# TO STUDY THE STRUCTURE OF NEUROLOGICAL DISEASES IN POSTMENOPAUSAL WOMEN INFECTED WITH COVID-19

**(literature review)**

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**Abstract.**
According to current data, SARS-CoV-2 can affect any organ in the body, leading to acute injury and long-term chronic consequences. With the collection of data from clinical and laboratory studies, it is clear that the SARS-CoV-2 virus can cause both direct and indirect damage to the central nervous system. The literature review provides a current understanding of the prevalence and nature of neurological disease in patients with COVID-19 syndrome.

**Keywords.** SARS-CoV-2, COVID-19, nervous system, neuroimmunological condition.
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After the first reports of novel coronavirus disease (COVID-19) in China in late 2019, severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection quickly spread, causing a global pandemic.

With the accumulation of data from clinical and laboratory studies, it becomes obvious that the SARS-CoV-2 virus is able to induce both direct and indirect damage to the central nervous system (CNS). During the acute phase of infection, some patients experience neurological symptoms such as headache, dizziness, or cerebrovascular disease even in the absence of severe respiratory and inflammatory syndromes [3, 4]. The ability of the SARS-CoV-2 virus to infect cells of the nervous system carries potential risks of long-term neurological complications. “Post-COVID-19 syndrome”, or “chronic COVID”, a synonym for COVID 19 (hereinafter this term is used), characterized by impaired function not only of the lungs due to pulmonary interstitial fibrosis, but affecting all levels of the nervous system, can have a serious impact on the quality of life [5-7]. It has been suggested that neuronal damage caused by SARS-CoV-2 may also be the driving force behind chronic degenerative diseases of the nervous system [6]. Regardless of direct or indirect exposure to the virus, damage to the central and peripheral nervous system due to COVID-19 may become irreversible.

The spectrum, nature and impact of neurological complications of COVID-19 on the health of an individual and his quality of life are not yet well described and studied due to the relatively short observation period, the complex nature of the pathology and the small number of scientific studies with a high level of evidence on this problem. For the same reasons, measures for the treatment and prevention of delayed and late neurological disorders in people who have had COVID-19 have not been developed. Despite the fact that the mechanisms of the formation of these disorders have not been fully elucidated and the period of follow-up observation is relatively short, at the moment it is obvious that a population of

patients who have undergone COVID-19 with persistent neurological disorders is being formed. Symptoms of damage to the central nervous system and peripheral nerves persist for more than 12 weeks after recovery from a viral infection and negatively affect the quality of life and health status. This group of patients requires constant medical support by doctors of various specialties and medical and psychological rehabilitation, the measures of which have not yet been developed.

The use of adult-type stem cells (SCs), including hematopoietic stem cells (HSCs), is a relatively new, promising area of regenerative medicine that allows successful rehabilitation of patients with residual CNS lesions caused by vascular, traumatic, and infectious causes [8-10].

Due to the relatively short period since the onset of the pandemic, there are few studies in the literature evaluating late neurological impairment in patients with long COVID. And even fewer works are devoted to therapy and rehabilitation schemes for this contingent. Inclusion in rehabilitation programs of patients with long COVID and neurological manifestations of therapy using autologous HSCs can potentially be considered as an attractive option and has a theoretical and practical justification.

The purpose of the review: to describe the pathophysiological mechanisms of CNS damage in COVID-19; to determine the frequency and nature of neurological disorders in patients with long COVID syndrome, as well as their impact on morbidity and quality of life; to evaluate the potential of cell therapy using adult-type hematopoietic CD34+ cells for the treatment of such patients. The search for potentially relevant articles was carried out in the databases MEDLINE / PubMed, Web of Science, Scopus and RSCI.

**Pathophysiological mechanisms of damage to the central nervous system in covid-19**

Initially, it was believed that SARS-CoV-2 could not cross the blood-brain barrier (BBB), but post-mortem studies of the cerebral pathology of patients with COVID-19 using a three-dimensional microfluidic model of the human BBB forced a reconsideration of this point of view [11]. First, the SARS-CoV-2 spike (S) protein binding receptor, angiotensin-converting enzyme-2, is widely expressed on endothelial cells of brain microvessels. Second, the S protein can directly damage the integrity of the BBB to some extent. Thirdly, the S protein can cause an inflammatory response of endothelial cells in the microvasculature, which changes the function of the BBB [12, 13]. These data confirm that SARS-CoV-2 can disrupt the BBB and penetrate the brain, and also contribute to the appearance of neurological symptoms, the formation of fatal microthrombi, and even the onset of encephalitis associated with COVID-19 [2, 11]. In addition, to cross the BBB, SARS-CoV-2 can enter the brain via transsynaptic transport, optic and olfactory nerve canals, and vascular endothelial cells [11-14]. There is also evidence that SARS-CoV-2 can use cells of the immune system (macrophages) to spread throughout the body and penetrate the BBB, the so-called “Trojan horse” mechanism [15].



Not the last role in both acute and delayed damage to the nervous system is played by the massive systemic inflammation syndrome caused by the virus and the specific damage to mitochondria. A systemic increase in inflammatory mediators such as interleukin 6 (IL-6, interleukin-6), IL-12, IL-15, and tumor necrosis factor alpha, referred to as “cytokine storm,” may explain the multi-organ damage found in some COVID patients -19, as well as the effect of SARS-CoV-2 on the central nervous system. The release of a large amount of pro-inflammatory cytokines increases vascular permeability in the CNS and causes a violation of blood clotting with the formation of microthrombi, facilitating the penetration of SARS-CoV-2 through the BBB into the brain [11, 16]. FLAIR (Fluid attenuation inversion recovery) magnetic resonance imaging of the brain in COVID-19 patients with neurological damage showed changes in the medial temporal lobe, multifocal lesions in white substance of the brain and microhemorrhage [17].

SARS-CoV-2 infection leads to organ damage at the cellular level in several ways. The SARS-CoV-2 RNA genome and all subgenomic RNAs integrate into the host's mitochondrial matrix, which causes viral-mitochondrial interaction leading to virus replication and SARS-CoV-2 RNA transcripts in cell mitochondria. Ultimately, infected cells, including neurons, may undergo

necrosis, apoptosis, or dysfunction due to oxidative stress and influx of calcium ions against the background of impaired mitochondrial function [18]. Rapid viral replication, direct cell damage, and activation of the immune system and inflammatory mediators, including cytokines, are likely causes of acute symptoms of COVID-19 and may explain the long-term effects of SARS-CoV-2 infection, including on all parts of the nervous system.

Iatrogenic factors undoubtedly play a role in the pathogenesis of late neurological complications. Long-term use of steroids in high doses, various vascular drugs, monoclonal antibodies aimed at various parts of the inflammatory cascade, long-term respiratory support are factors that actively affect blood flow in the brain and spinal cord and directly or indirectly affect the metabolism of nerve cells. . The observed trend towards an increase in the frequency and severity of neurological complications in cases of severe COVID-19 infection and in elderly patients testifies in favor of this assumption.

**Neurological complications associated with covid-19**

The frequency of neurological complications of SARS-CoV-2 is currently unknown, but there is a trend that patients with severe COVID-19 have neurological symptoms more often than patients with mild COVID-19 [19].

Headache, myalgia, dizziness, and fatigue are the most commonly reported non-specific symptoms of long COVID. In a retrospective study of 214 patients admitted with COVID-19 to a Wuhan hospital, 36.4% had some kind of neurological manifestation. In 24.8% of cases it was an isolated CNS lesion, in 21.4% peripheral nerves were affected, in other cases it was a combined lesion, including autonomic dysfunction. The most common neurological symptoms were dizziness (17%), headache (13%), impaired taste and smell (8%). Neurological symptoms were more common in patients with severe COVID-19: 45.5% versus 30% with mild [20].

Headache is the most common symptom in patients with COVID-19. In a retrospective study by W.J. Guan et al. [21], which included more than 1000 patients with COVID-19, 139 (13.6%) had headache, of which 15% of cases had headache resistant to therapy.

Anosmia and dysgeusia are very common in patients with COVID-19, even in the absence of catarrhal symptoms, and may appear suddenly [22]. The prevalence of olfactory and gustatory dysfunction was analyzed in a case register from 12 European hospitals. A total of 417 patients with mild to moderate COVID-19 completed the study. Smell and taste disorders were noted by 85.6% and 88% of patients, respectively, and olfactory dysfunction was the initial symptom in 12%. 18% of patients did not have rhinorrhea or nasal congestion, but in this subgroup, 80% had anosmia or hyposmia [23]. Dysgeusia and anosmia in 10% of patients may persist for 6 months or more after the disappearance of other symptoms [4].



Encephalopathy is another syndrome that can develop with COVID-19. The risk of changes in the mental state is higher in elderly patients, in the presence of: a history of cognitive impairment, risk factors (hypertension, diabetes mellitus in the stage of sub- or decompensation), concomitant diseases [18, 19]. Patients with prior neurological involvement are at increased risk of encephalopathy as an initial symptom of COVID-19. In a study by L. Mao et al. [20] 15% of patients with severe COVID-19 had an altered level of consciousness, in contrast to 2.4% with mild and moderate forms of the disease. Encephalopathy associated with COVID-19 can be caused by toxic and metabolic causes, as well as the effects of hypoxia or drugs used to treat coronavirus infection.

In the acute period of coronavirus infection, isolated cases of the development of encephalitis, hemorrhagic strokes, necrotic encephalopathies and demyelinating syndromes of the Guillain-Barré type are described. Early differential diagnosis is essential to ensure an appropriate treatment strategy as these symptoms may also occur in patients with COVID-19 with severe hypoxia due to lung injury. At least two cases of coronavirus encephalitis have been published [20, 21].

Elderly patients with vascular risk factors are at higher risk of developing cerebrovascular complications during COVID-19 infection than younger people without comorbidities. In a retrospective study including 221 patients with COVID-19, 11 (5%) were diagnosed with

ischemic stroke; in 1 (0.5%) - thrombosis of the venous sinus of the brain and in 1 (0.5%) - hemorrhage in the brain. Risk factors for stroke were: advanced age (mean age 71.6 years), severe COVID-19, a history of hypertension, diabetes, or cerebrovascular disease, or a pronounced inflammatory and procoagulant response (increased C-reactive protein and D-dimer, respectively) [1]. In the series given by L. Mao et al. [20], described five patients with stroke (in 4 cases, ischemic), who, against the background of a severe course of COVID-19, had an increase in the level of D-dimer, thrombocytopenia, and multiple organ failure. The proposed mechanism of the pathogenesis of stroke in COVID-19 is the fact that the SARS-CoV-2 virus binds to angiotensin-converting enzyme-2 receptors on endothelial cells, causing an increase in blood pressure [23], which, along with the presence of thrombocytopenia and disorders blood clotting is a factor that can contribute to an increased risk of both ischemic and hemorrhagic stroke. Simultaneously, the "cytokine storm" syndrome may be another additional risk factor for the development of cerebrovascular diseases.

There is no single definition of the term “long COVID”, or long COVID [24]. Most authors refer to "persistent COVID-19 syndrome" (subacute/ongoing COVID-19) if symptoms or sequelae persist between 4 and 12 weeks, and the term "chronic COVID-19", or "post-COVID - syndrome", is used in relation to symptoms without an alternative explanation, present after 12 or more weeks from the onset of the disease [5, 4]. Due to the peculiarities of the financing of the health care system in a number of Western countries, patient associations prefer to use the term "long-term COVID-19", or, for native English speakers, long COVID, fearing that the terms "post-", "chronic ” or “syndrome” can negatively affect the process of providing care to patients in this group [5].

Various pathological symptoms persist in 20% of patients after 5 weeks and in more than 10% of patients after 3 months after the initial manifestations of COVID-19 [6]. A study conducted in the Netherlands, involving mainly outpatients with a mild course of infection, showed a high incidence of various symptoms, including neurological, after 3 months and a significant deterioration in the state of health according to the subjective assessments of patients. Only 7.2% considered themselves healthy after 3 months (compared to 85% before infection), while 28.6% considered themselves unwell (compared to 0.6% before SARS-CoV infection). -2) [7].

A prospective study based on the observation of 4182 outpatients revealed the presence of symptoms in 13.3% of patients after 4 weeks, in 4.5% after 8 weeks and in 2.3% after 12 or more weeks after COVID-19 [8]. Long COVID was manifested by fatigue, headache, shortness of breath and anosmia. It has been found to be more common in women, the elderly, and those with a high body mass index.

A Swedish study based on a regular screening analysis of 323 SARS-CoV-2 seropositive healthcare workers found at least one moderate or severe symptom in 15% of cases over 8 months compared to 1072 seronegative employees. Neurological symptoms, including anosmia and fatigue, were observed in 9 and 4% versus 0.1 and 1.5%, respectively ($p < 0.05$ in both cases) [9].



Clinical symptoms associated with long COVID can occur even in people who have had mild or asymptomatic SARS-CoV-2. These symptoms are usually polymorphic and associated with CNS involvement. At the same time, the authors note their dynamic development over several weeks or months [26]. Survivors of COVID-19 may experience a range of psychiatric symptoms that persist or appear several months after initial infection. In a cohort of 402 people, 4-6 weeks after the onset of COVID-19, 56% of cases had at least one of the mental disorders (post-traumatic stress disorder, depression, anxiety, insomnia, and obsessive-compulsive symptoms) [ 2]. Anxiety, depression and sleep disturbances were present in about a quarter of patients after 6 months of follow-up in a study published by Chinese scientists [13]. Some of the long-term symptoms reported in the papers were absent in the acute phase of the infection [3]. The most common symptoms are severe fatigue with discomfort after exercise, cognitive impairment (decreased concentration of attention, memory, lack of words), sensory (tinnitus, dizziness), headache, shortness of breath, cough, pain and chest tightness, palpitations, smell and taste disturbance,

odynophagia, sweating, muscle-tendon pain, paresthesia ("burning sensation"), digestive disorders (anorexia, abdominal pain, dyspepsia, diarrhea), skin manifestations (itching, urticaria ), hair loss, sleep disturbances, irritability, anxiety and depression. Fibromyalgia syndrome is often observed, which is also referred to as long COVID [3].

A large-scale analysis of data from 62,354 SARS-CoV-2 survivors from 54 healthcare organizations in the United States showed an 18.1% incidence of primary or recurrent psychiatric illness at 2 to 13 weeks. from being diagnosed with COVID-19. The overall probability of being diagnosed with a new mental illness among 44,759 patients with no known mental illness within 13 weeks or more of being diagnosed with COVID-19 was 5.8% (anxiety disorder, 4.7%; mood disorder, 2%; insomnia - 1.9%). All these indicators were significantly higher than in comparable control groups of patients who did not have COVID-19, but were diagnosed with influenza or other respiratory tract infections [14].

Thus, neurological and psycho-neurological symptoms that persist in people who have had a SARS-CoV-2 infection lead to a decrease in the quality of life, reduce working capacity, can potentially negatively affect disability indicators, and necessitate frequent treatment for medical help. All this poses a serious challenge to modern healthcare and sets the neurological rehabilitation of patients with long COVID as an urgent task.

**Cell therapy in the rehabilitation of patients with diseases of the central nervous system**

In recent years, the inclusion of SC in the rehabilitation programs for patients with various injuries and diseases of the central nervous system has gradually turned into a new, promising area of research. SCs are cells that have the ability to proliferate and self-renew under certain conditions and differentiate into many other functional cells, including neuroglia, endotheliocytes, and neurons themselves [15]. Currently, more and more animal experiments and clinical trials show that the use of SCs for the treatment of CNS diseases can have a positive therapeutic effect and accelerate the restoration of nervous system function [10].

The pathophysiological mechanisms involved in damage to CNS cells are universal, regardless of the damaging agent. Differences are noted only in the first phase of the impact on neurons, cells of the microenvironment and adjacent vessels, that is, in the early phase of the pathological process, where the direct damaging factor can play the main role. The late phase is based on inflammatory reactions, tissue hypoxia and apoptosis of nerve cells. This long-term inflammatory process leads to significant neurotoxicity, myelin degradation and glial scarring, as well as the release of a variety of neuroinflammatory mediators, including cytokines (tumor necrosis factor alpha, IL-1b, IL-6, IL-20), chemokines ( monocytic chemotactic factor - MCP-1), cell adhesion molecules (immunoglobulins, cadherins, integrins), reactive oxygen species and matrix metalloproteases [8, 11].

Recent studies have shown that therapy for CNS damage based on the use of adult-type pluripotent stem cells from the bone marrow, including CD34+, can be highly effective in residual damage resulting from vascular and traumatic incidents. Against the background of SC use, damaged nerve cells and surrounding tissues, including neurons and glial cells, can be restored, which helps to ensure the integrity of the nerve conduction pathway and thus restore nerve function [10, 17]. At the same time, SCs interact with surrounding tissues, releasing various neurotrophic factors into the intercellular space, changing the microenvironment of the damaged area and accelerating the growth of axons, while intercalary neurons that differentiate under the influence of transplanted SCs can cause the growth of axons with the formation of new synapses [18]. SA therapy can suppress genes involved in inflammation and apoptosis, as well as activate genes with a neuroprotective effect, thereby protecting spinal neurons from secondary damage [8]. Some SCs injected into the injury site can differentiate into glial cells and promote myelination and functional recovery in patients with spinal cord injury and strokes [9].

In recent years, more and more studies have begun to focus on the use of autologous CD133+, CD34+ HSCs, which have a number of advantages over donor cells in the treatment of CNS diseases and injuries [10-12]. L.L. Xiong et

al. [3] administered HSC to rats after modeling spinal cord injury and found that it promoted neurological recovery through the formation of 5-HT-positive fibers and oligodendrocytes in the spinal cord, inhibition of astrocyte hyperplasia, and increased expression of mitogen-activated my protein kinase 1 (MEK-1 mitogen-activated kinase - 1), mediated by neurotrophin-3 (NT-3, Neurotrophin-3).

A group of Japanese scientists led by H. Yoshihara [4] presented data on the treatment of chronic CNS damage in rats by triple administration of CD34+ HSC bypassing the BBB. There was a sprouting of axons through areas devoid of astrocytes, and a decrease in the formation of cystic cavities. Bone marrow mononuclear cells were isolated by density gradient centrifugation and used without cultivation for transplantation into rats with chronic spinal cord injury.

The first phase I trials of autologous bone marrow HSC cells demonstrated that they can be safely administered to stroke patients through a variety of routes, including directly into the CNS. A group of Spanish researchers S. Suarez-Monteagudo et al. [5] implanted (1.4-5.5)x106 cells of the mononuclear fraction from the bone marrow by stereotaxic injection into the lesion in five patients with stroke in the late phase. This study showed that intracerebral transplantation of autologous HSCs is well tolerated and safe. Three out of five patients showed long-term (more than 6 months) improvement in neuropsychiatric status.

With intra-arterial or intravenous administration of autologous mononuclear cells containing stem cells in the acute and subacute phases of ischemic stroke, the safety of these routes of administration has also been demonstrated. However, with the intravascular route of administration, a significantly larger dose of cells (50-600 * 106 mononuclear cells) is used than with direct injection into the central nervous system (intracerebral, intrathecal or intraventricular injections), which is a limiting factor for outpatient obtaining material from patients, as a rule, requires their short-term hospitalization and significantly increases the risks of side effects and the cost of treatment [7]. At the same time, as was later shown, the biodistribution of intraarterially and intravenously transplanted autologous mononuclear cells obtained from the bone marrow is comparable to the introduction of a significantly smaller number of them directly to the lesion in the CNS [8].

A phase II randomized trial including 120 patients with acute stroke (first 7-30 days), where autologous bone marrow cells were administered intravenously, did not show clinical benefits compared with the placebo group [19]. On the contrary, with the intrathecal route of HSC administration at the rate of 1 * 106 bone marrow mononuclear cells per 1 kg of patient weight, 24 patients in the late phase of ischemic stroke showed an improvement in neurological symptoms. However, this study did not include a comparison group [10].



In another phase I/IIa study, the degree of recovery of neurological functions was shown to depend on the dose of intravenously injected cells [11]. A study by M. Barish additionally found that the improvement in neurological symptoms with the use of cell therapy with autologous SCs may be associated with paracrine effects due to the secretion of vascular endothelial growth factor (VEGF) and brain-derived neurotrophic factor (BDNF). , brain-derived neurotrophic factor) [12].

The introduction into practice of such a parameter as the number of CD34+ cells in the injected material made it possible to characterize stem cells more clearly and approach the standardization of the technique. The amount of SC administered is an important aspect influencing the therapeutic effect of cell preparations. In most studies on the treatment of traumatic and vascular injuries of the central nervous system, the dose varies significantly from 104 to 108 depending on the type of cells, the method of administration, the time of administration from the moment of the incident, and other factors. Published works on laboratory animals devoted to rehabilitation using cell preparations determine the minimum effective dose of target cells in the composition of a cell preparation as (1-5) * 105 per 1 injection (when administered directly into the CNS - intraventricular, intrathecal , directly around or at the site of damage during surgical treatment), noting a positive correlation with clinical effects as the dose of target cells increases. However, the optimal dose of

autologous HSCs used in the course of cell therapy for lesions of the nervous system has not yet been determined [13].

The average dose of HSC CD34+ in clinical studies, administered to a patient once directly into the CNS, ranges from 5 * 105 to (1-10) * 106 per 1 administration [10]. In the study by M. Zakerinia et al. [15] published in 2018, 80 patients with various neurological diseases received intrathecal transplantation of autologous SCs once. Bone marrow-derived mononuclear cells were separated on a ficol-hypac density gradient, washed and suspended in saline in order to enrich the input material. The relative content of HSCs was assessed by the number of CD34 + CD38 cells during flow cytometry. The introduction was carried out 3-4 hours after bone marrow sampling at an average dose of 5.6 * 106 CD34+. Clinical improvement of neurological functions was noted in 9 (75%) of 12 patients with Parkinson's disease, in 20 (71%) of 28 patients with cerebral palsy, in 6 (86%) of 7 patients with hypoxic brain damage, in 2 of 4 patients with multiple sclerosis, 4 of 5 patients with cerebellar atrophy, and 7 of 9 patients with other acquired non-hereditary neurological diseases. Positive dynamics was noted after 2-4 weeks from the beginning of cell therapy and in 90% reached its maximum in the period of 8-12 weeks. Overall, clinical improvement was observed in 60% of patients. There were no changes in the neurological status of patients with spinal cord injury accompanied by complete transverse injury, as well as in patients with autism and amyotrophic lateral sclerosis. Side effects of therapy were limited to mild transient headaches and vomiting in a few patients [15].

The standardization of the administered cell preparation seems to be all the more important, since not only bone marrow HSCs, but also HSCs obtained from peripheral blood have recently begun to be actively used. Obtaining HSCs from peripheral blood has several advantages. Firstly, it does not require the presence of an operating room and general or local anesthesia for the patient. Secondly, it can be performed in almost all neurological patients and has no contraindications. Thirdly, it can be carried out repeatedly and meet the patient's need for long-term restorative cell therapy. At the same time, HSCs carrying the CD34+ marker on their surface, obtained from peripheral blood, do not differ in their biological and immunological properties from those from bone marrow cells. After demonstrating the efficacy of blood SC transplantation in the treatment of chronic cerebral ischemia in rats, data on the safety and efficacy of using HSC CD34+ from peripheral blood were confirmed in a phase II study [16]. A group of Chinese scientists stereotactically transplanted mobilized with the help of granulocyte colony-stimulating factor autologous, selected HSC CD34+ at a dose of (3-8)x$10^6$ into 15 patients with stroke in the chronic phase by a group of Chinese scientists. The authors noted an improvement in neurological and functional parameters in patients in the treated group [17].



In general, the results of using HSCs obtained from the bone marrow or peripheral blood did not differ from those when using mesenchymal cells [18]. At the same time, in the chronic phase with vascular injuries (strokes) and traumatic injuries of the brain/spinal cord, the cellular mechanisms involved in secondary damage to neurons, axons, and microglia do not differ, as well as the mechanisms of repair of damaged tissues. CD34+ HSCs derived from peripheral blood or bone marrow have a number of advantages. First, they penetrate the BBB and migrate to the lesions in the brain tissues, which is especially important when they are administered intravenously. Secondly, their ability to neuronal differentiation has been shown. Thirdly, these cells can be obtained relatively easily, in real time and in practically unlimited quantities, from the patient himself, both for administration in a native form and for cultivation. Fourth, a sufficient amount of information has been accumulated on their therapeutic efficacy both in the case of the acute phase of CNS damage and in the treatment of traumatic or ischemic diseases of the brain and/or spinal cord at the late stages [11].

Autologous HSCs obtained from the patient himself do not cause immunological conflicts and, accordingly, do not require immunosuppressive therapy, unlike donor (allogeneic) and xenogenic cells. Thus, the patient does not experience disturbances in the

natural mechanisms of anti-infective and anti-tumor control.

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