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May Growth Hormone be Useful for Regenerative Therapies With Stem Cells?

Jesús Devesa[1*] and Pablo Devesa[2]

*[*1]Department of Scientific Direction, Medical Center Foltra. 15886-Teo, Spain*

[2]Department of Research and Development, Medical Center Foltra. 15886-Teo, Spain.

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ABSTRACT

This study was designed for analyzing the current concepts about GH and stem cells treatments in some acquired neurological injuries (cerebral palsy, stroke, traumatic brain injury) and myocardial infarction. From this analysis we can conclude that while it seems that GH plays an important therapeutic role, it is also clear that stem cells are a promising therapeutic alternative; althoughthere is still a need to clarify what is the optimal window of time for their administration after each one of these damages, as well as the best route of administration in each case and the most appropriate number of stem cells that should be administered. Since the largest number of implanted stem cells do not integrate into the damaged tissue, but rather exert their actions by releasing a number of trophic factors, most of them physiologically induced by GH, and die within a few days after being administered, studies must be done to try to genetically modify these stem cells in GMP facilities so that they can replace and repair the damaged tissues. Here we also provide evidences indicating that GH administration may be of utility for increasing the number of endogenous, and exogenously administered, stem cells allowing their survival, differentiation and migration to the damaged area. In adition, we suggest that each individual may have their stem cells stored in a cell bank, so that he could receive them early after any of these injuries.

Keywords: Growth hormone, Stem cells, Cerebral palsy, Stroke, Traumatic brain injury, Cardiac infarction

Abbreviations: GH: Growth Hormone; IPSCs: Induced Pluripotent Stem Cells; HSCs: Hematopoietic Stem Cells; MSCs: Mesenchymal Stem Cells; NSCs: Neural Stem Cells; GMP: Good Manufacturing Practice; TBI: Traumatic Brain Injury; CSCs: Cardiac Stem Cells; EPCs: Endothelial Progenitor Cells

INTRODUCTION

In this review we will analyze whether the administration of Growth hormone, concomitantly with the implants of stem cells and/or subsequently to these, could improve the results of stem cells therapies in four pathologies (cerebral palsy, stroke, traumatic brain injury and myocardial infarction), that due to their high prevalence, morbidity and mortality require the use of new therapeutic strategies.

We first analyze the therapeutic effects of GH, given alone, and then the current knowledge about stem cells therapies. Lastly we will consider whether GH might be useful for being administered conjointly with stem cells for improving the effects of these therapies.

Growth Hormone (GH)

Classically GH has been considered a metabolic hormone, produced by the pituitary gland, responsible for the longitudinal growth of the organism until the end of puberty. However, this quite simple concept has been changed in the last years because of a number of findings indicating that the hormone plays in the human body quite more and different important effects far beyond than those previously established [1]. Moreover, apart of its well known pituitary production and release for playing an endocrine role, we know since years ago, that both the hormone and its receptor (GHR) are expressed in practically all tissues, if not in all of them, in which the hormone plays an auto/paracrine role [2-5].

Corresponding author: Jesús Devesa, Medical Center Foltra, Travesía de Montouto 24, 15886-Teo, Spain, Tel: +34 981 802 928; E-mail: jesus.devesa@usc.es

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GH and brain

Particularly important is the expression of GH, and its receptor, in neural stem cells where it seems to play a key role in the proliferation, differentiation, migration and survival of these neural precursors [6,7], therefore suggesting that GH might be an important factor for brain repair after an injury, a hypothesis already proposed many years ago [8]. Apart of the crucial role that the GH/IGF-I system plays during the brain development in embryos [9,10], the expression of GH in neurogenic regions of the postnatal brain, as **Figure 1** shows, has been demonstrated in a number of already ancient studies [11,12]. These and many other studies led to the possibility that GH administration could be of utility, in humans and some laboratory animals, in the repair of brain after an injury (cerebral palsy, stroke or traumatic brain injury), a possibility already demonstrated by a number of studies from ours and other groups [13-34]. In fact, in rats, the expression of GH and its receptor is markedly upregulated after brain injury, suggesting that the hormone may enhance neuroregeneration after brain injury [35]. However, the positive effects of GH administration on brain repair, inducing the proliferation on stem cells existing in neurogenic niches of the brain **(Figure 2)**, could only be observed in laboratory animals in which brain injury had previously been induced [26,35,36] or in studies *in vitro* [28,37,38].

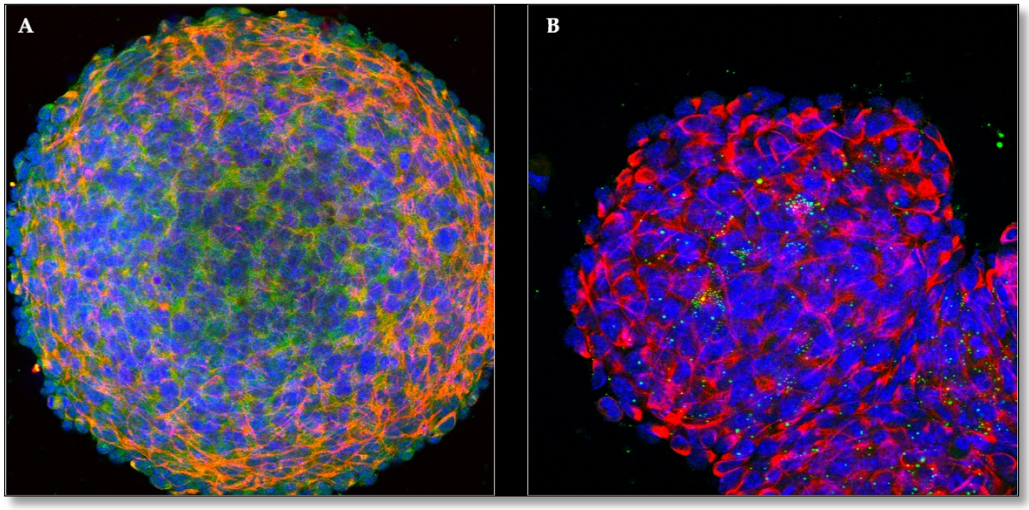

Figure 1. Confocal microscopy. Colocalization of GH and GHR with Nestin in mice neurospheres. Neurospheres derived from NSCs obtained from the dentate gyrus of 9 days old mice in proliferation medium showing immunorreactivity for GH (A, green) and immunoreactivity for GHR (B, green dots). The detection of immunoreactivity for Nestin (A and B, orange color) indicates that cells in neurospheres are stem cells in development.

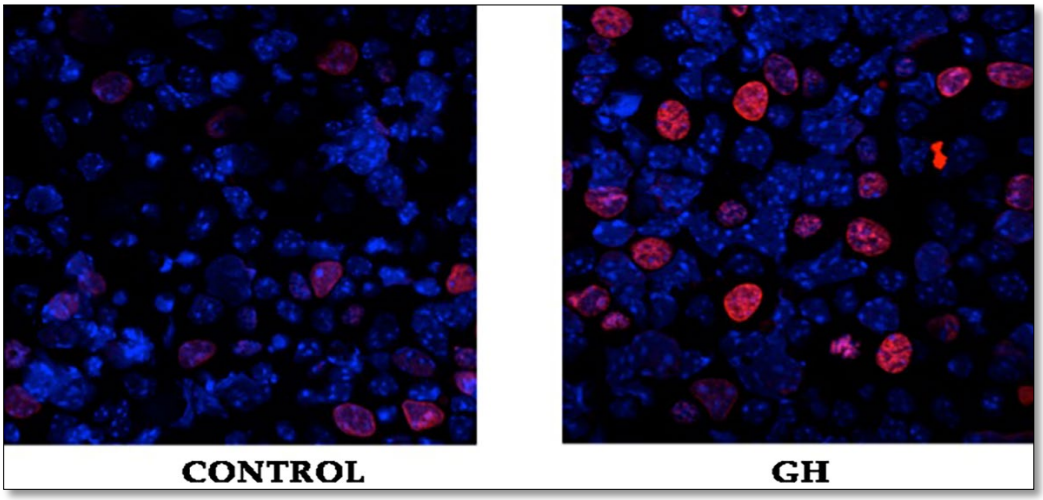

Figure 2. Immunofluorescence. NSCs obtained from the dentate gyrus of 9 days old mice in proliferation medium showing immunorreactivity for BrdU (red color) in control conditions and after administration of GH. Note the higher amount of BrdU+ cells induced by GH administration. Since BrdU is a marker of newly formed cells, this clearly indicates that GH induces the proliferation of NSCs. Blue color shows cells nuclei stained with Hoechst.

GH and cardiovascular system

GH plays also very important effects on the cardiovascular system. It has been shown that an endothelial dysfunction exists in GH-deficient (GHD) patients leading to a lesser edothelium-dependent vasodilation [39]. This is most likely produced by a lesser nitric oxide (NO) production by the endothelium [40]. The administration of GH restores the affected endothelial function and increases the production of NO [39-41], and decreases the oxidative stress associated to the endothelial damage [39]. Moreover, GH administration is able to reverse the intima-media thickness [5,39]. From this and other data it is likely that GH can play a very important role as an inductor of the mechanisms physiologically involved in recovery after a cardiovascular injury. Recent pre-clinical studies support such a possibility. For instance, it has been proven, in rats, that treatment with GH after myocardial infarction enhanced angiogenesis and myofibroblast activation and improves post-infarction remodeling [42]. This was also observed in another study in which GH was delivered from an alginate scaffold injected around the ischemic area of myocardium after coronary ligation, leading to a clear amelioration of ventricular function and exhibiting long-term antiarrhytmic potential [43].

Stem cells

Since the late 70's, stem cells therapies have been a promising strategy for the treatment of many diseases, including cancer, AIDS, heart infarctions, stroke, traumatic brain injuries, lung affectations, cerebral palsy, and a number of neurodegenerative and eye diseases, blood diseases, liver failure, diabetes, colitis, cartilage degenerations, among many others.

Stem cell therapies had their origin in older therapies, such as blood transfusion, bone marrow and organ transplantation and *in vitro* fertilization. Improvement of these therapies soon started to require *ex vivo* processing before their use as a pharmaceutical product, moving from "transplantation" to "stem cell therapy".

There are many potential forms of stem cells therapies depending on the finalaim of the therapeutic strategy. In general we can envisage three main different aims when a stem cell therapy strategy is designed:

1. To restore the cell population that has been lost or damaged. These include regeneration of blood vessels, brain, heart, liver, cartilage and bone.
2. To modify immune responses to either enhance (anti-tumor) or to lower (autoimmune diseases) T and B cell responses.
3. To restore normal functions of tissues or cells through paracrine secretions of soluble factors.

To date, according to the information provided by the U.S. National Library of Medicine (http://www.clinicaltrials.gov, November 2017), there are 4565 studies for stem cells therapies in a really high number of different diseases, including a rare form of Parkinsonism as it is the Progressive Supranuclear Palsy.

The different cell types used in the treatments currently carried out can come from the same patient (autologous) or can be derived from a donor (allogeneic). Depending on the country and its specific health laws, the origin of the cells used may be quite different; for instance, pluripotent stem cells (human embryonic stem cells or induced pluripotent stem cells (IPSCs) [44] and even stem cells obtained from parthenogenetically activated human oocytes [45]) are not allowed for its use in stem cells therapies in Europe but in other ountries, such as China and USA. However, due to ethical reasons and/or technical difficulties together with the possibility of inducing important adverse side effects (i.e., tumorigenicity in the case of human embryonic stem cells, and perhaps IPSCs too), during the last years the field of stem cells therapies is progressing towards the clinical use of multipotent adult stem cells obtained from many different sources. These adult stem cells are found in all adult tissues and they physiologically participate in the regeneration of the tissues where they belong. This is the case, for example, of hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs) and neural stem cells (NSCs).

HSCs

HSCs are able to migrate to the bone marrow and give rise to all hematopoietic cell types when injected intravenously; therefore they are useful for treating primary immunodeficiencies and hemoglobinopaties, but also for treating cancer, neurodegenerative and cardiac disorders. Of course these treatments would be ideally performed by using autologous cells, but HSCs (originally characterised in humans as CD34+, Lin- cells) from healthy HLA-compatible donors orgene-modified allogeneic HSCs could also be used. This would impede the appearance of graft versus host disease.

CD34 is a cell surface antigen, first discovered in a cell surface glycoprotein [46,47] that is early expressed in hematopoietic and vascular-associated tissue [48]. It is an adhesion molecule, but also facilitates cell migration [48], including chemokine-dependent migration of eosinophils, hence facilitatingthe development of allergic asthma [49]. Moreover, HSCS don't express mature blood cells markers, such as Lin (lineage-positive cells). Therefore, HSCs can be easily identified and isolated by flow cytometry from other blood cells in the sample, by staining them with specific markers for CD34 and Lin.

MSCS

MSCs are very attractive stem cells for use in clinic because: 1) they are able to give rise to different tissue types and

therefore could, at least theoretically, be used for tissue repair; 2) they are able to modulate the immune system and can therefore be used as a way to decrease immune responses; 3) MSCs are quite easy to be isolated and expanded.

MSCs can be obtained from many different tissues, such as: bone marrow, adipose tissue, dental pulp, synovial membranes, Wharton's jelly, umbilical cord blood, liver tissue, etc. They have to be positive for CD105, CD90 and CD73, negative for MHC-II, CD11b, CD14, CD31, CD34 and CD45 and also express low levels of MHC-I.

MSCs have shown important therapeutic benefits in several pathologies including graft versus host disease, diabetes, cardiovascular diseases, bone and cartilage diseases, neurological diseases, liver and lung diseases, Crohn disease [50] and recently they have been proved to be useful in spinal cord injuries [51]. In addition, the ability of MSCs to differentiate into epitelia-like cells have suggested that they could be useful to contribute to wound repair when administered locally [52-55]. Moreover, a special type of MSCs, the Muse cells (Multilineage-differentiating stress-enduring) can be obtained from cultured bone marrow-mesenchymal stem cells showing important repair effects after being transplanted into mice with neurological diseases because they differentiate into neurons and connect with host intact neurons [56].

NSCs

NSCs transplantation has been studied in animal models as an attempt to repair brain and spinal cord injuries. However, of all the possible neural sources of NSCs only the olfactory ensheathing cells, obtained from the olfactory mucosa, are readily accessible and capable of lifelong regeneration. They have been used in laboratory animals with spinal cord injuries, but it is still not clear that these cells will produce significant positive effects in humans with similar spinal cord injuries. However, a recent work in rats demonstrated that NSCs expanded from the postnatal subventricular zone engrafted into the hippocampus of young and aged animals leading to the production of newly born neurons and even to the appearance of new neurogenic niches in non-neurogenic regions, generating new neurons for a high period of time after grafting [57,58]. This opens new perspectives for treating a number of brain pathologies, including neurodegenerative diseases, but specially for recovering the lost recent memory and abnormal neurogenesis after hippocampal injury.

Recently, it has been reported that primitive NSCs (pNSCS) can be easily obtained from human induced pluripotent stem cells (hPSCS) [59]. These NSCs express neural stem cells markers (Pax6, Sox2 and Nestin and are negative for Oct4). They present the advantage that can be expanded for multiple passages, and can be differentiated into neurons, astrocytes and oligodendrocytes, which allow them to be useful for treating different neural diseases. Moreover, and depending on the brain area they can give origin to different neuronal subtypes, including dopaminergic, GABAergic and motor neurons. This, together with the fact that only 7 days are needed for inducing hPSCS into pNSCs opens new therapeutic perspectives which still have to be explored in clinical trials.

After this brief review about the sources and types of stem cells able to be infused in human patients, we will focus on four situations that, due to their high prevalence in the population and their extreme severity, require rapid action in terms of stem cell treatments.

Cerebral palsy (CP): Cerebral palsy is a non-progressive disease occurring in 2-2.5/1.000 live births, and is mainly characterized by motor disorders, although many of the children also suffer cognitive affectations, speech impairments or absence of language, hearing and visual affectations (these range from squint to absolute blindness), seizures, drooling, etc. CP is usually produced by damage to the developing brain, because of many causes, including maternal infections (such as those frequently produced by cytomegalovirus) or toxic habits, but also is produced by asphyxia before birth, hypoxia/ischemia at birth, brain trauma during labor and delivery or prematurity leading to a brain white matter affectation known as Periventricular Leukomalacia and parenchymal venous infarction complicating germinal matrix/intraventricular hemorrhage. Other causes are related to post-natal infections (i.e., meningitis) or traumas. In any case, given the age at which it occurs, CP represents a a great public health problem and tremendous economic costs for the patient's family and the state. According to a study carried out in Denmark, the cost of CP throughout the life of one of these patients is around $1.2 million of US dollars for men and about $1.1 million of US dollars for women [60].

Due to the magnitude of this problem in terms of both personal and familiar affectations, and social costs, the need exists for urgently finding a therapeutic solution for children with CP.

Stroke: In Spain, as in many other developed countries, cerebrovascular diseases are the second main cause of mortality in the population, and the first in women [61]. In 2011, the Hospital Morbidity Survey of the National Statistics Institute reported 116.017 strokes and 14.933 transient ischemic episodes; this implies an incidence of 252 strokes and 32 ischemic episodes per 100.000 people. These data presumably will increase in the coming years due to the habits of life and the aging of population.

There are two types of stroke, ischemic and hemorrhagic. Ischemic strokes represent about 86% of strokes [62] and are the consequence of blocked or narrowed arteries because the progression of a thrombus or the existence of atherosclerosis which leads to increased stiffness and endothelial

dysfunction. In turn, hemorrhagic strokes occur because of blood leaking into the brain, usually produced by increased blood pressure and the rupture of an existing aneurysm (usually leading to a subarachnoidal hemorrhage, which presents a very high morbidity and mortality) or a congenital arteriovenous malformation. As is logical, the severity of the stroke, independently of its origin, requires an inmediate intervention, different depending on whether the stroke is ischemic or hemorrhagic, but after the acute period remnant sequels exist. These depend on the brain area affected, but the most severe and difficult to be corrected are: hand paralysis, aphasia and loss of recent memory.

Traumatic brain injury (TBI): In the case of TBI, the annual incidence of new cases in Spain was estimated at 200 per 100.000 inhabitants, 40% of them being due to traffic accidents (data from 2006).

It is clear that, as it occurs in stroke, the high social and sanitary impact that TBI produces requires urgent measures in terms of prevention but also of recovery of the neural injuries suffered once the critical episode has been resolved in the hospital.

TBI is quite different from stroke, since the brain injuries produced after TBI usually are diffuse and progressive, while in stroke they are generally restricted to the area affected; the main problem associated with TBI is the development of a diffuse axonal injury, an event that can lead to instant death, or progress during days or weeks due to axonal shearing, and subsequent progressive brain inflammation, leading the patient to a vegetative coma or permanent disabilities. This is a main reason for treating to develop new therapeutic strategies in order to prevent these terrific consequences.

Myocardial infarction: This occurs when the blood supply to a part of the heart decreases or is fully interrupted because of the blockade of a coronary artery produced by the rupture of an atherosclerotic plaque. The result is heart damage that can lead to the sudden death of the patient. Urgent treatmet is therefore needed, with anticoagulants, such as aspirin, or percutaneous coronary intervention for trying to push open the affected coronary or perform a thrombolysis. Later, a stent can be placed in the location in which the coronary artery had been occluded, or a coronary bypass surgery can be carried out. However, none of these have been reported to recover the damaged muscle heart, rather they try to prevent the appearance of a new episode. Hypertension, smoking, obesity, increased LDL/HDL cholesterol ratio, sedentary life and excessive alcohol intake are risk factorsfor developing a myocardial infarction along the life.

DISCUSSION

After a brief description of the effects of GH at the neural and cardiovascular levels, as well as the main types of stem cells used in a series of treatments, and a schematic description of what four important pathologies mean, we will now analyze whether it would be feasible to combine the administration of GH, given its own effects and those exerted by the high number of trophic factors whose expression is induced by this hormone, with stem cell treatments in these pathologies, to try to achieve better results.

Cerebral palsy

While many recent studies analyzing the effects of stem cells treatments describe positive, although rather modest, results in cerebral palsy [63-68], most of them use cord blood stem cells, a treatment that is impossible to be carried out in Spain, because national health laws do not allow to store the umbilical cord of any newborn for its own use. Rather, these umbilical cords are stored for public use in any patient who could need it in a future; for example for cancer treatments once the HLA compatibility has been checked. This does not exclude that if the delivery has taken place in a private hospital, the family can request the collection of the cord to be stored in a private stem cells bank located in another country.

Some of the aforementioned studies utilized BMCs, but there were no clear differences in terms of the results obtained [69], perhaps because only some symptoms of the disease were improved after the therapies with stem cells. Moreover, it is unclear what should be the optimal route of administration or when it should take place or the minimum number of cells that should be administered. In any case, independently of their origin, stem cells need to be isolated and expanded in a GMP facility until reaching the needed amount for an adequate infusion and effectivity. This is not a major problem in the case of children under two years of age, more or less, a period of time during which the brain is still developing and has a great plasticity. However, it seems logical that an early intervention (after prematurity or perinatal hypoxia/ischemia) will reduce the brain damage and the recovery of it will be easier.In fact, we have been able to fully recover the brain of children with CP due to prematurity or perinatal hypoxia/ischemia,by treating him with GH as early as 16 days of age, after a cardiac arrest *in utero* of 20 min due to massive bleeding produced by Vasa previa **(Figure 3)** or in some other CP children who began to be treated during the first two years of life. In turn, older CP children in whom spasticity and motor disorders are well established experience lesser improvements when receiving GH and neurorehabilitation [70]. Therefore, it would be useful to study whether a combination of GH and stem cells therapies would produce more benefits to these older CP children, especially if we take into account that data from

our group indicate that at least 70% of children with CP lack normal GH secretion [71].

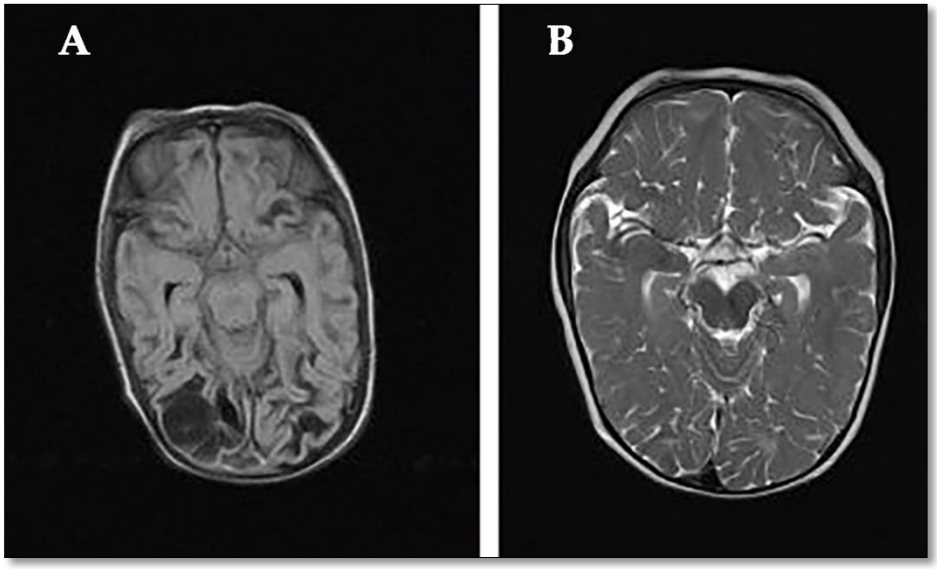

Figure 3. Magnetic Resonance Imaging (MRI) of the brain of a child who suffered a cardiac arrest *in utero*. A) Image taken at 15 days of age. Note the occipital cystic cavities and the marked encephalomalacia. After this image and the prognosis, the parents were asked to authorize the vital disconnection. B) One year later, after being treated with GH and neurorehabilitation beginning on day 16 of age. Although there is a small lack of myelination, cystic cavities disappeared and the brain was recovered. Currently the child is seven years old and lives a normal life.

Stroke

During the last years many studies analyzed the efficiency of the application of human adult stem cells from different sources (bone marrow, umbilical cord, adipose tissue, even menstrual blood, among others) for the recovery of the disturbed neuronal circuitry and disruption of the blood-brain-barrier after stroke [72-83]. These are only a small but representative sample of the high number of published articles about stem cells therapies for the treatment of stroke. The results have been controversial regarding the efficacy of this type of therapy. Most likely the finding of significant improvements or, on the contrary, the lack of beneficial effects depends on multiple factors, such as: the time elapsed between stroke and treatment, the via of administration of stem cells (intravenous, intra-arterial, intrathecal) and, perhaps, the age of the patients at which they are treated, because the reparative properties of the brain decrease while aging.

Regarding the time elapsed after the stroke occurred and the treatment with stem cells starts, a clinical trial administering intravenous MSCs in the acute phase of stroke has being carried out in UK and USA [79], without sigificant improvements observed at 90 days in neurological outcomes, and another one is commencing in many european countries including different Spanish hospitals. However, a recent clinical trial performed in Hong Kong in patients who had suffered cerebral haemorrhage one year before being treated with intravenous injections of autologous MSCs showed improvements of motor disabilities and cognitive impairments over a year after being treated [84].

While along the Introduction we have described many positive effects regarding the use of different types of stem cells for treating very complicated pathologies, a main problem, such as the integration and differentiation of these cells for repairing the damaged brain remains unsolved, at least in human patients. In fact, after a stroke, only a few number of exogenously administered stem cells integrated into the neural networks of recipients, while the majority of implanted cells die few time after being administered [85]. Even more, a minor fraction of surviving cells after being implanted is differentiated into astrocytes, but not into neurons [85]. Despite this, significant neurological recoveries have been reported, suggesting that they had to be due to the fact that the implanted stem cells release several neurotrophic growth factors [86], cytokines and immuno-modulators which would enhance the neurogenesis, that quickly is stimulated after a brain damage, and the generation of new blood vessels, reducing the neuroinflammation, and promoting the formation of new synaptic connections. This means that the main action of stem cells therapies for neurovascular regeneration after a stroke is based on its trophic support to the ischemic brain [87], mainly activating the neurons surrounding the damaged area (penumbra area), or, as recently described, inducing endogenous NSCs towards neuronal differentiation [88]. However, once again we have to remind that GH not only induces adult neurogenesis, but also induces the exppression of many neurotrophic factors, such as IGF-I, Erythropoietin

(EPO), EGF, bFGF, BDNF, VEGF, and the release of a number of cytokines; in addition, the hormone promotes an increased turnover of important neurotransmitters [1], therefore mimicking the action of transplanted stem cells, while increasing their survival via Pi3K/Akt. On these bases, it is reasonable to assume that a combination of a treatment with GH and stem cells would produce better results at the time of treating a stroke with stem cells transplants **(Figure 4)**.

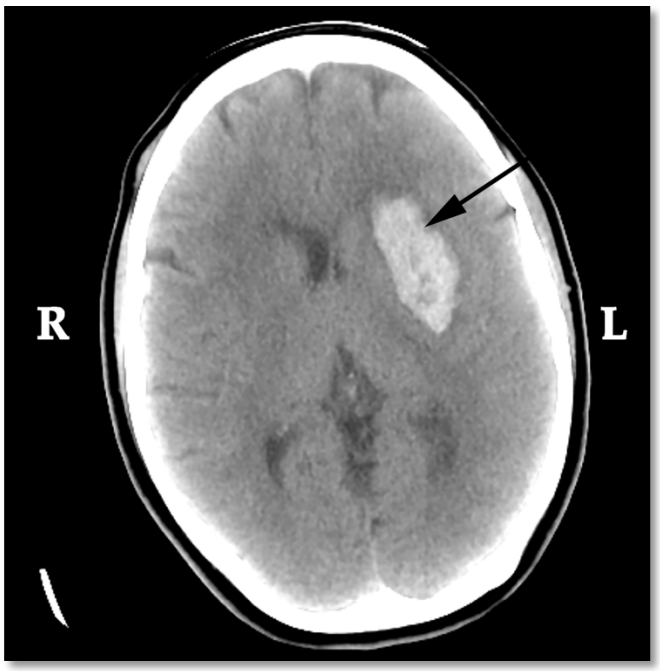

Figure 4. Stroke. Cerebral CT-SCAN showing a parenchymal hemorrhage (arrow) in the left capsule-ganglion that compresses the frontal horn of the lateral left ventricle.
R: Right side; L: Left side. The patient presented expressive aphasia, right arm flaccid paresis and fingers in reductible flexion, and frontal disinhibition. She was treated with GH, 0.8 mg/day, 5 days/week, during 9-months (every 3 months, 1-month resting without GH), and physiotherapy and speech therapy. Fourteen months after admission in our Medical Center she was discharged without sequels.

Traumatic brain injury

Due to its nature, TBI is lesser able to be treated with a local application of stem cells during the acute phase of the injury [89]. However, a number of preclinical studies indicate that administration of MSCs seem to be effective for brain repair after TBI in rats [90-104]. Despite these data, few studies have been done, until now, in human patients. In fact, when seeking for these studies on the website Clinicaltrials.gov, only five can be found. Three of them have been completed (one in children) and two are still recruiting patients (adult TBI Phase 2b).

In 2013, Tian et al. [105] reported the results of autologous bone marrow MSCs administration by lumbar puncture in 97 patients in the subacute stage of TBI. Interestingly, 24 of these patients were in persistent vegetative state and 11 of them showed significant improvements in consciousness after the treatment, while 27 of 73 patients with severe motor disorders also showed improvements in motor functions. They concluded that this kind of therapy is safe and effective, and also, as it seems to be logic, that young patients improved better than older ones. Another very important and also logical conclusion was that this therapy has to be applied early in the subacute stage of TBI for obtaining better results. More recently, an intravenous autologous bone marrow MSCs was shown to decrease the needs of intense treatment for decreasing intracranial pressure, the severity of brain injury and duration of neurointensive cares in children early receiving these stem cells after TBI [106]. These positive results have been postulated to be due to the effect of stem cells on the neuroinflammation that TBI produces. Another recent study in three patients suffering neurological sequelae after difusse axonal injury, showed that the intrathecal administration of autologous MSCs resulted in improvements of their neurological situation and a diffuse and progressive increase in the cerebral metabolism of glucose, as reflected by positron emission tomography (PET) [107]. Given that glucose is the main nutrient for neurons, this result clearly indicates that brain activity improved after the intrathecal administration of MSCs.

But, again, similar results occur when treating TBI with GH. We were the first to use this hormone (December 2002) at a very early stage of a TBI that produced diffusse axonal injury, traumatic subarachnoidal hemorrhage, multiple fronto-temporal and intraventricular bleeding and brainstem damage; fortunately, the patient had a very good recovery and eight months after his TBI produced by a car accident, he went back to his University studies and he reached the degree of European PhD and lives a fully normal life. We published it 11 years later (25, Case 1). Hence, GH might also be useful for treating TBI with stem cells transplants, helping these stem cells to survive, differentiate and release neurotrophic factors. Moreover, GHD is a common finding in TBI patients.

Myocardial infarction

In 1999 it was published, in rats, that autologous bone marrow cells transplanted into ventricular tissue damaged by an induced myocardial injury, produced 3 weeks before the stem cells transplant, induced angiogenesis and formed cardiac-like muscle cells improving myocardial function [108]. Since this pioneering study, many publications reported conflicting data about the potential of stem cells on regenerating contractile myocardial tissue after a myocardial infarction. However, in 2003 it was reported that in the human adult heart exists a subpopulation of replicating

myocytes (CSCs) able to act in normal hearts and pathological cardiac situations [109]. That is, as it occurs in the brain, the adult heart contains multipotent stem cells able to self-renewing, producing myocytes, smooth muscle, and endothelial cells. This opened a new therapeutic strategy for reduce the mortality of ischemic cardiomyopathy **(Figure 5)**.

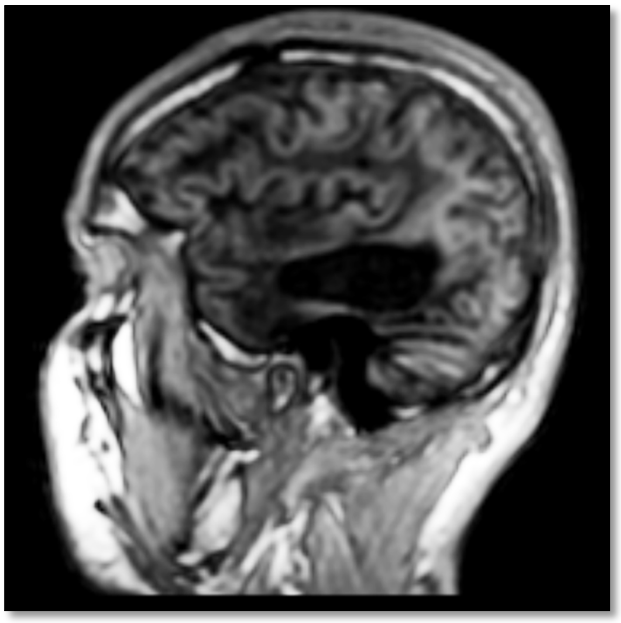

Figure 5. TBI. Cerebral MRI after difusse axonal injury occurred 8 years before. Chronic porencephaly area at the level of the right temporal lobe, with related enlargement of the temporal horn of the right lateral ventricle and signs of chronic break of the blood-brain barrier in practically the entire hemispheric area corresponding to the parieto-temporal region and right frontal. Lacunar infarction at the level of the right striated ganglion. This patient had been treated with an intra-arterial infussion of MSCs (1×10^6/kg) without reaching any significant improvement. At admission in our Center he presented an important loss of recent memory, cognitive deficits, dysarthria, and a complete loss of equilibrium. He was treated with GH, 1 mg/day, 5 days/week, in periods of 3 months each one followed by 1 month without the hormone and neurorehabilitation during 16 months. At discharge only the equilibrium remained affected, but he was able to walk with a walker.

However, three years later, the same group communicated that in response to different forms of stress, these CSCs acquire a senescent phenotype, thus losing their functional properties as reparative agents [110]. In order to avoid this problem, these authors proposed the search of mechanisms able to produce the activation of CSCs *in situ* and to clarify the mechanisms responsibles for the senescence to prevent or reverse its presentation [110].

CSCs have been successfully isolated from biopsies of human myocardium and expanded *ex vivo* without any lost of its potential for differentiating into cardiomyocytes and vascular cells [111], therefore allowing the autologous transplantation back into the heart mediating, together with the resident CSCs, myocardial regeneration to a significant degree.

These studies may explain the fact that intramyocardial injection of MSCs overexpressing the survival factor Akt may significantly repair infarcted myocardium in rats and improve cardiac function, as early as 3 days after the injection, despite that only a small number of MSCs differentiated into cardiomyocytes [112]. It seems to be clear that in addition of the survival role that Akt plays [113], cytokines and growth factors released by the impanted MSCs contribute to the results obtained in that study [112]. In addition, timing of intracoronary transplantation in acute myocardial infarction is another key factor for positive outcomes, as a recent meta-analysis of 34 randomized controlled trials shows [114]. Curiously, the ideal window of time for this therapy ranges from 3 to 7 days, rather than within 24 h after the acute myocardial infarction, as one would think. Another key factor for positive outcomes is the number of MSCs administered, no lesser than 10^8-10^9 [115].

Despite these promising previous studies, the current situation is still far from being clear. A number of preclinical and clinical studies have analyzed the potential of endothelial progenitor cells (EPCs) and CSCs for repairing cardiovascular diseases, but while some of these studies show improvements in left ventricular ejection fraction in patients with acute myocardial infarction, other results have been poor or no significant clinical benefit has been observed in many cases [116].

Another source of stem cells, possibly useful for being used after a cardiac infarction, is the adipose tissue surrounding the heart. From this tissue MSCs can be isolated, and when injected intramyocardially in postinfarcted mice and rats enhance myocardial vascularization, reduce the infarct size and express cardiac and endothelial markers [117]. However, these stem cells have not yet been tested in clinical studies [118].

GH plays a direct function on myocardial growth and heart functionality during the fetal development [119] and induces the expression of specific contractile proteins. The hormone also regulates cardiac metabolism, by increasing amino acid uptake, protein synthesis, the size of cardiomyocytes and the expression of specific genes, as well as reduces apoptosis of cardiomyocytes [120-126]. Due to the positive effects that GH exerts on heart, it may be hypothesized that GH treatment might be of utility in patients with heart failure, mainly in those GHDs. Moreover, the hormone increases VEGF expression and angiogenesis in the myocardium of rats after infarction [127,128]. Therefore, as in the other pathologies here analyzed, GH administration could be useful for enhancing the reparative strategies postulated to be used in transplanting stem cells in the heart to improve cardiac function after myocardial infarction [129].

These positive effects of the hormone on heart are not observed, just the contrary, in acromegalic patients, but in them, the hormone is released in high and sustained concentrations during years, a situation very different from the one we are suggesing.

In order to improve the survival and integration of administered stem cells in the damaged brain or heart, a number of *ex vivo* modifications of these cells (including gene therapies for enhancing the therapeutic effects of these cells or its specific delivery to a particular tissue) or implantable devices containing them, have been proposed [77,130-138].

As stated above, a number of references indicate that the administration of growth hormone (GH) might be of great utility when commencing a therapy with stem cells in any of the pathologies we analyzed.

The rationale of the use of GH together with stem cells administration comes not only for the already described actions of the hormone (for instance cells survival, and stem cells proliferation, differentiation and migration), but also from the fact that GH induces the expression of a number of factors with known neurotrophic and cardiac activity. For example, IGF-I, EGF, FGF, VEGF, BDNF, EPO, etc. [1]. In addition, it would not be necessary a long time GH administration, therefore avoiding the apparition of possible undesirable side-effects. Even more, GH could be administered early after the brain or cardiac injuries, before stem cells could be implanted.

With regard to stem cells administration, although it is not well established what would be the optimal window of time or the number of cells needed for that administration, it seems clear that the sooner they were administered and the higher the number the better the results would be. In this sense, we believe it would interesting to create a bank of adult stem cells in which, from a certain age, a certain person could store cryopreserved their own stem cells, so that if he/she later suffer a neurological or cardiac emergency their own cells would be available for a prompt administration, without needing to wait until these cells were harvested and proliferated. Harvesting would be not a problem, but reaching the needed amount of stem cells needed for the implant could represent a life-threatening time. This is schematized in **Figure 6.**

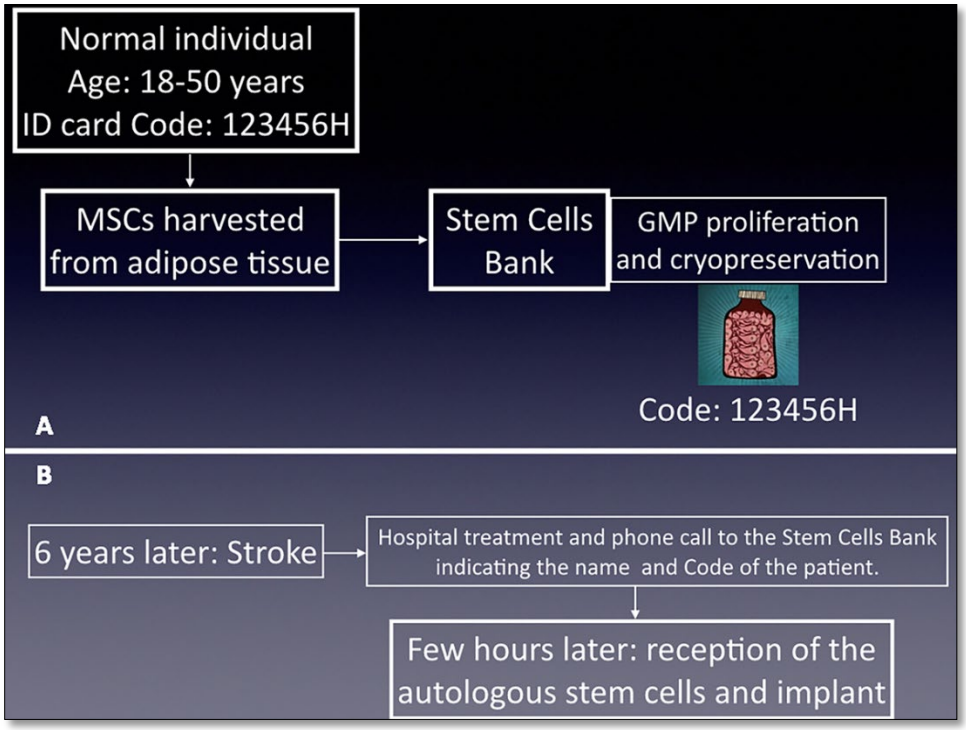

Figure 6. Individual stem cells bank. A: A normal subject decides at a any moment in his life to store his own MSCs for preventing any acute future situation in which treatment with stem cells could save his life or prevent important disabilities. MSCs are harvested from his adipose tissue and stored in a cell bank, with a code number. B) Six years later, for instance, this subject suffers a stroke. His health card indicates that there are MSCs from this patient stored in a Cell Bank under a specific code. A phone call from the Hospital where the patient is being treated allows the Cell Bank to send there in a few time the MSCs of te patient for being infussed.

Lastly, the best way for administration of stem cells seems to be intrathecally, for neurological injuries, whenever they do not increase brain inflammation and the immune response associated with stroke and TBI, although new neurosurgical techniques utilizing stereotaxy for intracerebral implants are

very promising. On the other hand, intra-arterial administration seems to be more effective than intravenous, since avoids microemboli formation and the loss of a large number of cells in lungs.

CONCLUSION

Stem cells implants from many different sources are a potential solution for several acquired neural and cardiac injuries. However, the time window for these implants achieve maximum restorative effectiveness is still under debate and dependent on the type and severity of existing damage, as it happens with the number of cells which need to be administered and the route of administration. The administration of GH, regardless of whether the patient is GH-deficient or not, can be an effective tool to make treatments with stem cells more efficient in these diseases.

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CONFLICT OF INTERESTS

The authors declare that no conflict of interests exists.

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