UDC/УДК 615.035:615.038:615.012.8
https://doi.org/10.30895/2221-996X-2025-25-3-343-356

Review | Обзор

Mesenchymal stromal cell-derived exosomes for acute respiratory distress syndrome treatment: A review of preclinical and clinical trials

Albina I. Kuralesova, Alla G. Grosheva, Elena N. Genkina, Ilias B. Esmagambetov✉

National Research Center for Epidemiology and Microbiology named after the honorary academician N.F. Gamaleya, 18 Gamaleya St., Moscow 123098, Russian Federation

✉ *Ilias B. Esmagambetov; esmagambetov@gamaleya.org*

ABSTRACT

INTRODUCTION. During the COVID-19 pandemic, acute respiratory distress syndrome (ARDS) was diagnosed in 15–33% of patients hospitalised for pulmonary diseases. Hospital mortality rates increased. The existing medicinal products lacked effectiveness. Thus unconventional treatment methods were needed, such as mesenchymal stromal cell (MSC) therapy. The risk of blood clotting in the lung vessels after MSC injection made exosomes from MSC secretome a therapy of choice. Exosomes cross the blood-brain barrier and have regenerative effect similar to that of MSC. The promising results of preclinical trials for exosome-based therapeutics have stimulated their clinical use. Analysing MSC safety and effectiveness will allow us to develop protocols for their production, storage, and transportation, as well as optimal dose regimens for cell-free therapy of ARDS and other pulmonary diseases.

AIM. This study aimed to analyse performed preclinical and clinical studies on safety and effectiveness of MSC-derived exosome therapeutics intended for cell-free ARDS therapy and other pulmonary diseases as an alternative to drug therapy.

DISCUSSION. Exosomes, the most important secretome compound in various cells, carry out horizontal transfer of genetic information and bioactive molecules. Animal models show that exosomes obtained from MSC secretome have regenerative abilities similar to MSC and offer various advantages: small size that prevents blood clotting in the pulmonary capillaries; ability to penetrate blood-brain barrier, non-teratogenicity, and exchange of epigenomic information in cell-cell interactions. Preclinical *in vivo* studies show that exosomes affect regeneration of damaged lung tissue in ARDS and other lung diseases. Clinical trials have confirmed safety and effectiveness of inhalation, intravenous or combined administration. Drug effectiveness can be increased by combining exosomes with MSC or enriching them with CD24 (key molecule of innate immunity). Due to regenerative, immunomodulatory properties of exosomes, their ability to reduce the level of cytokine storm and apoptosis, they are used to treat ARDS and other lung diseases. Exosomes reverse ARDS and other diseases due to their regenerative and immunomodulatory effect, and ability to reduce cytokine storm and apoptosis. Thus, exosomes are recognised as a new effective cell-free therapy.

CONCLUSIONS. Therapeutic effect of exosome-based preparations was analysed in experimental, preclinical, and clinical trials; however, further trials are warranted to determine ARDS safety and optimal treatment regimens.

Keywords: ARDS; acute respiratory distress syndrome; MSCs; mesenchymal stem cells; exosomes; exosomal therapy; vesicles; preclinical trials; clinical trials; regeneration; innate immunity; COVID-19; secretome

For citation: Kuralesova A.I., Grosheva A.G., Genkina E.N., Esmagambetov I.B. Mesenchymal stromal cell-derived exosomes for acute respiratory distress syndrome treatment: A review of preclinical and clinical trials. *Biological Products. Prevention, Diagnosis, Treatment*. 2025;25(3):343–356. https://doi.org/10.30895/2221-996X-2025-25-3-343-356

Funding. The study was carried out as a part of the State Assignment of the Federal State Budgetary Institution National Research Centre for Epidemiology and Microbiology named after the honorary academician N.F. Gamaleya of the Ministry of Health of the Russian Federation "Development of a technological platform based on exosomes produced by human bone marrow mesenchymal stem cells to obtain therapeutics for the treatment of acute respiratory distress syndrome", registration No. 1023022100011-3.
Disclosure. The authors declare no conflict of interest.

Экзосомы, продуцируемые мезенхимальными стромальными клетками, для терапии острого респираторного дистресс-синдрома: обзор доклинических и клинических исследований

А.И. Куралесова, А.Г. Грошева, Е.Н. Генкина, И.Б. Есмагамбетов✉

Федеральное государственное бюджетное учреждение «Национальный исследовательский центр эпидемиологии и микробиологии имени почетного академика Н.Ф. Гамалеи» Министерства здравоохранения Российской Федерации, ул. Гамалеи, д. 18, Москва, 123098, Российская Федерация

✉ *Есмагамбетов Ильяс Булатович; esmagambetov@gamaleya.org*

РЕЗЮМЕ

ВВЕДЕНИЕ. В период пандемии COVID-19 диагноз острый респираторный дистресс-синдром (ОРДС) констатировали у 15–33% пациентов, госпитализированных с заболеваниями легких. Вследствие возросших показателей больничной летальности и недостаточной эффективности существовавших на тот момент лекарственных средств, возникла необходимость применения терапии мезенхимальными стромальными клетками (МСК). Содержащиеся в секретоме МСК экзосомы обладают регенеративной активностью, как и МСК, причем введение последних может быть сопряжено с риском тромбообразования. Обнадеживающие результаты доклинических испытаний препаратов на основе экзосом обусловливают их клиническое применение. Анализ актуальных данных по безопасности и эффективности инновационных препаратов на основе экзосом позволит выработать протоколы получения, хранения, транспортировки, а также оптимальные схемы применения препаратов для бесклеточной терапии ОРДС и других заболеваний легких.

ЦЕЛЬ. Анализ результатов доклинических и клинических исследований безопасности и эффективности препаратов на основе экзосом, продуцируемых МСК и предназначенных для бесклеточной терапии ОРДС и других заболеваний легких в качестве альтернативы медикаментозному лечению.

ОБСУЖДЕНИЕ. Экзосомы, важнейший компонент секретомов различных клеток, осуществляют горизонтальный перенос генетической информации и биологически активных молекул. В доклинических испытаниях установлено, что полученные из секретома МСК экзосомы обладают выраженными регенеративными свойствами, схожими с МСК, и имеют ряд преимуществ: малые размеры, исключающие тромбообразование в легочных капиллярах; проникновение через гематоэнцефалический барьер; отсутствие тератогенности; обеспечение обмена эпигеномной информацией при межклеточных взаимодействиях. Введение препаратов на основе экзосом способствует регенерации поврежденной легочной ткани при ОРДС и других заболеваниях легких. Клинические исследования подтвердили безопасность и эффективность препаратов при ингаляционном, внутривенном или сочетанном введении. Эффективность препаратов может быть повышена

при совместном применении экзосом с МСК или при использовании экзосом, обогащенных гликопротеином CD24 (ключевая молекула врожденного иммунитета). Препараты на основе экзосом купируют ОРДС и другие заболевания легких благодаря своей регенеративной и иммуномодулирующей активности, а также способности снижать уровень «цитокинового шторма» и апоптоза и рассматриваются как перспективная бесклеточная (cells free) терапевтическая стратегия в лечении ОРДС.

ЗАКЛЮЧЕНИЕ. Проведенный анализ данных доклинических и клинических исследований свидетельствует о высокой эффективности терапевтического действия препаратов на основе экзосом, однако целесообразны дальнейшие исследования безопасности препаратов и определения оптимальных схем лечения ОРДС.

Ключевые слова: ОРДС; острый респираторный дистресс-синдром; МСК; мезенхимальные стромальные клетки; экзосомы; экзосомальная терапия; везикулы; доклинические исследования; клинические исследования; регенерация; врожденный иммунитет; COVID-19; секретом

Для цитирования: Куралесова А.И., Грошева А.Г., Генкина Е.Н., Есмагамбетов И.Б. Экзосомы, продуцируемые мезенхимальными стромальными клетками, для терапии острого респираторного дистресс-синдрома: обзор доклинических и клинических исследований. *БИОпрепараты. Профилактика, диагностика, лечение*. 2025;25(3):343–356. https://doi.org/10.30895/2221-996X-2025-25-3-343-356

Финансирование. Работа выполнена в рамках государственного задания ФГБУ «НИЦЭМ им. Н.Ф. Гамалеи» Минздрава России «Разработка технологической платформы на основе экзосом, продуцируемых костно-мозговыми мезенхимальными стволовыми клетками человека, для создания средств терапии острого респираторного дистресс-синдрома», регистрационный номер 1023022100011-3.

Потенциальный конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

INTRODUCTION

Currently, research of acute respiratory distress syndrome (ARDS) treatment strategies is gaining relevance; the condition develops due to various causes (bacterial or viral pneumonia, sepsis, chest injuries, gas poisoning, etc.) [1]. ARDS is an alveolar inflammatory pulmonary disease associated with a damaging factor and showing increased alveolar-capillary membrane permeability. This causes non-cardiogenic pulmonary oedema and decreases the number of ventilated alveoli due to lack of surfactant [2, 3]. Progressing inflammation is followed by an immune response resembling cytokine storm, with the release of pro-inflammatory cytokines and biologically active substances that affect vascular walls and effector cells. This results in alveolar and endothelial cell damage, the emergence of autoreactive plasma cell clones that destroy epithelial cells, and exudative inflammation, thus increasing mortality [4]. During a cytokine storm, ARDS rapidly peaks, causing disruption of cell-mediated cytotoxicity. ARDS responds poorly to non-specific treatment. Clinical settings often focus on preventing non-cardiogenic oedema, various ventilation methods, oxygenation to reduce hypoxia, and other methods targeting multifunctional insufficiency.

Xu *et al*. highlighted that variability of therapeutic outcomes in clinical settings is due to the existence of two ARDS types: primary (pulmonary) and secondary (extrapulmonary), with the latter further divided into two subtypes. ARDS classification into groups and subgroups is based on clinical, biological, radiological, and genetic criteria and is essential for phenotyping ARDS and selecting an effective patient treatment strategy [5]. To date, specific pharmacological agents (hormones, antibiotics, surfactants) lack effectiveness and do not provide full lung recovery.

According to Rosstat[1], Russia experienced increased primary incidence of bronchial asthma and chronic obstructive pulmonary disease (COPD) in 2010–2019. Since late 2019, ARDS has been diagnosed in 15–33% of patients hospitalised for COVID-19, thus increasing the social and economic burden on intensive care units. ARDS destructive impact on the body is comparable to that of malignant tumours, AIDS, or extensive myocardial infarction [6, 7]. Attempts were made to use convalescent plasma and specific antibodies for therapeutic purposes [8]. COVID-globulin was a certain success. Research results indicate that “COVID-globulin at a dose of 1 mL/kg alongside conventional therapy is more effective than placebo with conventional therapy in patients with moderate COVID-19” [9]; “administration of COVID-globulin is recommended at a dose of 1 mL/kg, ‘the earlier, the better’, but not later than on Day 7 of illness, and is contraindicated in patients with cytokine storm manifesting itself before Day 7” [9].

Cell-based therapy became a new successful treatment of diseases resistant to conventional pharmacotherapy. Mesenchymal stromal stem cells (MSCs)

[1] https://rosstat.gov.ru/statistic

found in bone marrow [10], adipose tissue, and other tissues [11], methods developed for obtaining diploid strains of these pluripotent cells [12], and the study of their differentiation potential [13] made it possible to recover damaged tissues using MSCs [14]. Due to positive preclinical results, cell therapy was translated into clinical practice. MSC-based methods were developed for treating musculoskeletal disorders (osteoporosis) [15], allergies [16], neurological conditions (Parkinson's disease) [17], cancers (invasive bladder cancer) [18], and other diseases [19]. NestCell® was developed for patients with severe pneumonia caused by COVID-19[2] [20].

Previous animal experiments [21, 22] and clinical studies [23–25] demonstrated that MSCs and MSC-conditioned medium[3] significantly reduced inflammation and associated pathological changes caused by COVID-19 and other infectious lung diseases. Following MSC administration, lung tissue recovers through stem cell transdifferentiation and paracrine/hormonal effects stimulating anti-inflammatory cytokine production, the latter being the dominant mechanism [20, 26].

MSC-based therapy has some significant limitations: low product stability, risk of pulmonary embolism, and tumorigenicity, among others [27, 28]. Exosomes derived from MSCs were found to have the same anti-inflammatory and regenerative properties as the cells [29]. Exosomes stand out due to their histocompatibility, low immunogenicity and oncogenicity, convenient storage, and high stability. Exosomes provide targeted delivery of drugs to the recipient cells. The discovery of exosomes derived from MSC-conditioned secretome medium represents a promising therapeutic approach for numerous severe diseases, including ARDS, allowing the use of exosomes instead of MSCs [30, 31]. Exosomes are 50–100 nm nanoparticles found in all cells, tissues, and body fluids, covered with a lipid bilayer membrane with associated cell adhesion molecules. Exosomes offer several advantages over MSCs that enhance therapeutic safety and effectiveness: small size; low immunogenicity; pronounced regenerative properties; absence of tumorigenicity; ability to cross the blood–brain barrier; and low thrombotic risk for pulmonary capillaries. Exosomes mediate epigenetic information exchange during intercellular interactions. Their therapeutic action is mediated by transfer of mRNA, proteins, and exosomal receptors to damaged tissues [32]. Another advantage includes more affordable production and storage compared with MSCs via lyophilisation or deep freezing, ensuring transportation without loss of therapeutic properties [33, 34].

MSC-derived exosomes have shown superior therapeutic effects in preclinical ARDS models. Exosome injection suppressed macrophage aggregation in lung tissue, reduced IL-27 secretion and pro-inflammatory factors, and improved survival in animals. Human umbilical cord MSC-derived exosomes decreased inflammatory factor levels and oxidative stress via autophagy induction in LPS-induced acute lung injury *in vivo* [35]. Bone marrow MSC-derived exosomes (BM-MSC) modulated macrophage metabolic state by inhibiting glycolysis, suppressed M1 polarisation, promoted M2 polarisation in lung tissue, and improved ARDS outcomes [36, 37].

Thus, a substantial body of data has been accumulated on MSC-derived exosome-based therapies for ARDS, and systematising these data allows more precise evaluation of unresolved issues and prospects. The study is aimed at analysing preclinical and clinical research results regarding safety and efficacy of MSC-derived exosome-based therapeutics for cell-free therapy of ARDS and other lung diseases as alternatives to pharmacotherapy.

MAIN PART

Preclinical studies of the exosome therapeutic effect

Analysis of animal experiments has indicated the potential therapeutic effects of exosomes in inflammatory processes of various aetiologies. Deng *et al.* [36] demonstrated that BM-MSCs, with their potent immunomodulatory and immunosuppressive properties via exosome secretion, improved the condition of sepsis-damaged lungs. Exosomes reduced the expression of genes involved in glycolysis by inhibiting HIF-1α transcription factor. Intratracheal administration of exosomes may be an effective approach for treating LPS-mediated ARDS [36].

Morrison *et al.* [37] established in a mouse model of LPS-mediated ARDS that extracellular vesicles from human BM-MSCs induced anti-inflammatory and highly phagocytic macrophage phenotype through mitochondrial transfer. Modulated macrophage function was associated with enhanced oxidative phosphorylation. After interacting with human BM-MSC-derived extracellular vesicles, alveolar macrophages reduced TNF-α and IL-8 production by 58±8% and 30±15%, respectively, thereby decreasing lung injury *in vivo* [37].

Xu *et al.* [38] demonstrated that exosomes derived from endothelial progenitor cells (EPCs) exerted protective effects on lung capillary endothelium and restored its integrity. This reduced

[2] https://clinicaltrials.gov/study/NCT04315987
[3] The culture medium containing proteins, growth factors, vesicles, including exosomes released into the medium by cells.

interstitial oedema and lung tissue damage in rats with ARDS (histological data). EPC cultures were obtained as follows: mononuclear cells isolated from bone marrow were centrifuged in a density gradient. On Day 8 of cultivation, the cells exhibited an endothelial phenotype, evidenced by uptake of acetylated low-density lipoprotein, binding of endothelial-specific lectin, and high expression of CD31 glycoprotein. The parameters confirmed their endothelial nature [38].

Monsel *et al.* [39] reported the effects of BM-MSC-derived vesicles on *Escherichia coli* LPS-induced pneumonia in mice. Intravenous administration of MSC-derived microvesicles (90 µL) 4 hours after LPS treatment increased 72-hour survival rate by 88% due to keratinocyte growth factor (KGF) secretion; reduced leukocyte influx by 40% and neutrophils by 53%; decreased total protein concentration in bronchoalveolar lavage by 22% 24 hours later compared to PBS-treated mice; and reduced inflammatory cells, cytokines, proteins, and bacteria due to increased phagocytosis [39].

In a preclinical study, Kaspi *et al.* [40] used Exo MSC-NTF (NurOwn®, Israel). To obtain Exo MSC-NTF, BM-MSCs were incubated in the medium containing 1 mM db-cAMP, 20 ng/mL human FGF2, 5 ng/mL human PDGF, and 50 ng/mL heregulin β1. In an LPS-induced lung inflammation mouse model, intratracheal Exo MSC-NTF administration demonstrated superior therapeutic effects compared to Exo MSC in reducing ARDS manifestations. Lung oxygenation increased by 10%, alveolar wall thickened by 43%; IL-6 levels decreased 7-fold, TNF – 2.3-fold; lung tissue damage was prevented. Neutrophil infiltration decreased by 26%; fibrin accumulation returned to reference values [38].

BrainStorm Cell Therapeutics has obtained a patent[4] for the method to produce cell-type specific exosomes from adult human BM-MSCs.

Tkachuk *et al.* [41] reported that in bleomycin-induced pulmonary fibrosis mouse models, intratracheal administration of extracellular vesicle-enriched conditioned MSC medium (CM-MSC) resolved fibrosis. Treated mice showed improved outcomes compared to controls. The clinical status was evaluated using a scoring system. The median maximum cumulative score in control animals reached 7, whereas in experimental mice (CM-MSC administration), it was 1, indicating better outcomes for mice receiving extracellular vesicle-enriched CM-MSC. In the fibrosis prevention group, median maximum cumulative scores were 9 for controls and 5 for experimental mice. These data suggest the efficacy of MSC secretome components not only for treatment but also for prevention of pulmonary fibrosis, including interstitial pneumonias of viral aetiology, such as coronavirus infections [41].

Shapira *et al.* [42] evaluated the efficacy and safety of EXO-mCD24 (murine homologue of human EXO-CD24) in moderate-to-severe ARDS. Efficacy was studied in mouse models of inflammatory diseases. EXO-mCD24 contains exosomes enriched with mCD24 glycoprotein (cluster of differentiation 24), a key molecule of innate immunity. Production of EXO-mCD24 by transfection of HEK cells with ExpiFectamine/plasmid DNA involved the following steps: 1) collection, centrifugation, and filtration of culture supernatant (0.22 µm); 2) precipitation with 30% polyethylene glycol (PEG) and 1.5 M NaCl for 15–16 hours, then centrifugation at 4,000 rpm; 3) resuspension of the pellet in saline, dialysis in PBS, and concentration using a filter MWCO 100 kDa [42].

Shapira *et al.* [43] assessed the toxicity, safety, and therapeutic effect of inhaled EXO-mCD24 in an LPS-induced confluent murine pneumonia model. Animals received 1×10^8 or 1×10^9 exosomes in saline once daily for 5 days. No adverse effects or behavioural differences were observed between the control and experimental groups. Administration of 1×10^8 exosomes did not influence moderate-to-severe lung damage, whereas 1×10^9 exosomes significantly improved lung condition and reduced serum levels of IL-6 (from 149 to 58 pg/mL), IL-12 (from 17 to 13 pg/mL), TNF-α (from 14 to 7 pg/mL), and IFN-γ (from 42 to 11 pg/mL). Bronchoalveolar lavage markers of inflammation were also reduced. EXO-mCD24 demonstrated efficacy and improved survival compared to controls: for 1×10^{10} and 1×10^{11} exosome groups, odds ratio (OR) was 0.069 (95% CI 0.016–0.292) and 0.155 (95% CI 0.043–0.555), respectively [43].

Key preclinical exosome data are summarised in *Table 1*.

Clinical trials of exosome-based preparations

According to Green *et al.* [44], EXO-CD24 is a promising therapeutic agent not only for ARDS but also for diseases resistant to standard treatments. Several animal models, including abdominal and pulmonary sepsis, pulmonary fibrosis, asthma, chronic obstructive pulmonary disease, and influenza, showed its therapeutic effectiveness [44, 45].

Based on preclinical EXO-CD24 results, Shapira *et al.* [42, 43] and Green *et al.* [44] suggested extrapolating the use of CD24-hyperexpressing exosomes for human disease treatment. This prompted

[4] https://patents.google.com/patent/AU2019252987B2

Table 1. Preclinical trials of exosome preparations *in vivo*
Таблица 1. Доклинические испытания препаратов экзосом на животных

Reference *Источник*	**Experimental model** *Экспериментальная модель*	**Inductors of pulmonary pathology** *Индукторы легочной патологии*	**Drug description** *Описание препарата*	**Therapeutic effect** *Терапевтический эффект*
[36]	C57Black/6, mice, males *Мыши, самцы*	LPS *ЛПС*	Bone marrow MSC exosomes *Экзосомы МСК костного мозга*	Improving lung function by modulating macrophage polarization and inhibiting glycolysis *Улучшение состояния легких посредством модуляции поляризации макрофагов и подавления в них гликолиза*
[37]	C57Black/6, mice, males *Мыши, самцы*	LPS *ЛПС*	Bone marrow MSC extracellular vesicles *Внеклеточные везикулы МСК костного мозга*	Reduction of lung damage by anti-inflammatory and highly phagocytic macrophage phenotype *Уменьшение повреждения легких путем формирования противовоспалительного и высокофагоцитарного фенотипа макрофагов*
[38]	Sprague Dawley rats *Крысы Спрег-Доули*	LPS *ЛПС*	Endothelial cell exosomes *Экзосомы эндотелиальных клеток*	Recovery of the endothelium of the lung capillaries *Восстановление эндотелия капилляров легких*
[39]	C57Black/6, mice, males *Мыши, самцы*	LPS *ЛПС*	Bone marrow MSC microvesicles *Микровезикулы МСК костного мозга*	An increase in animal survival *Увеличение выживаемости животных*
[40]	Mice *Мыши*	LPS *ЛПС*	Brainstorm company ExoMSC-NTF product *Препарат компании Brainstorm ExoMSC-NTF*	An increase in lung oxygenation, with reduced inflammatory cytokine levels *Повышение уровня оксигенации легких, снижение количества воспалительных цитокинов*
[41]	Mice *Мыши*	Bleomycin *Блеомицин*	MSC secretome enriched with extracellular vesicles *Секретом МСК, обогащенный внеклеточными везикулами*	Fibrosis resolving, improvement of animal health status compared to the control group *Разрешение фиброза, улучшение состояния животных по сравнению с контролем*
[42]	Mice *Мыши*	LPS *ЛПС*	EXO-mCD24 based on mouse cells *EXO-mCD24 на основе мышиных клеток*	A significant improvement in lung status and an increase in animal survival at a high dose (1×10^{10}) of exosomes *При высокой дозе 1×10^{10} экзосом — выраженное улучшение состояния легких и увеличение выживаемости животных*

The table is prepared by the authors using literature data / Таблица составлена авторами по данным литературы

Note. LPS, lipopolysaccharide; MSC, mesenchymal stromal cells.
Примечание. ЛПС — липополисахарид; МСК — мезенхимальные стромальные клетки.

clinical trials (CTs) assessing the safety and efficacy of exosome-based preparations for ARDS and other diseases. Randomised clinical trials used allogeneic exosome preparations derived from MSCs of various human tissues, administered to patients with moderate or severe ARDS by inhalation or intravenously. The placebo was typically saline.

Shapira *et al.* [42] developed the anti-inflammatory EXO-CD24 product using mCD24 murine homologue based on exosomes enriched with CD24 glycoprotein, molecules that form innate immunity. EXO-CD24 targets hyperactive immune cells in COVID-19-associated ARDS. CD24 is found to interact with DAMPs, including HMGB1, heat shock proteins, and nucleolin, selectively suppressing tissue damage responses via Siglec G (mouse) or Siglec10 (human) (sialic acid binding Ig like lectin) [46, 47].

Exosome-based therapeutics for inhalation

EXO-CD24

Shapira *et al.* [42] conducted a phase Ib/IIa CT in 35 patients with moderate-to-severe COVID-19. Increasing doses of Exo-CD24 (1×10^8–1×10^9 exosomes) were inhaled over 5 days. No treatment-related adverse effects were observed 443–575 days later. The product effectively reduced pro-inflammatory markers and cytokines. The levels of MIF3A, IL-17A, IL-1β, IL-6, TGF-α, TNF-α, and IL-1α decreased on Days 4, 7, and 35 of observation compared to the baseline levels (Day 0); the average C-reactive protein in the blood was 127.1±14.7 mg/L (± SEM[5]) on Day 0, with a further decrease to 66.6±10.4 and 19.3±7.7 mg/L on days 3 and 7, respectively [42].

Grigoropoulos *et al.* (Greece) conducted a phase IIb CT to determine dosing for patients with moderate-to-severe COVID-19-induced ARDS (*n*=91), administering 1×10^9–1×10^{10} EXO-CD24 exosomes for 5 days; efficacy and safety were assessed on Day 7, with a 28-day follow-up[6] [48]. Nimrod *et al.* (Israel) studied EXO-CD24 in 60 patients with mild-to-moderate ARDS. The exosomes (1×10^{10}) were diluted in 1.5 mL saline for inhalation via a standard jet nebuliser twice daily for 5 days[7]. The conducted CTs (phases I and II) found no adverse effects in patients. Despite the unique combination of the exosome (carrier) and CD24 (immunomodulator) in the inhalation medicinal product, further studies are warranted on a larger cohort of patients.

haMSC-Exos (Mexcovid)

Exosomes were obtained from human adipose tissue MSCs [49]. Passage 4 cells were transferred to a new culture tube (cell factory) at a density of $(1–1.5)\times10^4$ cells/cm^2 to obtain sufficient cell mass. Upon 90% confluence, the full growth medium (α-MEM with human platelet lysate) was replaced with exosome-free medium. The medium was centrifuged at 120,000 g for 6 hours; the supernatant was used as an exosome-free medium for further cell culture and exosome isolation. After 48 hours of incubation, the supernatant was cleared of debris via differential centrifugation, incubated with 12% PEG for 24 hours, centrifuged at 3,000 g for 60 min, resuspended in PBS, and centrifuged at 120,000 g for 70 min [49].

Efficacy and safety of inhaled haMSC-Exos was evaluated in a pilot, single-group, placebo-controlled phase IIa CT at Ruijin Hospital (China), in severe COVID-19 patients. Seven patients received 2×10^8 exosomes daily for 5 days via a nebuliser without adverse effects, maintaining clinical stability. Varying degrees of lung lesion improvement were observed[8] [50].

hMSC-Exos

hMSC-Exos, derived from human BM-MSCs [49], were tested in a randomised, placebo-controlled phase I/II CT at Ruijin Hospital (China) for inhaled ARDS therapy (*n*=18). Phase I: dose groups were low (2×10^8 exosomes/day for 7 days), medium (8×10^8/day), and high (16×10^8/day). Phase II: dose 1 – baseline + 1/4 MTD/day[9], dose 2 – baseline + MTD/day, control group – baseline + saline[10].

Samara Regional Medical Center Dinastiya (Russia) conducted a randomised double-blind CT to study the safety and efficacy of aerosol inhaled twice over 10 days at a dose of $0.5–2\times10^{10}$ exosomes[11]. Exosomes derived from BM-MSCs were used in patients with severe COVID-19-induced pneumonia[12]. Exosome inhalation aimed to ac-

[5] SEM, standard error of the mean.
[6] https://clinicaltrials.gov/study/NCT04902183
[7] https://clinicaltrials.gov/study/NCT05947747
[8] https://clinicaltrials.gov/study/NCT04276987
[9] MTD/day – maximum tolerated dose/day.
[10] https://clinicaltrials.gov/study/NCT04602104
[11] https://clinicaltrials.gov/study/NCT04491240
https://clinicaltrials.gov/study/NCT04602442
[12] https://clinicaltrials.gov/study/NCT04491240
https://clinicaltrials.gov/study/NCT04602442

celerate recovery, reduce lung lesion volume, and decrease the hospital stay.

Intravenous Exosome Preparations

Zofin™

Zofin™ (DrugBank ID 16519) is an acellular, minimally processed human amniotic fluid product containing extracellular vesicles/nanoparticles from amniotic stem and epithelial cells, with over 300 growth factors, cytokines, and chemokines. Exosomes are enriched with molecules such as CD63, CD81, CD9, in addition to the high expression of the CD133 glycoprotein. The CT objective (phases I and II) was to evaluate the safety and potential efficacy of intravenous product used to treat moderate to severe COVID-19 compared to placebo. Patients in the experimental group received 1 mL intravenously on Days 0, 4, and 8. The average concentration of vesicles with an average size of 125.2 nm was 5.24×10^{11} exosomes/mL. The product acts as a cytokine activation suppressor reducing COVID-19 severity[13].

In 2021, Organicell Regenerative Medicine (USA) reported positive results from the first use of the medication in India: 10 patients with COVID-19 receiving Zofin™ achieved remission (the study was conducted in 4 clinics). Subsequently, 65 patients with moderate to severe COVID-19 were included in the CT (treatment was completed by the end of June 2021). All patients who received the product achieved complete recovery[14]. An application was submitted to the Indian Council of Medical Research (ICMR) for emergency approval of Zofin™ in COVID-19.

ExoFlo™

ExoFlo™, a product containing BM-MSC-derived exosomes, demonstrated high tolerability in patients with COVID-19-associated-ARDS. The CT involved 102 patients receiving 100 mL infusions (15 mL drug and 85 mL saline) for 60 min on Days 1 and 4 of treatment. Patients with severe or critical COVID-19 received conventional treatment at the same time. ExoFlo™ dose was found to be safe for patients[15] [51].

Direct Biologics (USA) reported positive results obtained in CTs using ExoFlo™. Sengupta *et al.* [52] studied the safety and efficacy of exosomes (ExoFlo™) derived from allogeneic BM-MSCs in a non-randomised CT in patients with severe COVID-19, as well as severe and moderate ARDS. Patients received a single dose of ExoFlo™ (15 mL) intravenously, with a follow-up monitoring for 2 weeks after treatment. No side effects were reported within 72 hours after administration. The survival rate of patients was 83%. The average ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) increased by 192% ($p<0.001$). The average decrease in blood neutrophils was 32% ($p<0.001$), while the number of $CD3^+$, $CD4^+$, and $CD8^+$ lymphocytes increased by 46% ($p<0.05$), 45% ($p<0.05$), and 46% ($p<0.001$), respectively. The average levels of C-reactive protein, ferritin, and D-dimer decreased by 77% ($p<0.001$), 43% ($p<0.001$), and 42% ($p<0.05$), respectively [52]. Thus, due to its safety profile, ability to restore oxygenation, suppress cytokine storm, and strengthen immunity, the study product is a promising medication in severe COVID-19.

The Food and Drug Administration (FDA, USA) has granted ExoFlo™ the status of a promising drug for regenerative medicine and has also approved CT phase III in 2023. Given the limited number of approved drugs with proven efficacy in reducing mortality, timely results from phase III CTs will be important for the treatment of ARDS patients and eradicating morbidity and mortality caused by SARS-CoV-2[16].

Zofin™ and ExoFlo™ are recommended by the FDA for CT (*Table 2*).

ARDOXSO

A CT was conducted in the United States to evaluate the safety and efficacy of an intravenous exosome-based therapeutics obtained from BM MSCs for the treatment of severe ARDS. The trial design included 4 groups of 5 patients: Group 1 – administration of increasing drug doses (2×10^9, 4×10^9, 8×10^9 exosomes) every other day for 5 days; Group 2 – administration of 8×10^9, 4×10^9, 8×10^9 exosomes according to the same schedule; Group 3 – administration of a therapeutic dose of 8×10^9, 8×10^9, 8×10^9 exosomes; Group 4 – administration of placebo[17]. The data obtained from this pilot CT demonstrate the potential clinical applicability of the drug.

[13] https://clinicaltrials.gov/study/NCT04384445
[14] https://www.europeanpharmaceuticalreview.com/news/152560/100-percent-recovery-rate-for-covid-19-patients-treated-with-zofin/
[15] https://clinicaltrials.gov/study/NCT04493242
[16] https://bioinformant.com/direct-biologics-publication-in-chest/
[17] https://clinicaltrials.gov/study/NCT04798716

Combination Therapy

EV-Pure™ and WJ-Pure™

Vitti Labs has developed a product based on VL-P22 (EVPure) umbilical MSCs and VL-PX10 (WJ-Pure) placental exosomes. Phase I CT evaluated the safety and benefits of IV EVPure + WJPure in moderate-to-severe COVID-19 and ARDS[18]. Another CT phase II assessed the advantages of combination therapy in COVID-19 patients with pulmonary fibrosis[19]: the treatment group (*n=10*) received EV-Pure + WJPure besides standard care; the placebo group (*n=10*) received cryopreservation medium/saline with standard care. Treatment duration: 5 days, with a 12-week follow-up[20].

Exosome and MSC combination

New regimens combining exosomes and MSCs were explored in order to improve ARDS therapy. Zarrabi *et al*. [53] reported a phase II randomised multicenter trial in 43 COVID-19 / ARDS patients: 11 patients received two consecutive doses of allogeneic MSCs (100×10^6 each); in 8 patients, 100×10^6 MSCs + exosomes from 200×10^6±10% MSCs were administered via inhalation; control group included 24 patients. The products were administered every 48 hours. Systemic administration of MSCs and inhalation of exosomes using a nebuliser were shown to be safe and significantly reduced inflammatory markers (IL-6, TNF-α, IFN-γ, and CRP) in patients' blood serum. No deaths were reported among patients who received exosome and MSC preparations [53, 54].

The key data on the clinical trials of exosome-based therapeutics are presented in *Table 2*.

In 2022, Lotfy *et al*. presented data on the use of exosomes obtained from various cells (bone marrow, adipose tissue, endometrium, etc.) for the treatment of neurological (epilepsy, Parkinson's disease, stroke), autoimmune (multiple sclerosis, rheumatoid arthritis, type 1 diabetes), heart, and kidney diseases [55]. The below examples of exosome-based therapeutics confirm that their functional effect is determined by MSC source [56]. A total of 304 proteins, 150 microRNAs, and other bioactive molecules [55] were detected in exosomes, which together probably provide the therapeutic effect – repair of various tissue types in cardiovascular conditions, diseases of the liver, kidneys, lungs, and neurological disorders [57, 58].

Type 1 diabetes was treated using umbilical cord blood MSC-derived exosomes ($1.22–1.51\times10^6$ particles/kg, twice, 1-week interval)[21].

A study conducted at Isfahan University (Iran) investigated the possibilities of functional recovery after a stroke. Animal experiments showed that administered exosomes increased the number of neuroblasts and endothelial cells. Exosomes from BM MSCs were administered stereotaxically intraparenchymally to patients with ischemic stroke[22].

At Ruijin Hospital (China), MSCs-Exos isolated from allogeneic adipose tissue MSCs were used in a non-randomised CT for the treatment of mild to moderate Alzheimer's disease. Three patient groups received MSCs-Exos nasally at doses of 5 μg, 10 μg, and 20 μg (1 mL) twice a week for 12 weeks[23] [59].

In Egypt, research has been initiated for exosome-based therapeutics obtained from adipose tissue MSCs autogenously isolated from patients; the exosomes are intended for administration into periodontal pockets to assess their regenerative effect in periodontitis[24].

Challenges and prospectives

Exosome-based therapies are promising acellular treatments with demonstrated efficacy in ARDS and other diseases [60]. However, heterogeneity and rapid elimination are still a challenge [34]. Unresolved technical aspects include developing reproducible isolation and purification protocols [61], optimising storage, and defining therapeutic doses.

The discovery of stromal stem cells by Friedenstein and Chailakhyan's culture methods enabled large-scale MSC production without diploidy changes and enabled the therapeutic use of cells and their secretome. Chailakhyan *et al*. [12] reported the heterogeneity of primary *in vitro* BM-derived clones, later confirmed by Kuznetsov *et al*. [62] and Bianco *et al*. [63].

The secretome of BM-MSCs cultures contains exosomes that inherit the properties of their parent cells. Consequently, the pool of isolated exosomes is as heterogeneous as the MSC culture itself. Authors of numerous studies often use the term "exosomes" derived from MSCs of various tissues without providing detailed characteristics of the employed MSCs. Most studies utilising stem

[18] https://clinicaltrials.gov/study/NCT05387278
[19] https://clinicaltrials.gov/study/NCT05387239
[20] https://clinicaltrials.gov/study/NCT05387278
https://clinicaltrials.gov/stady/NCT05387239
[21] https://clinicaltrials.gov/study/NCT02138331
[22] https://clinicaltrials.gov/study/NCT03384433
[23] https://clinicaltrials.gov/study/NCT04388982
[24] https://clinicaltrials.gov/study/NCT04270006

Table 2. Application of exosome-based preparations in clinical trials[a]
Таблица 2. Препараты на основе экзосом, использованные в клинических исследованиях[a]

ClinicalTrials.gov ID	Preparation *Препарат*	Drug composition *Состав препарата*	Drug administration *Способ введения*	Country *Страна*
NCT04902183	Exo-CD24	Exosomes of allogenic MSCs *Экзосомы аллогенных МСК*	Inh *Инг/в*	Greece *Греция*
NCT05947747	Exo-CD24	Exosomes of allogenic MSCs *Экзосомы аллогенных МСК*	Inh *Инг/в*	Israel *Израиль*
NCT04747574	Exo-CD24	Exosomes of allogenic MSCs *Экзосомы аллогенных МСК*	Inh *Инг/в*	Israel *Израиль*
NCT04969172	Exo-CD24	Exosomes of allogenic MSCs *Экзосомы аллогенных МСК*	Inh *Инг/в*	Israel *Израиль*
NCT05787288	Exosomes *Экзосомы*	Exosomes of umbilical blood cells *Экзосомы клеток пуповинной крови*	Inh *Инг/в*	China *Китай*
NCT04276987	Mexcovid	Exosomes MSCs from human adipose tissue *Экзосомы МСК жировой ткани человека*	Inh *Инг/в*	China *Китай*
NCT04602104	hMSC-Exos	Human bone marrow MSC exosomes *Экзосомы МСК костного мозга человека*	Inh *Инг/в*	China *Китай*
NCT04491240	Exosomes *Экзосомы*	Human bone marrow MSC exosomes *Экзосомы МСК костного мозга человека*	Inh *Инг/в*	Russia *Россия*
NCT04602442	Exosomes *Экзосомы*	Human bone marrow MSC exosomes *Экзосомы МСК костного мозга человека*	Inh *Инг/в*	Russia *Россия*
NCT04384445	Zofinb	Human amniotic fluid exosomes *Экзосомы амниотической жидкости человека*	i/v *в/в*	USA, India *США, Индия*
NCT05228899	Zofinb	Human amniotic fluid exosomes *Экзосомы амниотической жидкости человека*	i/v *в/в*	USA *США*
NCT05643729	Zofinb	Human amniotic fluid exosomes *Экзосомы амниотической жидкости человека*	i/v *в/в*	USA *США*
NCT04493242	ExoFloc	Human bone marrow MSC exosomes *Экзосомы МСК костного мозга человека*	i/v *в/в*	USA *США*
NCT05127122	ExoFloc	Human bone marrow MSC exosomes *Экзосомы МСК костного мозга человека*	i/v *в/в*	USA *США*
NCT05116761	ExoFloc	Human bone marrow MSC exosomes *Экзосомы МСК костного мозга человека*	i/v *в/в*	USA *США*
NCT04798716	ARDOXSO	Human bone marrow MSC exosomes *Экзосомы МСК костного мозга человека*	i/v *в/в*	USA *США*
NCT05387278	EVPure WJPure	MSCs from umbilical cord and exosomes from placental MSC *МСК пуповины и экзосомы из МСК плаценты*	Comb/adm *Комб/в*	USA *США*
NCT05387239	EVPure WJPure	MSCs from umbilical cord and exosomes from placental MSC *МСК пуповины и экзосомы из МСК плаценты*	Comb/adm *Комб/в*	USA *США*

The table is prepared by the authors using literature data / Таблица составлена авторами по данным литературы

Note. MSC, mesenchymal stromal cells; Inh/adm, inhalation; i/v, intravenous administration; comb/adm, combined administration.
[a] According to clinical trials, all the drugs considered meet the criteria for safety and effectiveness.
[b] Pakistani regulatory authorities have approved the use of Zofin to treat a patient with severe COVID-19 (2021); FDA has approved the use of Zofin in patients with chronic obstructive pulmonary disease.
[c] FDA approved ExoFlo in patients with life-threatening COVID-19 complications (2020).

Примечание. МСК — мезенхимальные стромальные клетки; Инг/в — ингаляционное введение; в/в — внутривенное введение; комб/в — комбинированное введение.
[a] По результатам клинических исследований все рассмотренные препараты соответствуют критериям безопасности и эффективности.
[b] Регуляторные органы Пакистана разрешили использовать Zofin для лечения пациента с тяжелой формой COVID-19 (2021 г.); FDA одобрило применение Zofin для лечения пациентов с хронической обструктивной болезнью легких.
[c] FDA одобрило применение ExoFlo для лечения пациентов с угрожающими жизни осложнениями от COVID-19 (2020 г.).

cell-derived MSCs for the treatment of ARDS and complications following COVID-19 share the following limitations: a) the current methods do not always allow for isolation of a sufficient number of exosomes to conduct serial investigations; b) there are no standardised protocols for obtaining homogeneous material (every subsequent batch of exosomes derived from MSCs may present somewhat different characteristics).

Thus, it is necessary to scale up cell cultivation for exosome production intended for therapeutic use and to standardise treatment protocols, including dosage, administration routes, and treatment regimens.

The primary goal of future CTs should be to evaluate the long-term safety, immunogenicity, and efficacy of exosome-based products for cell-free therapy.

CONCLUSIONS

The authors have analysed data on exosome-based therapeutics derived from MSC cultures of bone marrow, adipose tissue, umbilical cord, cord blood, and placenta, which exert therapeutic effects on lung tissue regeneration in ARDS. In preclinical and clinical studies, exosome-based therapeutics were administered both as part of combination therapy and as monotherapy. Inhalational, intravenous, and combined routes of administration demonstrated efficacy.

There is a pressing need to standardise the criteria for exosome-based therapeutic production, optimise the efficacy of therapeutic regimens, and define conditions for long-term storage.

References/Литература

1. Kostinov MP, Shmitko AD, Polishchuk VB, Khromova EA. Modern representations of the new coronavirus and the disease caused by SARS-COV-2. *Infectious Diseases: News, Opinions, Training*. 2020;9(2):33–42 (In Russ.). Костинов МП, Шмитько АД, Полищук ВБ, Хромова ЕА. Современные представления о новом коронавирусе и заболевании, вызванном SARS-COV-2. *Инфекционные болезни: новости, мнения, обучение*. 2020;9(2):33–42. https://doi.org/10.33029/2305-3496-2020-9-2-33-42
2. Yaroshetskiy AI, Gritsan AI, Avdeev SN, et al. Diagnostics and intensive therapy of acute respiratory distress syndrome (clinical guidelines of the federation of anesthesiologists and reanimatologists of Russia). *Russian Journal of Anesthesiology and Reanimatology*. 2020;(2):5–39 (In Russ.). Ярошецкий АИ, Грицан АИ, Авдеев СН и др. Диагностика и интенсивная терапия острого респираторного дистресс-синдрома (Клинические рекомендации Общероссийской общественной организации «Федерация анестезиологов и реаниматологов»). *Анестезиология и реаниматология*. 2020;(2):5–39. https://doi.org/10.17116/anaesthesiology20200215
3. Vinogradov VA, Skvortsova VI, Karkishchenko VN, et al. Method of treating acute respiratory distress syndrome with dolargin and a pulmonary surfactant. Patent of the Russian Federation No. 2728821 C1, 2020 (In Russ.). Виноградов ВА, Скворцова ВИ, Каркищенко ВН и др. Способ лечения острого респираторного дистресс-синдрома доларгином и легочным сурфактантом. Патент Российской Федерации № 2728821 C1, 2020. EDN: KBSGOR
4. Wang J, Yang X, Li Y, et al. Specific cytokines in the inflammatory cytokine storm of patients with COVID-19-associated acute respiratory distress syndrome and extrapulmonary multiple-organ dysfunction. *Virol J*. 2021;18:117. https://doi.org/10.1186/s12985-021-01588-y
5. Xu H, Sheng S, Luo W, et al. Acute respiratory distress syndrome heterogeneity and the septic ARDS subgroup. *Front Immunol*. 2023;14:1277161. https://doi.org/10.3389/fimmu.2023.1277161
6. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification and supplementary material. *Intensive Care Med*. 2012;38(10): 1573–82. https://doi.org/10.1007/s00134-012-2682-1
7. Zhao L, Su F, Zhang N, et al. The impact of the new acute respiratory distress syndrome (ARDS) criteria on Berlin criteria ARDS patients: a multicenter cohort study. *BMC Med*. 2023; 21:456. https://doi.org/10.1186/s12916-023-03144-7
8. Sizikova TE, Lebedinskaya EV, Lebedev VN, Borisevich SV. The therapeutics, based on virus specific antibodies, for special prophylactic and current of COVID-19. *Infectious Diseases: News, Opinions, Training*. 2021;10(4):98–104 (In Russ.). Сизикова ТЕ, Лебединская ЕВ, Лебедев ВН, Борисевич СВ. Применение вируснейтрализующих антител для экстренной профилактики и лечения COVID-19. *Инфекционные болезни: новости, мнения, обучение*. 2021;10(4):98–104. https://doi.org/10.33029/2305-3496-2021-10-4-98-104
9. Arutyunov AG, Avdeev SN, Batyushin MM, et al. Using COVID-globulin in COVID-19 treatment. *Experimental and Clinical Pharmacology*. 2022;85(3):13–20 (In Russ.). Арутюнов АА, Авдеев СН, Батюшкин ММ и др. Применение КОВИД-глобулина в терапии COVID-19. *Экспериментальная и клиническая фармакология*. 2022;85(3):13–20. https://doi.org/10.30906/0869-2092-2022-85-3-13-20
10. Friedenstein AJ, Petrakova KV, Kuralesova AI, Frolova GP. Heterotopic transplants of bone marrow. Analysis of precursor cells for osteogenic and hemopoietic tissues. *Transplantation*. 1968;6(2):230–47. https://doi.org/10.1097/00007890-196803000-00009

11. Melnikova EV, Merkulova OV, Merkulov VA. Clinical trials for cellular therapy products: conclusions reached by foreign regulatory bodies. *Russian Journal of Transplantology and Artificial Organs*. 2020;22(2):139–50 (In Russ.). Мельникова ЕВ, Меркулова ОВ, Меркулов ВА. Клинические исследования препаратов клеточной терапии: опыт рассмотрения зарубежными регуляторными органами. *Вестник трансплантологии и искусственных органов*. 2020;22(2):139–50. https://doi.org/10.15825/1995-1191-2020-2-139-150
12. Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Tissue Kinet*. 1970;3(4):393–403. https://doi.org/10.1111/j.1365-2184.1970.tb00347.x
13. Fridenstein AYa, Latsinik NV, Kuralesova AI, et al. Cell-precursors of hemopoietic microenvironment. In: *Results of science and technology. Immunology*. Moscow: VINITI; 1983. Vol. 12. P. 5–28 (In Russ.). Фриденштейн АЯ, Лациник НВ, Куралесова АИ и др. Клетки-переносчики кроветворного микроокружения. В сб.: *Итоги науки и техники. Иммунология*. М: ВИНИТИ; 1983. Т. 12. С. 5–28.
14. Chailakhyan RK, Kon E, Shekhter AB, et al. Autologous bone marrow-derived mesenchymal stem cells provide complete regeneration in a rabbit model of the Achilles tendon bundle rupture. *Int Orthop*. 2021;45(12):3263–76. https://doi.org/10.1007/s00264-021-05168-1
15. Gol'dshtein DV, Makarov AV, Fatkhudinov TKh, et al. Biotransplant and method for treating the cases of osteoporosis. Patent of the Russian Federation No. 2265442 C1, 2005 (In Russ.). Гольдштейн ДВ, Макаров АВ, Фатхудинов ТХ и др. Биотрансплантат и способ лечения остеопороза. Патент Российской Федерации № 2265442 C1, 2005. EDN: HXYKOL
16. Granov AM, Zharinov GM, Zverev OG, et al. Method for treating the cases of allergic diseases. Patent of the Russian Federation No. 2250773 C1, 2005 (In Russ.). Гранов АМ, Жаринов ГМ, Зверев ОГ и др. Способ лечения аллергических заболеваний. Патент Российской Федерации № 2250773 C1, 2005. EDN: HRCAVW
17. Mironov NV, Gol'dshtejn DV, Gorjajnova II, et al. Biotransplant and method for treating the cases of parkinsonism. Patent of the Russian Federation No. 2259836 C1, 2005 (In Russ.). Миронов НВ, Гольдштейн ДВ, Горяйнова ИИ и др. Биотрансплантат и способ лечения паркинсонизма. Патент Российской Федерации № 2259836 C1, 2005. EDN: NLVOIT
18. Granov AM, Zharinov GM, Neklasova NJu, et al. Method for treating noninvasive cancer of urinary bladder. Patent of the Russian Federation No. 2257219 C1, 2005 (In Russ.). Гранов АМ, Жаринов ГМ, Некласова НЮ и др. Способ лечения инвазивного рака мочевого пузыря. Патент Российской Федерации № 2257219 C1, 2005. EDN: SARJIW
19. Shahpazian NK, Astrelina TA, Yakovleva MV. Mesenchymal stem cells from various human tissues: biological properties, quality and safety assessment for clinical use. *Cell Transplantation and Tissue Engineering*. 2012;7(1):23–33 (In Russ.). Шахпазян НК, Астрелина ТА, Яковлева МВ. Мезенхимальные клетки из различных тканей человека: биологические свойства, оценка качества и безопасности для клинического применения. *Клеточная трансплантология и тканевая инженерия*. 2012;7(1):23–33. EDN: NKDSLH
20. Deev RV. Cell transplantation in the COVID-19 treatment program: stem stromal (mesenchymal) cell transplantation. *Genes & Cells*. 2020;15(2):10–19 (In Russ.). Деев РВ. Клеточная трансплантация в программе лечения COVID-19: пересадка стволовых стромальных (мезенхимальных) клеток. *Гены и клетки*. 2020;15(2):10– 19. https://doi.org/10.23868/202004012
21. Chailakhyan RK, Aver'yanov AV, Zabozlaev FG, et al. Comparison of the efficiency of transplantation of bone marrow multipotent mesenchymal stromal cells cultured under normoxic and hypoxic conditions and their conditioned media on the model of acute lung injury. *Bull Exp Biol Med*. 2014;157(1):138–42. https://doi.org/10.1007/s10517-014-2509-x
22. Aslam M, Baveja R, Liang OD, et al. Bone marrow stromal cells attenuate lung injury in a murine model of neonatal chronic lung disease. *Am J Respir Crit Care Med*. 2009;180(11):1122–30. https://doi.org/10.1164/rccm.200902-0242OC
23. Gorman E, Millar J, McAuley D, O'Kane C. Mesenchymal stromal cells for acute respiratory distress syndrome (ARDS), sepsis, and COVID-19 infection: optimizing the therapeutic potential. *Expert Rev Respir Med*. 2021;15(3):301–24. https://doi.org/10.1080/17476348.2021.1848555
24. Walter J, Ware LB, Matthay MA. Mesenchymal stem cells: mechanisms of potential therapeutic benefit in ARDS and sepsis. *Lancet Respir Med*. 2014;2(12):1016–26. https://doi.org/10.1016/S2213-2600(14)70217-6
25. MatthayMA, Calfee CS, ZhuoH, et al. Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. *Lancet Respir Med*. 2019;7(2):154–62. https://doi.org/10.1016/S2213-2600(18)30418-1
26. Nauta AJ, Fibbe WE. Immunomodulatory properties of mesenchymal stromal cells. *Blood*. 2007;110(10):3499–506. https://doi.org/10.1182/blood-2007-02-069716
27. Jung JW, Kwon M, Choi JC, et al. Familial occurrence of pulmonary embolism after intravenous, adipose tissue-derived stem cell therapy. *Yonsei Med J*. 2013;54(5):1293–6. https://doi.org/10.3349/ymj.2013.54.51293
28. Abraham A, Krasnodembskaya A. Mesenchymal stem cell-derived extracellular vesicles for the treatment of acute respiratory distress syndrome. *Stem Cells Transl Med*. 2020;9(1):28–38. https://doi.org/10.1002/sctm.19-0205
29. Bruno S, Deregibus MC, Camussi G. The secretome of mesenchymal stromal cells: Role of extracellular vesicles in immunomodulation. *Immunol Lett*. 2015;168(2):154–8. https://doi.org/10.1016/j.imlet.2015.06.007
30. Konala VB, Mamidi MK, Bhonde R, et al. The current landscape of the mesenchymal stromal cell secretome: A new paradigm for cell-free regeneration. *Cytotherapy*. 2016;18(1):13–24. https://doi.org/10.1016/j.jcyt.2015.10.008
31. Johnstone RM, Adam M, Hammond JR, et al. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). *J Biol Chem*. 1987;262(19):9412–20. PMID: 3597417
32. Zhang K, Cheng K. Stem cell-derived exosome versus stem cell therapy. *Nat Rev Bioeng*. 2023;1:608–9. https://doi.org/10.1038/s44222-023-00064-2
33. Ratushnyak MG, Syomochkina YuP. Exosomes — natural nanoparticles for use in therapy. *Russian Nanotechnology*. 2020;15(4):435–50 (In Russ.). Ратушняк МГ, Семочкина ЮП. Экзосомы — природные наночастицы для использования в терапии. *Российские нанотехнологии*. 2020;15(4):435–50. https://doi.org/10.1134/S1992722320040123
34. Zhuang X, Jiang Y, Yang X, et al. Advances of mesenchymal stem cells and their derived extracellular vesicles as a promising therapy for acute respiratory distress syndrome: from bench to clinic. *Front Immunol*. 2023;14:1244930. https://doi.org/10.3389/fimmu.2023.1244930
35. Liu C, Xiao K, Xie L. Advances in the use of exosomes for the treatment of ALI/ARDS. *Front Immunol*. 2022;13:971189. https://doi.org/10.3389/fimmu.2022.971189
36. Deng H, Wu L, Liu M, et al. Bone marrow mesenchymal stem cell-derived exosomes attenuate LPS-induced ARDS by modulating macrophage polarization through inhibit-

ing glycolysis in macrophages. *Shock*. 2020;54(6):828–43. https://doi.org/10.1097/SHK.0000000000001549
37. Morrison TJ, Jackson MV, Cunningham EK, et al. Mesenchymal stromal cells modulate macrophages in clinically relevant lung injury models by extracellular vesicle mitochondrial transfer. *Am J Respir Crit Care Med*. 2017;196(10):1275–86. https://doi.org/10.1164/rccm.201701-0170OC
38. Xu W, Zilong L, Lijuan H, et al. Exosomes derived from endothelial cells ameliorate acute lung injury by transferring miR-126. *Exp Cell Res*. 2018;370(1):13–23. https://doi.org/10.1016/j.yexcr.2018.06.003
39. Monsel A, Zhu YG, Gennai S, et al. Therapeutic effects of human mesenchymal stem cell-derived microvesicles in severe pneumonia in mice. *Am J Respir Crit Care Med*. 2015;192(3):324–36. https://doi.org/10.1164/rccm.201410-1765OC
40. Kaspi H, Semo J, Abramov N, et al. MSC-NTF (NurOwn®) exosomes: a novel therapeutic modality in the mouse LPS-induced ARDS model. *Stem Cell Res Ther*. 2021;12:72. https://doi.org/10.1186/s13287-021-02143-w
41. Tkachuk VA, Akopian ZhA, Efimenko AYu, et al. Agent for treating tissue fibrosis based on components of mesenchymal stromal cell secretome, method for preparing and using the agent. Patent of the Russian Federation No. RU2766707 C1, 2020 (In Russ.). Ткачук ВА, Акопян ЖА, Ефименко АЮ и др. Средство для лечения фиброза тканей на основе компонентов секретома мезенхимных стромальных клеток, способ получения и применения средства. Патент Российской Федерации № RU2766707 C1, 2020. EDN: CBDVKA
42. Shapira S, Schwartz R, Tsiodras S, et al. Inhaled CD24-enriched exosomes (EXO-CD24) as a novel immune modulator in respiratory disease. *Int J Mol Sci*. 2023;25(1):77. https://doi.org/10.3390/ijms25010077
43. Shapira S, Shimon BM, Hay-Levi M, et al. A novel platform for attenuating immune hyperactivity using EXO-CD24 in COVID-19 and beyond. *EMBO Mol Med*. 2022;14(9):e15997. https://doi.org/10.15252/emmm.202215997
44. Green O, Shenberg G, Baruch R, et al. Inhaled exosomes genetically manipulated to overexpress CD24 (EXO-CD24) as a compassionate use in severe ARDS patients. *Biomedicines*. 2023;11(9):2523. https://doi.org/10.3390/biomedicines11092523
45. Liu Y, Zheng P. CD24-Siglec interactions in inflammatory diseases. *Front Immunol*. 2023;14:1174789. https://doi.org/10.3389/fimmu.2023.1174789
46. Fang X, Zheng P, Tang J, et al. CD24: from A to Z. *Cell Mol Immunol*. 2010;7:100–3. https://doi.org/10.1038/cmi.2009.119
47. Chen G-Y, Tang J, Zheng P, LiuY. CD24 and Siglec-10 selectively repress tissue damage-induced immune responces. *Science*. 2009;323(5922):1722–5. https://doi.org/10.1126/science.1168988
48. Grigoropoulos I, Tsioulos G, Kastrissianakis A, et al. The safety and potential efficacy of exosomes overexpressing CD24 (EXOCD24) in mild-moderate COVID-19 related ARDS. *Resp Res*. 2024;25:151. https://doi.org/10.1186/s12931-024-02759-5
49. Shi M-M, Yang Q-Y, Monsel A, et al. Preclinical efficacy and clinical safety of clinical-grade nebulized allogenic adipose mesenchymal stromal cells-derived extracellular vesicles. *J Extracell Vesicles*. 2021;10(10):e12134. https://doi.org/10.1002/jev2.12134
50. Zhu Y-G, Shi M-M, Monsel A, et al. Nebulized exosomes derived from allogenic adipose tissue mesenchymal stromal cells in patients with severe COVID-19: a pilot study. *Stem Cell Res Ther*. 2022;13(1):220. https://doi.org/10.1186/s13287-022-02900-5
51. LightnerAL, Sengupta V, Qian S, et al. Bone marrow mesenchymal stem cell-derived extracellular vesicle infusion for the treatment of respiratory failure from COVID-19: A randomized, placebo-controlled clinical trial. *Chest*. 2023;164(6):1444–53. https://doi.org/10.1016/j.chest.2023.06.024
52. Sengupta V, Sengupta S, Lazo A, et al. Exosomes derived from bone marrow mesenchymal stem cells as treatment for severe COVID-19. *Stem Cells Dev*. 2020;29(12):747–54. https://doi.org/10.1089/scd.2020.0080
53. Zarrabi M, Shahrbaf MA, Nouri M, et al. Allogenic mesenchymal stromal cells and their extracellular vesicles in COVID-19 induced ARDS: a randomized controlled trial. *Stem Cell Res Ther*. 2023;14(1):169. https://doi.org/10.1186/s13287-023-03402-8
54. Hashemian SM R, Aliannejad R, Zarrabi M, et al. Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: a case series. *Stem Cell Res Ther*. 2021;12(1):91. https://doi.org/10.1186/s13287-021-02165-4
55. Lotfy A, AboQuella NM, Wang H. Mesenchymal stromal/stem cell (MSC)-derived exosomes in clinical trials. *Stem Cell Res Ther*. 2023;14(1):66. https://doi.org/10.1186/s13287-023-03287-7
56. Börger V, Bremer M, Ferrer-Tur R, et al. Mesenchymal stem/stromal cell-derived extracellular vesicles and their potential as novel immunomodulatory therapeutic agents. *Int J Mol Sci*. 2017;18(7):1450. https://doi.org/10.3390/ijms18071450
57. Xun C, Ge L, Tang F, et al.Insight into the proteomic profiling of exosomes secreted by human OM-MSCs reveals a new potential therapy. *Biomed Pharmacother.* 2020;131:110584. https://doi.org/10.1016/j.biopha.2020.110584
58. Hassanzadeh A, Rahman H, Markov A, et al. Mesenchymal stem/stromal cell-derived exosomes in regenerative medicine and cancer; overview of development, challenges, and opportunities. *Stem Cell Res Ther.* 2021;12(1):297. https://doi.org/10.1186/s13287-021-02378-7
59. Xie X, Song Q, Dai C, et al. Clinical safety and efficacy of allogenic human adipose mesenchymal stromal cells-derived exosomes in patients with mild to moderate Alzheimer's disease: a phase I/II clinical trial. *Gen Psychiatr.* 2023;36(5):e101143. https://doi.org/10.1136/gpsych-2023-101143
60. Lee BC, Kang I, Yu KR. Therapeutic features and updated clinical trials of mesenchymal stem cell (MSC)-derived exosomes. *J Clin Med*. 2021;10(4):711. https://doi.org/10.3390/jcm10040711
61. Sheveleva ON, Domoratskaya EI, Payushina OV. Extracellular vesicles and prospects of their use for tissue regeneration. *Biological Membranes*. 2019;36(1):3–14 (In Russ.). Шевелева ОН, Домарацкая ЕИ, Паюшина ОВ. Внеклеточные везикулы и перспективы их использования для регенерации тканей. *Биологические мембраны*. 2019;36(1):3–14. https://doi.org/10.1134/S0233475518050109
62. Kuznetsov SA, Krebsbach PH, Satomura K, et al. Single-colony derived strains of human marrow stromal fibroblasts form bone after transplantation in vivo. *J Bone Miner Res*. 1997;12(9):1335–47. https://doi.org/10.1359/jbmr.1997.12.9.1335
63. Bianco P, Gehron Robey P. Marrow stromal stem cells. *J Clin Invest*. 2000;105(12):1663–8. https://doi.org/10.1172/JCI10413

Authors' contributions. All the authors confirm that they meet the ICMJE criteria for authorship. All the authors conceptualised, drafted the manuscript, and formulated the conclusions.

Acknowlegements. We would like to thank our colleagues for their critical comments on our article.

Вклад авторов. Все авторы подтверждают соответствие своего авторства критериям ICMJE. Все авторы разрабатывали концепцию рукописи, участвовали в написании текста и формулировке выводов.

Благодарности. Выражаем признательность коллегам, высказавшим критические замечания в адрес нашей статьи.

Authors / Об авторах

Albina I. Kuralesova, Dr. Sci. (Biol.) / **Куралесова Альбина Ивановна**, д-р биол. наук
ORCID: https://orcid.org/0000-0003-2935-1325
Alla G. Grosheva, Cand. Sci. (Biol.) / **Грошева Алла Германовна**, канд. биол. наук
ORCID: https://orcid.org/0000-0002-0951-5380
Elena N. Genkina / **Генкина Елена Николаевна**
ORCID: https://orcid.org/0000-0002-7594-0473
Ilias B. Esmagambetov, Cand. Sci. (Biol.) / **Есмагамбетов Ильяс Булатович**, канд. биол. наук
ORCID: https://orcid.org/0000-0002-2063-2449

Received 28 March 2025
Revised 11 July 2025
Accepted 12 September 2025

Поступила 28.03.2025
После доработки 11.07.2025
Принята к публикации 12.09.2025