cells, related to the preservation of cardiac muscle contractility, stimulation of new vessel formation, and control of inflammation and fibrosis, have encouraged preclinical and clinical studies evaluating the role of these cells in several cardiovascular diseases (1-3).

REFRACTORY ANGINA

Referred as refractory since angina persists even after several months of standard treatment. Patients are often not candidates for revascularization due to the presence of diffuse coronary lesions or severe comorbidity. Stem cell therapy is now a valuable resource for the treatment of these patients and clinical trials highlight that although available data are not yet conclusive, due to the lack of therapeutic alternatives, authors consider stem cell–based therapy to be a viable option to add to the conventional treatment of refractory angina; when comparing patients on conventional treatment plus stem cells and patients with only optimal conventional treatment, studies found improvement of angina indicators and frequency of attacks, increased exercise time and decreased all-cause mortality, without an increase in adverse reactions, among those who received stem cells (4-6).

ACUTE MYOCARDIAL INFARCTION (AMI)

Cell death secondary to AMI causes a strong inflammatory reaction in order to repair the heart muscle, but that unleashes a process of ventricular remodeling, and its duration and intensity determines the prognosis of the infarction. According to available evidence, anti-inflammatory and immunomodulatory activity, on the one hand, and regenerative activity, on the other, explain why stem cells restore the balance between inflammation and repair, control cardiac remodeling and improve the prognosis of infarction (7). In studies carried out with patients with AMI who underwent surgery and/or received conventional medication in a timely manner, stem cell application is associated with significant clinical improvement and better indicators of cardiac function. Although, there are still gaps in knowledge that must be filled (such as dose, cell

type, time of application), the role of stem cells in ischemic heart disease is becoming increasingly clear, to the point where regenerative stem cell therapy is considered as an option with sufficiently strong evidence to be advised in AMI treatment protocols (8-13).

CARDIOMYOPATHY (ISCHEMIC AND NONISCHEMIC)

As mentioned above, ischemic injury and death of cardiac muscle cells leads to cardiac fibrosis, in which the damaged tissue is replaced by a fibrous scar, which is important to prevent ventricular wall rupture in the infarction zone. However, it expands over time to non-infarcted areas. which end up deteriorating cardiac function. Despite optimal medical and surgical management, many patients with heart disease are inevitably exposed to this long process of heart muscle damage, which reduces its contraction and relaxation capacity. Which means that current treatment protocols are unable to prevent the loss of vitality of heart muscle over time (cardiomyopathy) (14). Under these circumstances, it was to be expected that the medical community would want to explore the potential benefits of stem cells, due to their anti-inflammatory, anti-fibrotic, angiogenic, and immunomodulatory properties. In fact, since 2018, several meta-analyses have been published, including dozens of studies on thousands of patients with heart failure in which the effect of stem cell–based therapy was examined. In general terms, results can be summarized as follows: compared to controls treated with conventional management, patients who received stem cells had a significant improvement in cardiac function parameters, heart failure severity classification, 6-minute walk distance, quality of life, and mortality; there was not attendant increase in serious adverse events or hospitalization rates (15-24).

ATHEROSCLEROSIS AND PERIPHERAL ARTERIAL DISEASE

Atherosclerosis has a dual inflammatory and immune nature. Due to their anti-inflammatory, immunomodulatory, and angiogenic properties (new blood vessels), stem cells control atheroma formation and stabilize the formed atheromatous plaque, decreasing its risk of inflammation, rupture, and formation of thrombi (25-28). On the other hand, beneficial and safety results are already beginning to be reported on the administration of stem cells in patients with critical peripheral arterial disease (29,30).

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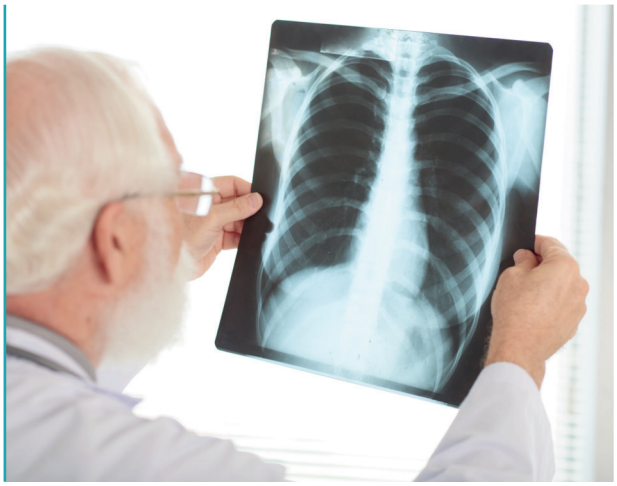
PULMONARY DISEASES

The lung has an extraordinary capacity for self-repair, but it is exposed to numerous damaging environmental and endogenous factors. From the moment it was demonstrated in human lung tissue cultures that stem cells inhibit the formation of fibrous tissue and stimulate repair, numerous studies have been conducted in a variety of animal models of obstructive, restrictive and inflammatory lung diseases (such as pulmonary hypertension, bronchopulmonary dysplasia, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, asthma, obstructive sleep apnea, acute injury, and infection), with safety and effectiveness results that have provided the basis for the beginning of clinical research.



Different clinical investigations and meta-analyses have yielded very reliable results in terms of safety and effectiveness of the use of stem cells in patients with chronic lung diseases, such as pulmonary fibrosis (1-6), pulmonary hypertension (7), COPD and asthma (8-14), among others, although benefits are limited in advanced stages of the disease and issues such as optimal source of cells, dose, route and frequency of administration have not yet been resolved. Since the prevalence of these diseases is increasing worldwide and therapeutic alternatives are so scarce, there is no doubt that this is one of the fields in which evidence of benefit will quickly accumulate.

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LIVER DISEASES

Although the liver has extraordinary regenerative capacity, viral infections, drugs, toxins, metabolic disorders, genetic and immune diseases, among others, can cause acute liver failure or can lead to chronic inflammation and cirrhosis, despite adequate medical and surgical treatment. For some patients, liver transplantation is not an accessible option due to the scarcity of donors, complications related to immunosuppression, complexity and high costs of surgery.

There is sufficient evidence in preclinical studies regarding the ability of stem cells to differentiate into liver cells, attesting to their anti-inflammatory, anti-fibrotic and immunoregulatory properties and of their therapeutic effect on acute liver failure, in different animal models (1). Studies in humans with hepatopathies have been ongoing since 2015 (2) and the majority of individual investigations and meta-analyses, which include thousands of patients, confirm the benefits in the treatment of fatty liver, liver cirrhosis of different causes and acute liver failure, with biochemical, histological, functional and clinical improvement (edema, fatigue, anorexia, abdominal distension) (3-23).

In addition, two recent studies report, on the one hand, a decrease in the incidence of liver cancer in terminal stages of liver failure, up to 5 years after the application of stem cells (24) and, on the other hand, an increase in survival rates at 3- and 5-years post treatment, in cirrhotic patients who received stem cells (25).

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INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) is divided into three types: chronic IBD, ulcerative colitis (UC) and Crohn's disease (CD). All of them share an autoimmune disorder that alters the normal intestinal flora, and its ability to respond to pathogenic bacteria, which causes an intense inflammatory reaction of the intestinal wall; therefore, treatment focuses on the normalization of the immune system and control of inflammation (1-3). However, despite the increase in anti-inflammatory and immunosuppressive drugs, up to 30% of patients with IBD do not respond to the different protocols available, and up to half of the patients who benefited initially stop responding over time (3).

The benefit of stem cell treatment of IBD has been confirmed in numerous clinical trials and meta-analyses, including severe forms of CD, with fistula formation (4,5). Reports show that stem cell-based regenerative medicine is associated with reduction of autoimmune inflammation activity and stimulation of the intestinal mucosa repair process, increasing the duration of remissions and reducing the frequency of hospitalizations and surgeries (6-16).

Although studies evaluating potential interactions between stem cells and conventional drugs have reached contradictory results and, therefore, the evidence is not conclusive, everything indicates that the combination of stem cells with glucocorticoids or azathioprine (and perhaps other drugs) enhances its benefits in IBD (3,17).

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METABOLIC SYNDROME AND TYPE 1 AND 2 DIABETES MELLITUS

Metabolic syndrome (MS) is a set of cardiovascular risk factors, which include abdominal obesity, high triglycerides with or without high cholesterol, low HDL, high blood pressure, hyperglycemia, and nonalcoholic fatty liver. The common denominator of these entities is a chronic inflammatory state, atherosclerosis, and insulin resistance. A vicious circle is also generated in which each of these pathologies amplifies the damage caused by the others. There is an accumulation of preclinical and clinical evidence that stem cells can control several of the aforementioned components of MS (1-4).

On the other hand, the main damaging event of type 1 ***Diabetes Mellitus*** (T1DM) is autoimmune destruction of pancreatic β-cells (responsible for producing insulin) (5), while in type 2 Diabetes Mellitus (T2DM), which is associated with insulin resistance, there is β-cell inflammation, a loss of β-cell maturity and of their ability to produce insulin (6,7).

The differentiation potential of stem cells and their anti-inflammatory and immunomodulatory properties have drawn increased interest in researchers and clinicians, which generated a wave of preclinical and clinical studies, whose purposes range from evaluating the safety and effectiveness of stem cells in the treatment of MS and T1 and T2DM, through the definition of mechanism of action of these cells, as well as their optimal sources, doses, routes of administration, dose intervals, etc. Results aim to have abundant scientific evidence that supports the use of stem cells as a safe and cost-effective option for the treatment of these three pathologies.

In fact, according to meta-analyses and systematic reviews that were published in recent years, intravenous administration of stem cells is associated with clinical and quality of life improvement, better glycemic control, a decrease in glycosylated hemoglobin and insulin requirements, as well as an increase in C-peptide (8-20). Moreover, a recent research with an 8-year follow-up found an association between stem cells and a reduced risk of chronic complications of T1DM, such as nephropathy, retinopathy and neuropathy (21).

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CHRONIC RENAL FAILURE (CRF)

The key pathological mechanisms of CRF are inflammation and remodeling (replacement of normal structures by fibrous tissue, and dysfunction or destruction of blood vessels) (1).

Considering the anti-inflammatory and anti-fibrotic activity of stem cells, studies performed in animal models confirmed that these cells attenuate kidney damage, improving function and protecting the glomerular and tubular structure. The next step was to evaluate the nephroprotective effect of stem cells in humans with CRF, with positive results, including kidney injuries secondary to lupus erythematosus, diabetes and in children with nephrotic syndrome resistant to conventional treatment (2-13).

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GRAFT-VERSUS-HOST DISEASE

Hematopoietic stem cell transplantation (from bone marrow, peripheral blood, or cord blood) is indicated for diseases such as leukemia, lymphomas, and some anemias and immune disorders, among others. In fact, the highest prevalence of these diseases in elderly individuals is caused by aging and dysfunction of their own hematopoietic stem cell (1).

However, post-transplant mortality rates remain high, mainly due to recurrence of the primary disease, infections, and graft-versus-host disease: (GVHD), which can occur acutely or chronically. Although some immunosuppressive drugs can reduce its incidence, it remains high since the acute form of GVHD, for example, affects between 40% and 80% of transplant patients, which makes it necessary to investigate new therapeutic alternatives (2).

GVHD is the result of a complex immune response. Since stem cells have strong anti-inflammatory and immunomodulatory activity, the usefulness of mesenchymal stem cell transplantation (for example, from Wharton's jelly) to treat GVHD has been studied. Although strengthening the evidence is still necessary, especially with controlled clinical trials, several investigations report beneficial effects of stem cells in the prophylaxis and treatment of acute and chronic GVHD in children and adults, with increased survival rates. It is important to highlight that the benefit extends to patients with steroid-resistant GVHD (3-14).

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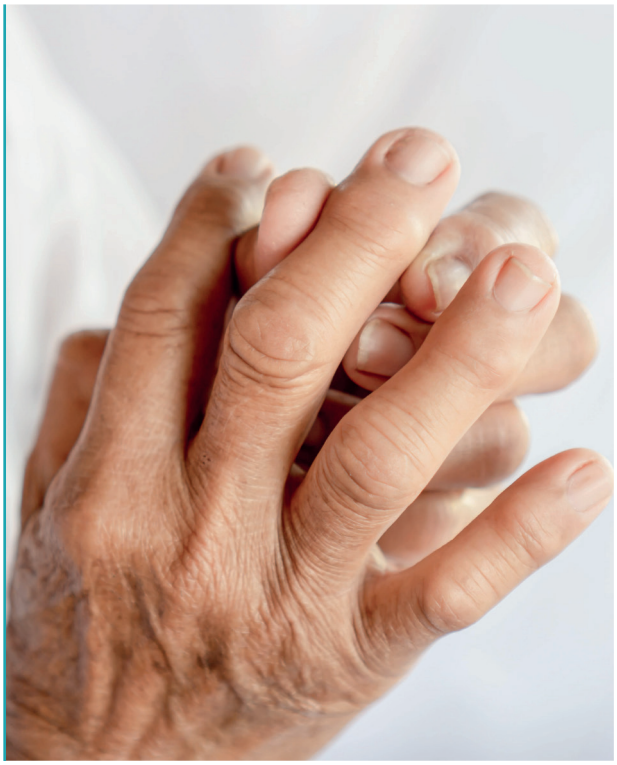
AUTOIMMUNE AND ALLERGIC DISEASES

Once the immunomodulatory and anti-inflammatory activity of stem cells had been demonstrated in *in vitro* and preclinical studies, the exploration of the effect of these cells on an increasing series of autoimmune diseases in humans started. However, it should be noted that the therapeutic effect in these cases is not curative and effectiveness decreases over time, which suggests that it is still necessary to enhance different treatment protocols (1,2).



RHEUMATOID ARTHRITIS (RA)

In a significant number of patients, conventional therapy for RA is associated with poor response or intolerance; in such cases, stem cells are emerging as a novel therapeutic option. In fact, preclinical evidence regarding safety/efficacy in RA animal models is considered sufficiently strong and, evidence of its benefit in patients with poor response to standard treatment is accumulating, with decrease in inflammation markers, and clinical improvement (1-10).

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

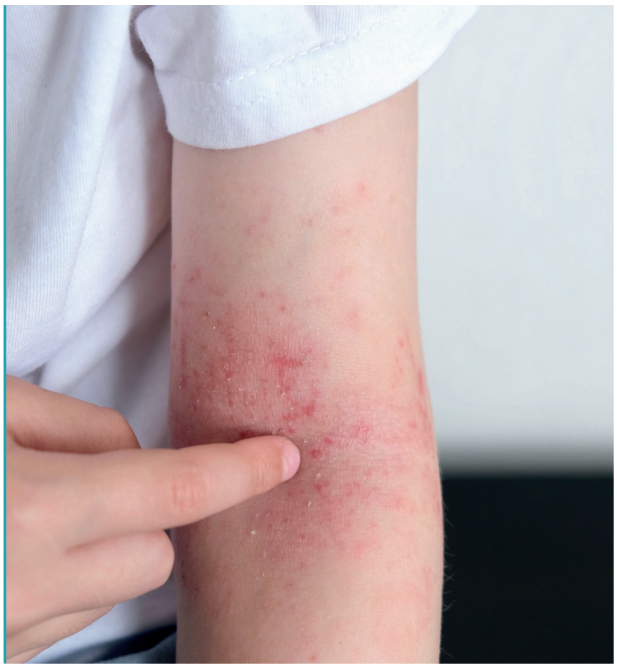
SLE is one of the autoimmune diseases with greater evidence on benefits and safety of stem cells in animal models and in humans. Keeping in mind that clinical evidence is still limited, results of clinical trials on the safety and efficacy of stem cells in SLE give us reasons to be optimistic. As indicated by molecular mechanisms studies, where stem cells can be beneficial, and by reports of survival rates, clinical improvement, and treatment tolerability in patients with several autoimmune diseases, including SLE (1-3,11-18).

SYSTEMIC SCLEROSIS (SS)

This is a rare autoimmune disease that affects skin and multiple internal organs and may have a severe course. Its treatment options are very limited, and medications that may be useful have a narrow safety margin. Cell therapy has emerged as an option, not only safe but capable of correcting many of the inflammatory and immune system disorders that characterize SS. Its safety has been confirmed in individual clinical studies and reviews and, significant benefits have been obtained from the application of stem cells in patients with SS (19-28).

PSORIASIS

A significant number of patients with psoriasis do not respond satisfactorily to current therapies. Since it is an autoimmune disease, in which the patient's own stem cells are involved with excessive and sustained production of inflammatory substances, a good response to stem cell therapy was to be expected, due to the anti-inflammatory and immunomodulatory actions of these cells. This hypothesis has been confirmed by several clinical studies (29-33).



ATOPIC DERMATITIS

Stem cells emerge as a potential strategy to treat allergic diseases (asthma, rhinitis, dermatitis, conjunctivitis and anaphylaxis), probably due to their immunoregulatory and anti-inflammatory characteristics. This therapeutic potential has been demonstrated by preclinical and clinical studies. But atopic dermatitis is the allergic disease that has the greatest evidence on the benefit and safety of stem cell treatment (22,34-37).

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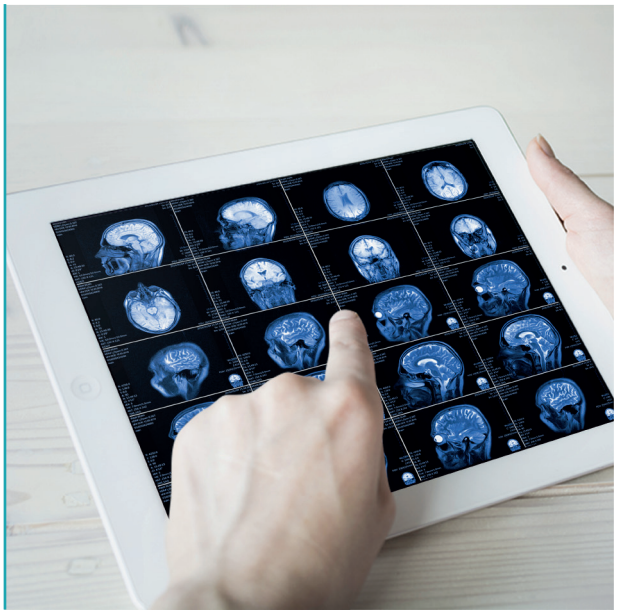
NEURODEGENERATIVE DISEASES

Traditionally, several neurodegenerative diseases (multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease) have been considered incurable, and current medicine can only offer palliative treatment, as in the case of disease-modifying medications, which manage to control progression of intermittent forms of multiple sclerosis, but none of them can repair the existing damage. In recent years, great interest in determining the role of stem cell therapies in several neurodegenerative diseases has arisen. Multiple *in vitro* and animal model studies have confirmed the following properties of different types of stem cells: formation of new myelin, prolongation of neuronal vitality, reduction of oxidative stress, immunomodulation, and formation of new blood vessels, which translate into neuroprotection. Although evidence on safety/efficacy, cell type, dose, routes of administration, etc., require further elucidation (1-4).



MULTIPLE SCLEROSIS (MS)

Multiple sclerosis (MS) is caused by the destruction of myelin, which damages the electrical activity of neurons, with subsequent loss of brain function. Its treatment, based on regenerative medicine, has reached such a level of evidence, that it has been recommended by scientific organizations in severe forms of the disease. In fact, compared with standard immunotherapy, stem cells have been associated with stabilization and delay in the progression of the disease and increased life expectancy, and also a decrease in activity biomarkers in blood and cerebrospinal fluid. On the other hand, safety/efficacy of intrathecal application of stem cells, such as those from Wharton's jelly, have already been widely documented (5-13).

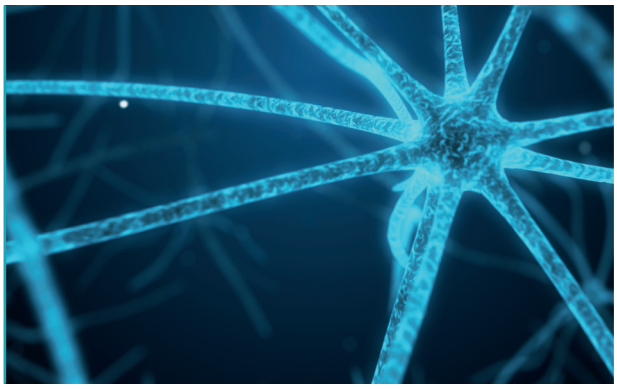
AMYOTROPHIC LATERAL SCLEROSIS (ALS).

ALS is a disease characterized by destruction of motor neurons, neurovascular damage and muscle degeneration, which leads to paralysis, respiratory failure and death. Stem cell treatment has been consolidating as a safe procedure and a promising strategy to protect motor neurons and slow down ALS progression (14-21).

PARKINSON'S DISEASE (PD)

Parkinson's disease (PD) is caused by a progressive loss of neurons in specific brain areas. Current treatment approaches aim to improve symptoms with medications or neurosurgery, but they are not focused in preventing damage to the neurons involved, which means that neuroprotective strategies that provide the possibility of replacing

lost neurons need to be developed (22). Stem cells' ability to repair the damage caused by PD has been demonstrated *in vitro*, and studies on safety and efficacy of stem cell-based treatment in animal models are conclusive. Currently, clinical evidence from clinical trials and meta-analysis can be summarized as follows: i) Safety studies of their application in humans leave no doubt: stem cells are a therapeutic tool with a very low rate of undesirable effects and are not associated with serious adverse events. ii) Evidence from efficacy studies is getting stronger, and stem cells are emerging as a therapy associated with improvement in patient's clinical condition, imaging features, and neuropsychological scores. (23-31).



Regarding the role of stem cells in ***Alzheimer's disease***, there is a good theoretical basis for a potential benefit. Some studies in animal models confirm this. Evidence in humans is limited but promising. Since this is a highly prevalent disease and one of the leading causes of death in the elderly, it is expected that in the future evidence on the safety/efficacy of regenerative medicine in the treatment of this disease will accumulate rapidly (32-37).

Epilepsy is an electrical disorder of the brain, characterized by recurrent convulsive seizures, which cause progressive damage of neurons. Approximately 70% of patients respond satisfactorily to existing anti-epileptic agents, but up to 30% of them are refractory to pharmacological therapy, which is not exempt from significant undesirable effects. In these circumstances, discovery of new therapeutic options is a priority of neuroscience research. As potent anti-inflammatory, anti-oxidant, immunomodulatory and neuroprotective effects of stem cells have been confirmed, safety/efficacy evidence has also been consolidated in preclinical (38-40) and clinical studies, including drug-resistant forms (39-49). It should be noted that, in some of the aforementioned studies, improvement of electrophysiological markers and neuropsychiatric comorbidity (depression, anxiety) has also been reported.

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PERINATAL NEUROLOGICAL DISORDERS

ISCHEMIC-HYPOXIC ENCEPHALOPATHY (IHE)

Ischemic-hypoxic encephalopathy (IHE) is a neurological condition with high mortality and long-term complications, with significant personal, family, medical and socio-economic costs. The damage is caused by conditions that affect blood circulation and oxygenation of nervous tissue that lead to deprivation of energy sources and cell death in the affected area. When IHE is not fatal, a great majority of patients present neurological deficits, such as hearing and vision loss, developmental delay, cerebral palsy and epilepsy. Hypothermia had been established as the main current therapy, which must be initiated within the first 6 hours after birth, is not without risks and, its role is neuroprotective, not neurorestorative. This devastating scenario reinforces the urgent need to develop new strategies to manage IHE. Stem cells in the central nervous system can sense the microenvironment in the damaged area and secrete paracrine factors with reparative functions, which control phenomena such as inflammation, oxidative stress, cell death, and fibrosis (1).

Upon gathering sufficient evidence on safety and efficacy of stem cells in HIE animal models, made it possible to undertake the corresponding safety/efficacy clinical trials with promising results. Although evidence in humans is still limited, regenerative medicine based on stem cells and their derivatives has shown clinical and paraclinical results that were never achieved with current therapeutic options available (1-5).

CEREBRAL PALSY AND GLOBAL DEVELOPMENT DELAY

Due to its neuroprotection and neuroregeneration potential, stem cell transplantation has emerged as a promising therapeutic alternative to improve performance of several components of brain injury in children (intellectual disability, global developmental delay, cerebral palsy), in conjunction with conventional rehabilitation programs. Different clinical studies (case series, controlled clinical trials, and meta-analyses), which included hundreds of patients between 6 months and 15 years of age, have confirmed the safety and efficacy of several types of stem cells protocols. Although results of these studies are not unanimous, most have reported positive responses in areas such as cognition, language, self-care, motor function, social adaptability and, quality of life. Adverse events have been minimal and temporary (6-18).

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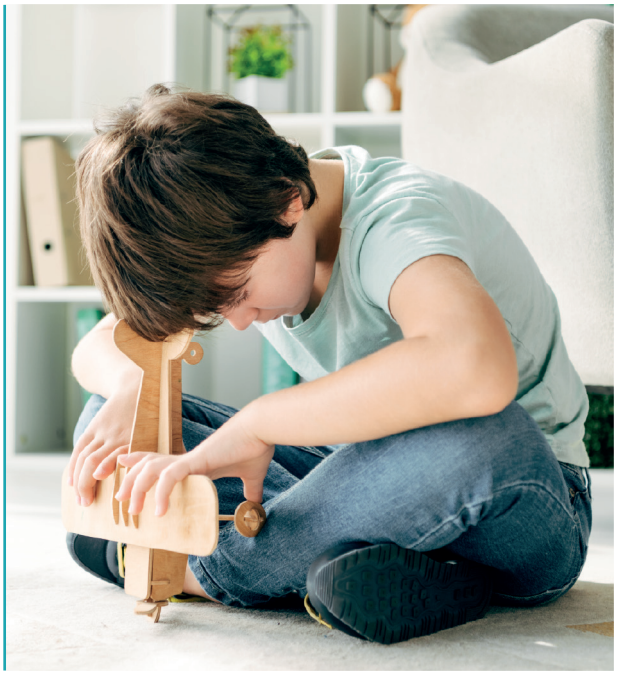
AUTISM SPECTRUM DISORDERS (AUTISM)

Autism spectrum disorders (ASD) are a group of clinical conditions characterized by communication and social behavior disorders and repetitive behaviors. Although their pathophysiology is not clear, evidence suggests that immune system dysfunction and neuroinflammation, which begin in the prenatal period, cause neurodevelopmental damage and structural alterations of the brain (1,2).



Current treatment options are few and limited to control some symptoms, hence the need to explore new treatment strategies. Due to anti-inflammatory, neuromodulatory, and neuroregenerative properties of stem cells, a growing number of individual research and meta-analysis have investigated the effect of these cells on patients with ASD. Benefits in biochemical markers of neuroinflammation and in scales measuring the severity of ASD symptoms (such as language, social communication, repetitive behavior, and hyperactivity) have been found in patients in the range of 2 years and 15 years of age, while none of the studies reported serious adverse events related to the intervention (2-8).

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No effective treatment is available for conditions associated with death of neurons and glial cells, since nerve regeneration capacity is very weak. Therefore, one of the focuses of attention of the scientific and clinical community is directed toward reduction of permanent damage, promote the reconstruction of nervous tissue, and recover its structure and function after any type of injury.

Stroke is the most common neurological disorder in adults, and its incidence has increased mainly due to population aging and the increased prevalence of cardiovascular disease. In addition, current measures to overcome an acute injury reduce stroke mortality. However, many patients present residual cognitive, sensory, and/or motor disabilities. Thus, interventions aimed at preventing and treating the acute phase and sequelae of stroke are urgently needed, and cell therapy represents a new option to reduce the disability caused by stroke.

Safety and functional improvement associated with angiogenesis, neurogenesis and inflammation control in animal models of ischemic stroke has already been confirmed (1). Evidence in humans has rapidly accumulated and, in 2020 a meta-analysis, which included 13 clinical studies with 704 patients, found benefits in daily activities, neurological damage and mortality of patients with ischemic stroke treated with different types of stem cells, in different doses and by different routes of administration (2). Since then, evidence on safety of stem cell transplantation in acute and chronic ischemic stroke and its association with improvement of neurological function, in follow-up trials for durations of up to several years, has become even stronger (3-14). It should be noted though that evidence of risk/benefit of stem cells in hemorrhagic stroke is still very poor, although results in animal models allow us to be optimistic (15,16).

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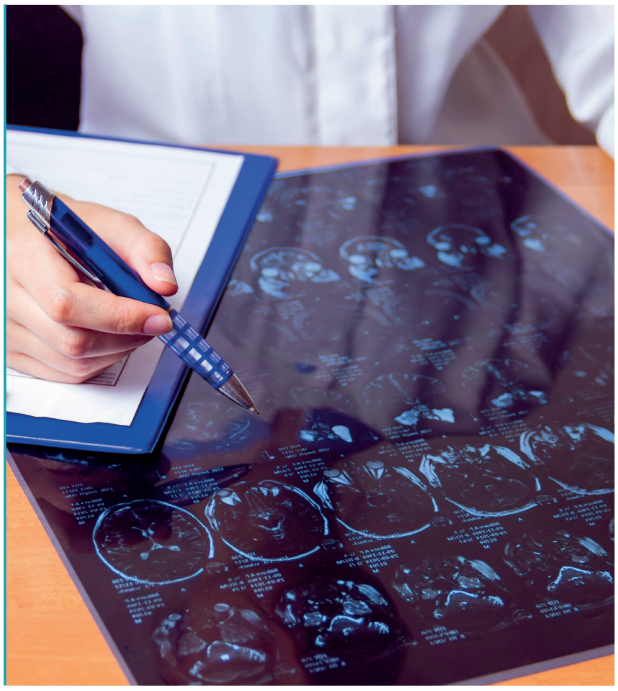
CENTRAL NERVOUS SYSTEM (CNS) TRAUMAS

Regarding potential benefits of stem cells in central nervous system (CNS) traumas, it should be noted that several *in vitro* and preclinical trials have found that these cells: a) can differentiate into various types of nervous system cells; b) secrete neuroprotective substances; c) stimulate myelin formation and neuronal development; d) inhibit scar formation (1).

In ***head trauma***, practically all types of stem cells have been evaluated in preclinical and clinical trials, on the acute, subacute, or chronic phase of trauma, with or without biomaterials that serve as an extracellular matrix, and showed significant reduction in neurological deficits and cognitive sequelae. Nevertheless, several problems still need to be solved before stem cell–based therapy becomes part of conventional protocols for clinical management of head trauma (2-5).



When a ***spinal trauma*** occurs, a cascade of events is unleashed, known as "secondary injury", consisting of hemorrhage, ischemia-reperfusion injury, oxidative stress, neuroinflammation and degeneration of nervous tissue. Most patients present permanent disabilities such as motor dysfunction, spasticity, sensory and urinary disorders and neuropathic pain. Conventional therapies have very limited scopes.

Due to their biological properties (regenerative, anti-inflammatory, immunomodulatory, antifibrotic, neuroprotective and analgesic), stem cells have been clinically assessed and have emerged as a therapeutic option for spinal trauma with increasing scientific support; to the point that their use in brain and spinal trauma has already been authorized by the FDA under the figure of "experimental therapy with expanded access" (6-18).

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FEMALE INFERTILITY

Female infertility, which is the inability to achieve pregnancy with regular sexual intercourse for at least 12 months, has multiple causes, and its treatments vary according to the type of infertility. Premature ovarian failure (POF: ovaries stop working before the age of 40) and endometrial disorders are two common forms of infertility in which the safety and efficacy of stem cells have been studied. The mechanism of action in POF is not clear, but experiments conducted *in vitro* have shown that different types of stem cells stimulate the growth, maturation, and viability of cultured mouse follicles (1-3).

On the other hand, in some uterine diseases, intrauterine application of stem cells improves endometrium thickness and quality and increases implantation and probability of pregnancy (4). In summary, from a clinical perspective, stem cells have been beneficial in restoring fertility among women with infertility due to several causes (5-15). Although clinical experience is relatively scarce, some authors consider that, according to current evidence, cell therapy has proven to be the most efficient way to treat POF, compared to other therapeutic options (16).

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AGING AND FRAILTY

As age advances, there is an inevitable and progressive loss of the ability to maintain biological balance, with an increase in prevalence of debilitating and painful chronic diseases. Thus, aging and its associated diseases represent an increased burden on the family, society, and health systems. Therefore, identification of mechanisms responsible for aging and the development of new therapeutic strategies aimed at making aging more bearable is essential. This is why the World Health Organization is committed to promoting measures that ensure the so-called "healthy aging" (https://www.who.int/es/initiatives/decade-of-healthy-ageing).

Although chronological age correlates with several clinical conditions, it is not always a faithful reflection of an individual's functional capacity, well-being, or their risk of mortality. On the contrary, biological age provides better information about the state of health, and indicates how rapidly or slowly a person ages. Currently, construction of biological-mathematical models to estimate the biological age is under investigation (1).

On the other hand, frailty syndrome is characterized by reduced muscle volume, tone, and strength; slowed mobility and, reduced physical activity, weight loss, fatigability, decline in physiological functions, and elevation of molecular markers of inflammation which predispose elderly individuals to falls, disabilities and hospitalizations. Although timely health care (exercise, nutrition, drugs) improves quality of life and costs of patient care, there is no specific treatment for the management of frail elderly adults (2).

Since stem cells have biological properties that could be useful to control or reverse many of the signs and symptoms of frailty, regenerative medicine has aroused interest as a therapeutic option, especially when it has been demonstrated that, as stem cells become senescent, they begin to secrete degenerative factors that negatively affect young stem cells and lose their therapeutic virtues (3). Regenerative capacity, modulation of chronic inflammation, reduction of biochemical markers of senescence, restoration of mitochondrial function (power production plants of cells) from the senile patient's own stem cells,

control of immunosenescence (aging of the immune system) and loss of muscle tone and mass (sarcopenia) (4-8), are promising stem cell actions, not only for the treatment of frailty but also of other clinical conditions frequently associated with it, such as chronic lung disease, cardiovascular disease, diabetes, osteoarthritis, osteoporosis, among others. Regenerative medicine based on allogeneic stem cells, from a young donor or umbilical cord, has the additional advantage that safety and tolerability has already been validated in several preclinical and clinical studies.

Even though results of preclinical researches (*in vitro* or in animals) cannot be automatically applied to humans; some published papers are still interesting and promising. For example: i) mice that received stem cells experienced an increase in life expectancy compared to that of a group of control mice (9); ii) in old mice, application of stem cells from other old mice, but not those from young mice, was associated with worsening of physical dysfunction (walking speed, grip strength, daily activities and endurance) (10); iii) it has been confirmed, in animal models, that stem cells are able to slow down the aging process and restore the metabolic balance from a catabolic state (protein destruction) to an increase in protein synthesis (protein anabolism). This finding gives hope for the control of diseases associated with aging, such as osteoporosis and sarcopenia (loss of muscle mass) (11); iv) stem cells from young macaques were applied intravenously to old macaques and their serum protein expression profiling related to senility was compared, before and four months after the application of the cells. Protein expression profiling in macaques that received stem cells tended to resemble that of young macaques, in the sense of decreasing or increasing the expression of senescence or anti-aging marker proteins, respectively (12); v) some patients who have survived certain anti-cancer treatments suffer a process of brain deterioration similar to that related to aging. Nasal administration of stem cells has been reported to prevent this cognitive deficit syndrome in mouse models (13).

Although scientific literature on therapeutic effects of stem cells on frailty is still limited, regenerative medicine represents a promising therapeutic strategy to treat this syndrome in humans. In 2017, two clinical trials conducted in frail elderly treated with allogeneic stem cells were published, in which the safety of the procedure and, improvement in six-minute walking distance, pulmonary function tests, cognition and physical component of quality of life were confirmed, and concentrations of some markers of inflammation were reduced (14,15). In the following years, results of several reviews and clinical studies conducted in patients with frailty have been published, showing that allogeneic stem cells have a wide margin of safety and improve physical performance, markers of inflammation and other signs and symptoms of frailty (16-25).

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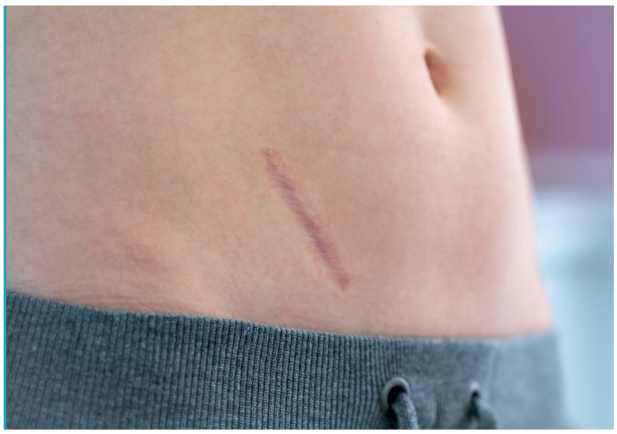
SKIN DISORDERS AND ALOPECIA. AESTHETIC MEDICINE

The therapeutic potential of stem cells and growth factors has been widely studied in a variety of skin diseases and injuries caused by chronic inflammation, infection, trauma, burns, surgery, neuropathies, and vascular insufficiency, with variable results (1).



SCARS AND ULCERS

Intralesional application of stem cells for the treatment of scars is simple, safe, and effective, not only in clinical but also in histological terms. In fact, prophylactic intradermal application of stem cells in surgical wounds prevents formation of post-surgical hypertrophic scars, with preservation of the normal structure and function of the skin (2,3).

Different reviews and meta-analyses of clinical trials that studied effects of stem cells for treatment of ulcers and chronic skin wounds confirm that stem cell therapy is a safe procedure that is associated with significant improvement in conditions such as venous ulcers, diabetic foot ulcers and those with secondary to severe ischemic disease, resulting in a reduction in the rate of amputations. Thus, many experts consider cell therapy as a novel and effective therapeutic option when accompanied by adequate medical and surgical measures (4-15).

ALOPECIA

Minoxidil and finasteride are the only drugs that are currently approved for the treatment of androgenic alopecia, but their effectiveness is limited, and they have frequent undesirable effects. Thanks to the regenerative mechanisms of stem cells and the fact that they release factors that promote hair growth, hair regeneration has become a target of regenerative medicine, with several beneficial results and minimal adverse events, which makes stem cell therapy one of the most promising and potentially effective treatments for different causes of alopecia (16-20).

AESTHETIC MEDICINE

The skin has a high renewal capacity, but as it is continuously exposed to adverse environmental conditions, its vitality decreases over time, and its aging is inevitable, although it can be slowed down. Regenerative medicine has become a new strategy for facial rejuvenation, filling of furrows and expression lines, and elimination of scars, acne and vitiligo lesions, among others (21-31).

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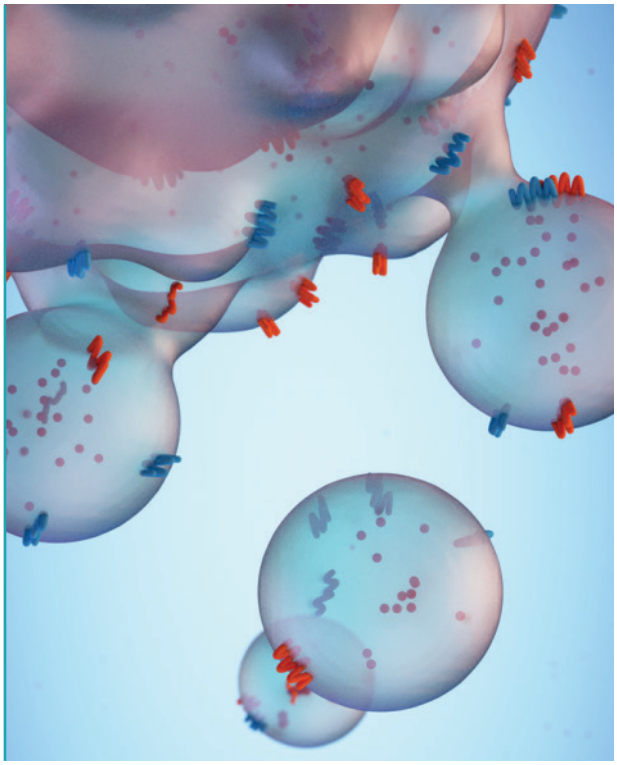
EXTRACELLULAR VESICLES (VEs)



All cells have the ability to secrete biologically active molecules into their surrounding environment to help repair damages and maintain their own vitality or that of other organs (paracrine activity). One mechanism to optimize this function is to release hundreds of active molecules, packed in vesicles covered by membranes similar to the cell membrane. Proteins, lipids, nucleic acids and other biologically active factors are transported inside these vesicles, which can be transferred into other recipient cells, in order to modify their functional state. Therefore, these vesicles are considered to play pivotal role in the paracrine activity of cells and in cell-to-cell communication (1).

These vesicles have been classified based on their size and the cellular compartment that originates them. ***Exosomes*** range in size from 30 nm to 120 nm; ***microvesicles*** (or ectosomes) have a diameter of 50 nm to 1 μm, while ***apoptotic bodies*** range in size from 50 nm to 2 μm. Apart from their size, their differences also lie in the type of biologically active molecules, which depends on the intracellular site from which they are derived and the activation state of the cell. This explains the fact that thousands of proteins, lipids and nucleic acids have been identified inside EVs. However, mechanisms for EVs secretion are much more complex and new vesicles are discovered continuously; in addition, isolation techniques are not sufficiently developed to ensure isolation of homogeneous fractions. Thus, to classify vesicles into these three categories is imprecise, and the use of the generic term of "extracellular vesicles" (EVs) has been proposed (1,2).

Although they are released by all types of cells, this section refers only to EVs derived from stem cells, since they exhibit biological characteristics similar to their source cells, such as the ability to replicate practically all the therapeutic activity demonstrated with stem cells. In fact, growing evidence shows that EVs share the regenerative, cytoprotective and immunomodulatory potential of parental stem cells (1), confirming that they can be used with the same therapeutic indications, in the broad spectrum of diseases mentioned in this booklet.

Additionally, EVs possess some advantageous characteristics in relation to cells from which they are derived. Thanks to their small size and their membrane's physicochemical properties, they are able to overcome several biological barriers and distribute successfully throughout the body, reaching organs that are difficult to access, such as the brain (3); Furthermore, because of their small size and because their low immunogenicity, they can avoid destruction by the patient's

immune system. They are not living organisms, they cannot self-replicate and cannot induce tumors, overcoming many ethical-legal issues of the use of living cells; they can easily be modified, they are stable and can be stored for longer periods (4,5).

This emerging role of EVs allows us to envision them as a new generation of regenerative therapy, making them an attractive and novel option (6). However, medical scope of EVs goes much further: their promising use to transport and deliver drugs in tissues that are, otherwise, unable to reach the target organ cannot be ignored. On the contrary, they can be distributed to organs where they could cause damage (1); as drug delivery systems, EVs are less immunogenic and more biocompatible than synthetic particles conventionally used for drug transport in the body (7). Finally, since any cell is capable of producing EVs, they can serve as biomarkers for early diagnosis of several diseases, including cancer and neurodegenerative diseases (8).

Although the use of EVs as therapeutic instruments is very promising, this strategy still faces many challenges and limitations, which include the availability of an adequate source of stem cells, difficulties in identification, isolation and purification methods; storage conditions to preserve their biological activity, definition of doses and routes of administration, as well as confirmation of their safety/efficacy through clinical studies (1,9-11).

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