

## REVIEW

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# New therapeutic approaches of mesenchymal stem cells-derived exosomes

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## Abstract

Mesenchymal stem cells (MSCs) have been demonstrated to have a great potential in the treatment of several diseases due to their differentiation and immunomodulatory capabilities and their ability to be easily cultured and manipulated. Recent investigations revealed that their therapeutic effect is largely mediated by the secretion of paracrine factors including exosomes. Exosomes reflect biophysical features of MSCs and are considered more effective than MSCs themselves. Alternative approaches based on MSC-derived exosomes can offer appreciable promise in overcoming the limitations and practical challenges observed in cell-based therapy. Furthermore, MSC-derived exosomes may provide a potent therapeutic strategy for various diseases and are promising candidates for cell-based and cell-free regenerative medicine. This review briefly summarizes the development of MSCs as a treatment for human diseases as well as describes our current knowledge about exosomes: their biogenesis and molecular composition, and how they exert their effects on target cells. Particularly, the therapeutic potential of MSC-derived exosomes in experimental models and recent clinical trials to evaluate their safety and efficacy are summarized in this study. Overall, this paper provides a current overview of exosomes as a new cell-free therapeutic agent.

Keywords: Mesenchymal stem cells, Exosomes, Cell-free therapy, Therapeutic potential

## Background

Nowadays, multipotent mesenchymal stem cells (MSCs) have been extensively examined because of their usage in clinical trials. Their effective influence in cellular therapy and regenerative medicine is known for their strong immunosuppressive, immunomodulatory and regenerative activity [1, 2]. In addition, their considerable potential was demonstrated in the treatment of immune-mediated, inflammatory and degenerative diseases [3–9].

MSCs generally are multipotent, somatic progenitor/ stem cells first isolated from adult bone marrow [10, 11] and successfully differentiated from marrow hematopoietic cells according to their adherent nature in in vitro cell lines and fibroblastic morphology. They are able to self-recover and retain variable differentiation potency

\*Correspondence: jana.janockova@gmail.com Associated Tissue Bank, Faculty of Medicine, P. J. Safarik University in Kosice, Tr. SNP 1, 04011 Kosice, Slovakia toward multi-lineages [12, 13]. The International Society for Cellular Therapy has officialy defined minimal criteria for MSCs, following as (a) being plastic-adherent cells, (b) having adipogenic, osteogenic and chondrogenic trilineage mesenchymal differentiation capacity and (c) being positive (>95%) for surface antigens CD73, CD90 and CD105 and negative (<2%) for hematopoietic markers CD34, CD45, CD14 or CD11b, CD79α or CD19 and HLA-DR (typical markers of hematopoietic cells) [14]. Human MSCs were described in many tissues (Fig. 1), not only in those of mesodermal origin (bone marrow, bone, adipose, synovial membrane and muscle) but also in skin, heart, lungs, brain, kidneys, thymus, liver and pancreas [14, 15]. Another excellent sources of human MCSs are umbilical cord tissue and placenta [16-18]. However, it was revealed that MSCs obtained from various tissues have differences in gene expression, proliferation activity and differentiation potencial. In addition, some variations in surface antigens expression compared to requirements of minimal criteria were reported. Existing variances



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indicate specific features of MSCs from different tissues and organs or are related with isolation and cultivation protocols [19]. MSCs from different tissues can be cultured prior to clinical use. They can grow easily in the culture dish which leads to an easy manipulation in terms of isolation and cultivation. Subsequently, prepared MSCs suspensions may be introduced intravenously or trough local injection to obtain the required therapeutic effects directly or indirectly [20]. Further characteristics include typical plasticity, intrinsic tropism towards injured or inflammed area (known as homing) and an extensive release of numerous useful growth factors, cytokines and another bioactive soluble factors as important indication of their potential clinical applications in tissue repair and regeneration [21].

There is an evidence of tissue alteration by MSCs through secretion of paracrine factors contained in extracellular vesicles (EVs). EVs are a group of cell-derived structures (composed of lipid bilayer membranes), which play an essential role in intercellular communication via transfer of bioactive proteins, lipids and RNAs and represent a potential source for circulating biomarkers of diseases [22]. EVs are generally divided, depending on their biogenesis, into subgroups, like exosomes (40–150 nm in diameters), microvesicles (150–1000 nm in diameter) and apoptotic bodies (50–2000 nm in diameter) [23]. Recent studies suggest possible substitution of the biological MSCs activity with MSC-derived exosomes [24–26]. Therefore, exosomes could represent a considerable alternative to cell therapy.

This review is focused on the characterization of MSCs-derived exosomes and their perspective using in

cell-free therapeutic applications, as well as on the summarization of important facts about general MSCs' paracrine secretion.

#### Paracrine secretion of MSCs

MSCs perform their immunomodulatory activity not only through cell–cell interactions but also via strong paracrine impact. The MSCs' paracrine effect was firstly described by Heynesworth et al. They notified secretion of a large spectrum of cytokines, chemokines and growth factors by MSCs with possible significant effects on cells in their periphery [27]. However, precise mechanism of action is still unknown and under examination. Numerous studies confirmed that factors secreted by MSCs could regenerate injured myocardium and improve cardiac function in porcine model [28], ameliorate acute renal failure and protect against limb tissue injury [29], promote in vitro and in vivo arteriogenesis [30] or support neovascularization [31].

One of the main pattern representing MSCs secretion of biological factors is by EVs which are classified as membrane vesicles filled with plenty of different proteins, microRNAs or/and messenger RNAs and have been progressively studied as the therapeutic agent in MSCs secretion [32]. The lipid bilayer of EVs encloses their bioactive capacity and protects them from enzymatic degradation. EVs are nowadays defined by their size, sedimentation rate, biogenesis pathway or protein delivery, but most of these parameters are neither terminal nor specific for any of EVs type. They have different structural and biochemical properties depending on their intracellular site of origin, which can affect their given functions [33]. Regardless of their origin, EVs are circular membrane particles possesing the characteristics of the origin cells, containing cytosol. In regard to their intracellular origin and the mechanisms of formation, EVs may be classified as exosomes, microvesicles and apoptotic bodies [23].

Apoptotic bodies are released as products of an appoptotic cell disassembly into subcellular fragments. There is an evidence that EVs generated during apoptosis have an important immunoregulatory role in autoimmunity, infection and cancer [34]. Microvesicles, also called as ectosomes or shedding vesicles, represent a heterogenous population formed by external budding and cleavage of the cell membrane. There is a large volume of phosphatidylserine on their surface and great number of proteins associated with lipid rafts (cholesterol-rich microdomains). Assembling of microvesicles is related to an increase of calcium ions which by calpain activation supports the cytoskeleton reorganization leading to the separation of plasma membrane protrusion from the cortical actin [35, 36]. Microvesicles may contain several plasma proteins

depending on the type of the cell they originated and therefore specific markers are required for their identification. The generic marker is Anexin V. CD45 is used to identify leukocyte-derived microvesicles, CD42b/ CD31- and CD62P for plateled-derived microvesicles, and CD31+/CD42-, CD62E and CD144 are used for characterization of endothelial-derived microvesicles [37]. In addition, microvesicles may contain selectins, integrins, metalloproteinases and CD40 ligand [38]. On the other hand, exosomes are smaller and homogenous, have an endosomal origin and are formed by the internal budding of the multivesicular body membrane. The mechanism of their assembling and separation is still unknown [31]. Lipid bilayer of exosomes contains sphingomyelin, phosphatidylserine, phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol and monosialotetrahex-osylganglioside, which are similar to the cell plasma membrane composition [39]. Considered markers of exosomes are tetraspanins (CD9, CD63, CD81 and CD82), TSG101 (tumour susceptibility gene 101), heat shock proteins HSP70 and HSP90 and ALIX [39].

In general, it was shown that EVs are able to effectively copy the therapeutic effect of MSCs, mainly in tissue repair and regeneration in some preclinical models, e.g. exosomes potentially applied in wound healing and cutaneous regeneration [40], human adult liver stem cells—derived microvesicles increased hepatocyte proliferation associated with an accelerated morphological and functional recovery in a rat model [41] or human bone marrow MSCs—derived microvesicles increased proliferation and reduced apoptosis of tubular cells in a mice model [42].

#### Exosomes

Presently, the best characterized EVs are exosomes, which secretion into extracellular area by hematopoietic cells, more specifically by reticulocytes, was firstly described in late 1980s [43-45]. Initially, exosomes secreted from cells were considered as homeostasis secondary products or cellular waste from cell injury without any significant influence on cells nearby. Nowadays, exosomes are considered as a special agent of intracellular communication, playing a major role in cellular processes including immune response [46], antigen presentation [47] and signal transduction [48]. It was indicated that exosomes are produced and released by various types of healthy cells involving adipocytes, epithelial cells, fibrolasts, neurons, astrocytes and Schwann cells. In addition, they were found in numerous types of body fluids including cerebrospinal, synovial and amniotic fluid, urine, sperm, saliva, blood, ascites, vitreous and brest milk [49].

#### The biogenesis/formation and secretion of exosomes

In general, the biogenesis of exosomes begins within the endosomal system (Fig. 2) during which early endosomes (generated by internal budding) are unfolded into the late endosomes or multivesicular bodies (MVBs) and the endosomal membrane is invaginated to form intraluminal vesicles (ILVs) in the lumen of the organelles. The MVBs can either fuse with lysosomes to degrade their content or fuse with the plasma membrane to secrete the volume of ILVs as exosomes [50].

The endosomal sorting complex required for transport (ESCRT) machinery is very important for the MVBs/ ILVs formation, vesicle budding and protein cargo sorting [51]. Ubiquitin is a relevant signal agent that transports membrane proteins and/or damaged cellular elements to lysosomes for degradation. It is also known as signal molecule for exosomal cargo sorting on the endosome membrane [52]. ESCRT machinery is composed from four multiprotein complexes, namely ESCRT-0, -I, -II, -III and the associated AAA ATPase VPS4 complex [51]. Separation of proteins to MVBs includes segregation of the ubiquitinated proteins into lipid rafts with ESCRT-0. TSG101 (ESCRT-I protein) is able to bind to ubiquitinated cargo proteins and sorts endocytic ubiquitinated cargos into MVBs. Subsequently, ESCRT-II complex is activated, which starts the oligomerization and production of the ESCRT-III complex. This complex is involved in proceeding of the budding process responsible for the sequestration of MVBs proteins, sends the deubiquitinating enzyme to remove the ubiquitin label from the cargo proteins and then sorts them into ILVs. Finally, ESCRT-III complex is separated from MVB membrane by sorting protein VPS4 and is unfolded by ATPase [53, 54]. The precise role of ESCRT machinery in the generating



of ILVs secreted later as exosomes is still unclear. In the screening study of RNA interference targeting ESCRT associated proteins in HeLa cells was shown that the depletion of Hrs, TSG101 and STAM1 proteins can reduce the exosomes secretion [55]. It was examined by nanoparticle tracking analysis that knockdown of Hrs reduced exosome secretion from head and neck squamous cell carcinoma cells [56]. Likewise, exosome secretion was increased by knockdown of the ESCRT-III and associated proteins ALIX, VTA1, VPS4B and CHMP4C [55]. Specifically, increase of exosomal level and typical exosomal markers (CD63, HSP70) was confirmed after syndecan – syntenin – ALIX depletion in MCF-7 cells [57].

Alternatively, sorting of exosomal cargo into MVBs and following ILVs formation can occur via ESCRT independent mechanism. Proteolipid protein containing exosomes requires for their secretion ceramide which is able to initiate the exosome budding into MVBs [58]. Expression of tetraspanins (transmembrane proteins rich in exosomes) CD9 and CD82 increased the exosomal release of  $\beta$ -catenin (involved in regulation and organization of cell-cell adhesion and gene transcription) from HEK293 cells [59]. The oligomerization of oligomers could play a significant role in exosome biogenesis based on CD43 exosomal sorting in Jurkat T-cells [60]. Observably, there are various possible mechanisms for separation of bioactive molecules into exosomes, either ESCRT dependent or independent, allow to work depending on the cell type and/or cellular homeostasis. In addition, it was shown that numerous diseases and other pathological conditions enhance exosome secretion. Increased quantity of exosomes were noticed in tumor cells, by progression of inflammation, angiogenesis and coagulation [61-63].

#### Molecular composition of exosomes

The molecular structure of exosomes is related not only to the cell type of origin but also to the microenvironment involving mechanical properties, biochemical impulses and topography, which could influence protein cargo regulation of the secreted exosomes [39]. Exosome secretion and their composition can also be modulated by other environmental factors such as oxygen level, type of disease, mechanical stress or media composition [64].

Exosomes are composed of various macromolecules involving unique lipid and protein structures and nucleic acids (Fig. 3). Exosomes are characterized by abundant amount of miRNAs with majority in the form of premiRNAs, which are inactive until their conversion to mature miRNAs [65]. Considering the endosomal origin of exosomes, they contain proteins participating in membrane transport and fusion (e.g. annexins, Rab, flotillin, GTPases), MVBs biogenesis (e.g. ALIX, TSG101) and



also proteins associated with lipid microdomains (integrins and tetraspanins). Besides that, another frequently determinated proteins are associated with cytoskeleton (e.g. tubulin, myosin, actin) and metabolism (e.g. GADPH) [54], heat shock proteins (HSC70, HSC90), tissue specific proteins (e.g. MHC II located on the surface of exosomes secreted by dendritic cells or by B-lymphocytes) or proteins specific for cancer cell lines (e.g. glioma EGFR, breast cancer HER2, ovarian cancer CD24) [66].

Specifically, numerous studies on the protein and RNA composition of MSC-derived exosomes have been reported. Lai et al. investigated the proteome of HPLC-purified human embryonic stem cells—derived exosomes using mass spectrometry and cytokine array. They identified more than 850 proteins and detected total protein complement of a 20S proteasome with very high reliability [67]. Kang's group realized proteomic analysis of the nanoscale size-based fractionation of exosomes from human neural stem cells and identified 103 proteins. Results from their study confirmed, that exosomes larger than  $\sim$ 50 nm were morphologically different from those which were smaller than  $\sim$ 50 nm [68]. MSC-derived exosomes were found to contain also all five enzymes involved in the ATP synthesis of glycolysis, namely

glyceraldehyde 3-phosphate dehydrogenase, phosphoglycerate kinase, phosphoglucomutase, enolase and pyruvate kinase m2 isoform [69]. Furthermore, Arslan's group detected enzymatically active CD73 in MSCderived exosomes responsible for the generating of extracellular adenosine from released adenine nucleotides [69]. Exosomes are able to activate adenosine receptors and thus generate adenosine-affected phosphorylation of ERK1/2 and Akt in H9C2 cardiomyocytes [70].

The genetic information in RNAs of exosomes which are endocytosed by acceptor cells is allow to influence the protein expression in those cells. Exosomes contain RNAs mostly in size range less than 700 nt. Chen et al. identified the presence of small RNAs (less than 30 nt) in human embryonic stem cells-derived MSCs' conditioned medium, which were encapsulated in cholesterol rich phospholipid vesicles [65]. Plethora of miRNAs responsible for post-transcriptional maintainig of gene expression were detected in MSC-derived exosomes which are active in acceptor cells [71] and participate in physiological and pathological processes. Research group of Ratajczak et al. reported that embryonic stem cells - derived exosomes are highly enriched in mRNA (for numerous transcription factors, receptors and cytokines) [72]. Furthermore, Valadi et al. identified different miRNAs including let-7, miR-1, miR-15, miR-16, miR-181 and miR-375 in exosomes isolated from mastcell line (MC/9), primary bone marrow-derived mast cells (BMMC) and human mast-cell line (HMC-1) [73], which have been suggested to play an important role in exocytosis, tumorigenesis, angiogenesis and haematopoiesis [74]. Ono et al. reported that miR-23b promotes dormancy in breast cancer cells [75]. Exosomal miRNAs derived from umbilical cord MSCs, mainly represented by let-7f, miR-145, miR-199a and miR-221 supported the suppression of hepatitis C virus RNA replication [76]. Results of several sequencing studies also demonstrated, that exosomes isolated from human blood serum and urine contain marked amount of other RNA types, such as tRNA, rRNA, snRNA snoRNA, piRNA and scaRNA [77].

The current studies of the structure and composition of exosomes have relevant importance and are still under examination. Wang et al. compared paracrine functions in vivo and exosomal profiles of human endometrium-, bone marrow- and adipose-derived MSCs in a rat model of myocardial infarction. Analyses of exosomal micro-RNAs showed that miR-21 expression was improved in exosomes derived from endometrium [78], suggesting that innate differences of various MSC-derived exosomes have substantial influence on their clinical efficacy. The importance of exosomes has long been recognized also due to their capability to transfer important cellular cargoes (proteins, DNA, mRNA, miRNAs) to target cells. Recent evidences suggest that exosomes are involved both in normal physiological functions and in pathological conditions. Deeper understanding of the exosomes content may influence the study of various diseases. Some research groups demonstrated that tetraspanin complexes significantly contributes to selective target binding of exosomes to target cells [79, 80]. Thakur et al. showed that the presence of dsDNA in exosomes represented the whole genomic DNA and could be used for identification of mutations in parental tumor cells. They determined that tumor-derived exosomes carry dsDNA and may be use as a circulating biomarker in the early detection of cancer and metastasis [81]. Liang et al. used engineered exosomes for co-delivery of chemotherapeutic drug 5-fluorouracil and chemoresistance miR-21 inhibitor oligonucleotide to reduce the drug resistance in colorectal carcinoma and thus to improve the efficacy of cancer treatment [82]. Yang et al. demonstrated the capability of brain endothelial cell-derived exosomes to deliver siRNA across the brain-blood barrier in zebrafish and thus inhibit VEGF [83]. Results suggested potential application of natural exosome vesicles in the treatment of brain disease [83]. Raposo et al. showed that both human and murine B-lymphocytes secrete exosomes to induce antigen-specific MHC (major histocompatibility complex) II-restricted T cell responses, reffering to exosome usefulness as biological instruments in immunotherapy [84].

The therapeutic effect and biodistribution of exosomes is also greatly affected by the origin of exosome producing cells. MSC-derived exosomes regarding to their inner properties and source of origin may play a relevant role in their clinical efficiency and represent an ideal delivery system for intermediate processes in specific target cells.

#### Therapeutic potential of MSC-derived exosomes

MSC-derived exosomes increasingly play an important role in intracellular communication mechanism and tissue repair and their clinical use may supply substantial advantages in comparison with their live cells due to potential to reduce undesirable side effects after application as well as infusional toxicities, uncontrolled cell growth and possible tumor formation. Moreover exosomes transplantation seems to be less risky and may have several advantages in contrast to cell applications. Exosomes are neither able to mutate and duplicate, nor induce metastasis. They have been tested in various animal models (Table 1) for human diseases (e.g. hypoxic pulmonary hypertension [85], acute kidney injury [86], liver fibrosis [87]) and it was detected that their functions are very similar to MSCs. First therapeutic potential of MSC-derived exosomes was described in a Langendorff

| MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo   | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo  | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo  | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the   | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Wnt/β-catenin   | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Whrt/8-catenin<br>pathway   | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Whr/β-catenin<br>pathway<br>Fxosome treatment  | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Wntr/β-catenin<br>pathway<br>Exosome treatment<br>reduces the exones- | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Wnt/β-catenin<br>pathway<br>Exosome treatment<br>reduces the expres-<br>sion of PDARy | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Wht/β-catenin<br>pathway<br>Exosome treatment<br>reduces the expres-<br>sion of PPARN,<br>Wort3-3, Wort10b | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Whrt/β-catenin<br>pathway<br>Exosome treatment<br>reduces the expres-<br>sion of PPARY,<br>Whrta, Wrrt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Whrt/β-catenin<br>pathway<br>Exosome treatment<br>reduces the expres-<br>sion of PPARY,<br>Whrta, Whrt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Whrt/β-catenin<br>pathway<br>Exosome treatment<br>reduces the expres-<br>sion of PPARY,<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>calls and liver<br>fibrosis tissue | MSC-derived [108]<br>exosomes reduced<br>liver fibrosis in vivo<br>through the<br>Whrt/β-catenin<br>pathway<br>Exosome treatment<br>reduces the expres-<br>sion of PPARY,<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis stissue  
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  | Exosomes derived [1<br>from human RM-  | Exosomes derived [1<br>from human BM-<br>MSCs in 2D or 3D  | Exosomes derived [1<br>from human BM-<br>MSCs in 2D or 3D   | Exosomes derived [1<br>from human BM-<br>MSCs in 2D or 3D<br>cultures improved   | Exosomes derived [1<br>from human BM-<br>MSCs in 2D or 3D<br>cultures improved<br>functional recov-               
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| Wnt/β<br>Wnt/β<br>pathw<br>Exosom   | Wht/Å<br>pathw<br>Exosome<br>reduce  | wnt/b<br>pathw<br>Exosome<br>reduce  | Exosome<br>reduce  | Exosome<br>reduce   | reduce  | 5  |   | Wht3a   |  | hepati   | cellsa   | fibrosi   | fibrosi   
  | Exosome  | fibrosi<br>Exosome<br>from h   | fibrosi<br>Exosome<br>MSCs 1  | fibrosi<br>Exosome<br>from h<br>MSCs i<br>culture  | fibrosi<br>froom<br>MSCS i<br>function<br>function  
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  | fibrosi<br>from h<br>from h<br>MSCs i<br>MSCs i<br>MSCs i<br>culture<br>frunctic<br>frunctic<br>frunctic<br>frunctic<br>frunctic<br>frunctic<br>frunctic<br>frunctic<br>frunctic<br>frunctic<br>from h<br>brain i<br>regula                
  | fibrosi<br>from h<br>from h<br>MSCs i<br>MSCs i<br>MSCs i<br>culture<br>functio<br>erv, pr<br>erence<br>inflam<br>brain i<br>sion of<br>sion of<br>sion of  | fibrosi<br>from h<br>from h<br>MSCs i<br>MSCs i<br>MSCs i<br>culture<br>functio<br>ery, pre-<br>neuroo<br>reduce<br>brain i<br>brain i<br>sion of<br>genes<br>i nats of<br>brain i<br>sion of   | fibrosi<br>from h<br>MSCs i<br>MSCs i<br>MSCs i<br>culture<br>functio<br>ery, pr<br>erats aff<br>brain i<br>brain i<br>genes<br>sion of<br>genes<br>blast o  
  | fibrosi<br>from h<br>from h<br>MSCs i<br>MSCs i<br>MSCs i<br>culture<br>functio<br>ery, pre<br>reduce<br>reduce<br>brain i<br>brain i<br>sion da<br>sion da<br>genes<br>blast o<br>in vivo-E<br>in vivo-E  | fibrosi<br>from h<br>from h<br>MSCs i<br>MSCs i<br>MSCs i<br>culture<br>functio<br>evy, pr<br>evy, pr<br>evy, pr<br>evro<br>inflam<br>brain i<br>sion of<br>sion of<br>blast of<br>ln vivo-E<br>lated t<br>tion in h<br>for in h<br>lated t  |
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  | N.D  | N.D  | D.N   | D.N  | Q.<br>Z   
   | C.N   | Q.<br>Z   | Q.<br>Z  | Q.<br>Z  
   | Q.<br>Z  | <u>О</u> .<br><i>Z</i>   
   
  | <u>О</u> .<br><i>Z</i>   
                | N.D<br>miR-196a miR-   | N.D<br>miR-196a, miR-<br>miR-206   | N.D<br>miR-196a, miR-<br>miR-206   
  | N.D<br>miR-196a, miR-<br>miR-206   
  | N.D<br>miR-196a, miR-<br>miR-206  | N.D<br>miR-196a, miR-<br>miR-206  | N.D<br>miR-196a, miR-<br>miR-206   
  | N.D<br>mir-196a, mir-<br>mir-206   | N.D<br>miR-196a, miR-<br>miR-206   |
|   |  |  |  |   |   |  |   |   |  |  |  |   |   
  | Intravenously via the  | Intravenously via the tail vein  | Intravenously via the tail vein   | Intravenously via the I<br>tail vein   | Intravenously via the I<br>tail vein  
   | Intravenously via the I<br>tail vein  | Intravenously via the I<br>tail vein  | Intravenously via the I<br>tail vein   | Intravenously via the I tail vein  
   | Intravenously via the I<br>tail vein   | Intravenously via the I tail vein  
   
  | Intravenously via the I tail vein  
                | Intravenously via the I<br>tail vein<br>Defects treated with   | Intravenously via the I<br>tail vein<br>Defects treated with<br>hydgogel + EVs   | Intravenously via the I<br>tail vein<br>Defects treated with<br>hydgogel + EVs   
  | Intravenously via the I<br>tail vein<br>Defects treated with<br>hydgogel + EVs   
  | Intravenously via the I<br>tail vein<br>Defects treated with<br>hydgogel + EVs  | Intravenously via the I<br>tail vein<br>Defects treated with<br>hydgogel + EVs  | Intravenously via the I<br>tail vein<br>Defects treated with<br>hydgogel + EVs   
  | Intravenously via the I<br>tail vein<br>Defects treated with<br>hydgogel + EVs   | Intravenously via the I<br>tail vein<br>Defects treated with<br>hydgogel + EVs   |
|   |  |  |  |   |   |  |   |   |  |  |  |   |   
  | Wistar rats model  | Wistar rats model  | Wistar rats model<br>of traumatic brain   | Wistar rats model<br>of traumatic brain<br>injury  | Wistar rats model<br>of traumatic brain<br>injury   
   | Wistar rats model<br>of traumatic brain<br>injury   | Wistar rats model<br>of traumatic brain<br>injury   | Wistar rats model<br>of traumatic brain<br>injury  | Wistar rats model<br>of traumatic brain<br>injury  
   | Wistar rats model<br>of traumatic brain<br>injury  | Wistar rats model<br>of traumatic brain<br>injury  
   
  | Wistar rats model<br>of traumatic brain<br>injury  
                | Wistar rats model<br>of traumatic brain<br>injury  | Wistar rats model<br>of traumatic brain<br>injury<br>Calvarial defects in<br>SD rats   | Wistar rats model<br>of traumatic brain<br>injury<br>Calvarial defects in<br>SD rats   
  | Wistar rata model<br>of traumatic brain<br>injury<br>Calvarial defects in<br>SD rats   
  | Wistar rats model<br>of traumatic brain<br>injury<br>Calvarial defects in<br>SD rats  | Wistar rats model<br>of traumatic brain<br>injury<br>Calvarial defects in<br>SD rats  | Wistar rats model<br>of traumatic brain<br>injury<br>Calvarial defects in<br>SD rats   
  | Wistar rats model<br>of traumatic brain<br>injury<br>Calvarial defects in<br>SD rats   | Wistar rats model<br>of traumatic brain<br>injury<br>Calvarial defects in<br>SD rats   |
|   |  |  |  |   |   |  |   |   |  |  |  | Trout matic brain   |   
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                | Injury<br>Bone defects   | injury<br>Bone defects   | Injury<br>Bone defects   
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|   | protein assav). TEM.   | protern assay), i Livi,  | NTA, western blot-   | ting (CD9, CD63,  | CD81. TSG101. and   | Alix markers)  |   |   |  |  |  |   | of total protein  
  |  | Concentration (RCA   | concentration (BCA  | concentration (BCA protein assay),   | concentration (BCA<br>protein assay),<br>qNano nanopore-  
   | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),   | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase   
   | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass   
   
  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry   
                | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Determination  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>dased detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Determination<br>of total protein  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Determination<br>of total protein<br>concentration (BCA  
  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Determination<br>of total protein                
  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-bhase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Determination (BCA<br>of total protein<br>concentration (BCA  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Determination<br>of total protein<br>concentration (BCA<br>protein assay), elec-<br>tron microscopy,<br>tron microscopy,  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Determination<br>of total protein<br>concentration (BCA<br>protein assay), elec-<br>tron microscopy,<br>flow cytometry   
  | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Q Exactive mass<br>spectrometry<br>D Etermination<br>of total protein<br>concentration (BCA<br>protein assay), elec-<br>tron microscopy,<br>flow cytometry<br>(CD63)   | concentration (BCA<br>protein assay),<br>qNano nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase<br>chromatography,<br>Q Exactive mass<br>spectrometry<br>Q Exactive mass<br>spectrometry<br>Determination (BCA<br>protein assay), elec-<br>tron microscopy,<br>flow cytometry<br>(CD63)   |
|   |  |  |  |   |   |  |   |   |  |  |  | Descipitation /Evo  | Duick exosome   
  |  | isolation)   | isolation)  | isolation)   | isolation)  
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  | isolation)   
                | Isolation)<br>Gradient ultracentrif-   | isolation)<br>Gradient ultracentrif-<br>ugation, ultrafiltra-  | isolation)<br>Gradient ultracentrif-<br>ugation, ultrafiltra-<br>tion  
  | isolation)<br>Gradient ultracentrif-<br>ugation, ultrafiltra-<br>tion  
  | isolation)<br>Gradient ultracentrif-<br>ugation, ultrafiltra-<br>tion   | isolation)<br>Gradient ultracentrif-<br>ugation, ultrafiltra-<br>tion   | isolation)<br>Gradient ultracentrif-<br>ugation, ultrafiltra-<br>tion  
  | isolation)<br>Gradient ultracentrif-<br>ugation, ultrafiltra-<br>tion  | isolation)<br>Gradient ultracentrif-<br>ugation, ultrafiltra-<br>tion  | | | | | | | | | | | |
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| Protein assay, i.t.m,<br>NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers)  | NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers)  | NIA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers)  | ting (CD9, CD63, pathway<br>CD81, TSG 101, and Exosome treatment<br>reduces the expres-<br>sion of PPARy, Wrt3a, Wnt10b  | CD81, TSG101, and Exosome treatment<br>Alix markers)<br>Wrt3a, Wnt10b   | Alix markers)<br>sion of PPARY,<br>Wh13a, Wh10b   | sion of PPARY,<br>Wh13a, Wh10b   | WIT31 WITJOD<br>WIT32 WITJOD  |   |  | what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both  | what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate  | what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tisue  | What contributed what contributed to inhibition of downstream gene expression (WISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue futured to be added fibrosis tissue  | Human Precipitation (Exo- Determination Traumatic brain Onlick exosome of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate
cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both Hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both Hepatic stellate cells and liver fibrosis tissue of rotal Induction (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver (MISP1, Cyclin D1) in both Hepatic stellate cells and liver ( | Human Precipitation (Exo- Determination Injury Wistar rats model tail vein for for the month man BM- isolarion (RCA) of trainmatic hrain and invertige to the month man BM- MCCs in 20 or 30 m MCCs in  | Human Precipitation (Evo- Determination Injury Wistar rats model injury Wistar rats work with Wistar Wistar rats work with Wistar Rats Wis      | Human Precipitation (Exo-<br>bioliticion (KP1), Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue<br>isolation) concentration (BCA<br>injury Wistar rats model<br>isolation) concentration (BCA<br>injury Wistar rats model<br>injury wistar rats model<br>injury concentration (BCA<br>injury wistar rats model<br>injury wistar rats model<br>injury wistar rats model<br>injury concentration (BCA<br>injury wistar rats model<br>injury wistar rats model<br>intervention wistar rats model<br>inter             | Human       Precipitation (Exo-<br>isolation)       Determination<br>from histor       Traumatic brain<br>of traumatic brain<br>injury       Contral impact<br>Mistar rats model<br>tail vein<br>injury       Intravenously via the<br>Mistar rats model<br>tail vein<br>injury       Intravenously via the<br>Mistar rats model<br>tail vein<br>Mistar rats model<br>tail vein<br>tail vein<br>tai  | Human Precipitation (Exo-<br>isolation) concentration Branch injury<br>(2vclin D1) in both<br>reparts stellate<br>expression (WJSP),<br>Cyclin D1) in both<br>reparts stellate<br>expression (WJSP),<br>Cyclin D1) in both<br>hepatic stellate<br>expression (WJSP),<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue<br>fibrosis tissue<br>fib  | Human Precipitation (Exo-<br>Duick exosome of total protein<br>isolation) concentration (BCA<br>Name of total protein<br>isolation) concentration (BCA<br>Duick exosome of total protein<br>isolation) concentration (BCA<br>Name namopore-<br>based detection,<br>SDS-page (CD9,<br>SDS-page (CD9,   | Human Precipitation (Evo-<br>Duick exosome of rotal protein<br>Solation) assay,<br>protein assay,<br>protein assay,<br>Solation) anopore-<br>based effort,<br>injury<br>protein assay,<br>protein assa | Human Precipitation (Exo Determination Traumatic brain Outick exosome of total protein assay).<br>Duck exosome of total protein injury Vistar rats model tail vein injury dan N.D. Exosomes derived fillen for human BM. For filter and liver filter assats and a fraumatic brain of traumatic brain injury data tail vein injury injury injury injury injury injury are consecuted and induced neuro-assats and induced neuro-assats and induced neuro-assats and a fraumatic brain injury   | Human Precipitation (Evo Determination Fraumatic brain Outload downstream gene scont WISP1, Cyclin D1) in both hepatic stellate constreamed of total protein injury Wistar rats model injury Wistar rats model injury of traumatic brain injury of traumatic brain injury injury of traumatic brain injury injury injury intervolus via the N.D Excosmes derived [114] from human BM- MSCs in 20 or 3D protein assay).   | Human Precipitation (Exo-<br>Buman Precipitation (Exo-<br>Buman Contrast chain<br>Ouck exosome of total protein<br>solation)<br>Ouck exosome of total protein<br>solation)<br>Determination<br>Traumatic brain<br>Ouck exosome of total protein<br>injury<br>Solation)<br>Determination<br>Traumatic
brain<br>Solation)<br>Determination<br>Traumatic brain<br>Solation<br>Determination<br>Traumatic brain<br>Solation)<br>Determination<br>Traumatic brain<br>Solation<br>Determination<br>Traumatic brain<br>Solation<br>Determination<br>Traumatic brain<br>Solation<br>Determination<br>Traumatic brain<br>Solation<br>Determination<br>Traumatic brain<br>Solation<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determination<br>Determinat  
   
   | Human Pecipitation (Exo Determination<br>Human Pecipitation (Exo Determination<br>Human Pecipitation (Exo Determination<br>Human Pecipitation (Exo Determination<br>Quick exosome of total protein<br>Solation) concentration (BCA<br>Duck exosome of total protein<br>Solation) concentration (BCA<br>Solation) (MSP1,<br>Cyclin D1) in both<br>hepatic stellare<br>Protein assay,<br>of traumatic brain<br>Solation) concentration (BCA<br>Solation) (MSP1,<br>Cyclin D1) in both<br>hepatic stellare<br>Protein assay,<br>of traumatic brain<br>Solation) (SP1,<br>Cyclin D1) in both<br>hepatic stellare<br>Protein assay,<br>of traumatic brain<br>Solation) (SP1,<br>Cyclin D1) in both<br>hepatic stellare<br>Protein assay,<br>of traumatic 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| Human Precipitation (Evo Determination Traumatic brain Ordical impact Intravenously via the NLD Evosome downstream gene expression (WISP), Cyclin D1) in both hepatic stellare for the and liver fibritistic stellare for the and liver in traumatic brain injury of traumatic brain injury of traumatic brain injury detection, 2005, 205, 2010, 2011   | Human Precipitation (Exo-<br>Betantic brain<br>Quick evosome of total protein<br>Quick evosome of total protein<br>Siolation)<br>Precipitation (Exo-<br>Betantictic<br>Nitraumatic brain<br>Quick evosome of total protein<br>Siolation)<br>Precipitation (Exo-<br>Betantictic<br>Distribution<br>Precipitation (Exo-<br>Betantictic<br>Distribution<br>Precipitation (Exo-<br>Betantictic<br>Distribution<br>Precipitation (Exo-<br>Betantictic<br>Distribution<br>Precipitation (Exo-<br>Betantictic<br>Distribution<br>Precipitation (Exo-<br>Betantictic<br>Distribution<br>Precipitation<br>Distribution<br>Precipitation 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| Human     Pecipitation (kso-<br>concentration (ks),<br>solution)     Determination<br>ownstream gene<br>constream gene<br>constream gene<br>constream gene<br>constream gene<br>constream gene<br>constream gene<br>consentration (ks),<br>solution)     Mat.conntouerd<br>ownstream gene<br>constream gene<br>constream gene<br>constream gene<br>consentration (ks),<br>solution)     Mat.conntouerd<br>ownstream gene<br>constream gene<br>constream gene<br>constream gene<br>consentration (ks),<br>solution)     Mat.conntouerd<br>ownstream gene<br>constream gene<br>constream gene<br>propertion       Human     Pecipitation (kso-<br>ouck exosome     Determination     Traumatic brain     Intravenously via the     ND     Exosomes derived<br>final
viantic brain       Name     Concentration (kso-<br>souck exosome     Determination     Intravenously via the     ND     Exosomes derived<br>final viantic brain       Name     Social (kso)     Concentration (kso-<br>souck exosome     Intravenously via the     ND     Exosomes derived<br>final viantic brain       Name     Social (kso-<br>social (ksocial reported<br>final viantic brain     Concentration (kso-<br>final viantic brain     Exosomes derived<br>final viantic brain     No       Human     Gadient utracentrif-<br>spectrometry     Detects in<br>hydgogel+tiss     No     Exosomes derived<br>final viantic brain     No       Human     Gadient utracentrif-<br>spectrometry     Detects in<br>hydgogel+tiss     No     No     No       Materion     Solution     Exosomes derived<br>final viantic filtion     No     No     No       Human     Gadient utracentrif <t< td=""><td>Human     Precipitation (So-<br/>overstream gene<br/>concentration)     Term nation<br/>from hibbition of<br/>concentration (SP),<br/>cyclin D1) in both<br/>concentration (SC)     Intervenuely value     ND     Exosome concentration<br/>concentration<br/>from human BM,<br/>from human human BM,<br/>from human human human human human human human</td><td>Human Pecipitation (Exo-<br/>bereariser) (MST, Cyclin D)) in both concentration (MST, Cyclin D) in concentrati</td><td>Human     Precipitation (Exo     Determination     Traumatic brain     Controllege     controllege       Human     Precipitation (Exo     Determination     Traumatic brain     Controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1       SS page (CD9, CD8), controllege     of traumatic brain     Mata controllege     Cycin D1       Mata controllege     of traumatic brain     Mata controllege     Cycin D1     Cycin D1       Mata controllege     of traumatic brain     Mata controllege     Cycin D1     Cycin D1       Mata controllege     Of traumatic brain     Mata controllege     Cycin D2     Cycin D1       Mata controllege     Of traumatic br</td><td>Human Precipitation (Exc. Determination Industries of total impact industries of controllated industri</td><td>Human     Precipitation (Exo     Determination     Traumatic brain     Controllate     Matcrontrollate     Matcrontrollate       Human     Precipitation (Exo     Determination     Traumatic brain     Cortical impact.     Intravenously via the ND     Exosmose     Exosmose       Rolation)     Concentration     Traumatic brain     Cortical impact.     Intravenously via the ND     Exosmose     Exosmose       Rolation)     Concentration     Traumatic brain     Wistar rats model     Tal vieln     Exosmose     Exosmose       Solation)     Concentration     Mistar rats model     Tal vieln     Mistar rats     Exosmose     Exosmose       Solation     Concentration     Mistar rats     Mistar rats     Mistar rats     Exosmose     Exosmose       Solation     Concentration     Mistar rats     Mistar rats     Mistar rats     Exosmose     Exosmose       Solation     Concentration     Mistar rats     Mistar rats     Mistar rats     Exosmose     Exosmose       Solation     Concentration     Mistar rats     Mistar rats     Mistar rats     Exosmose     Exosmose       Concentration     Concentration     Mistar rats     Mistar rats     Mistar rats     Mistar rats     Mistar rats       Human     Grotal protein     Detertion     Sorad</td></t<> <td>Human     Precipitation (Evo-<br/>outic exosome<br/>solation)     Termination<br/>receptation (Evo-<br/>outic exosome<br/>solation)     Termination<br/>receptation (Evo-<br/>outic exosome<br/>of total protein<br/>solation)     Termination<br/>receptation<br/>outic exosome<br/>of traumatic bain<br/>of traumatic bain<br/>injury     Termeously value<br/>value<br/>injury     N/S     Exosome<br/>of traumatic<br/>protein<br/>solation)     Termination<br/>receptation<br/>of traumatic bain<br/>injury     Termeously value<br/>value<br/>injury     N/S     Exosome<br/>of traumatic<br/>protein<br/>solation)     Termination<br/>receptation<br/>or of traumatic<br/>protein<br/>solation)     Termination<br/>recetoring<br/>of traumatic bain<br/>injury     Termeously value<br/>value<br/>injury     N/S     Exosome<br/>of traumatic<br/>protein<br/>solation     Termination<br/>receptation       Human     Gadient uftracentri-<br/>toring concentration<br/>(Coal)     Determination<br/>injury     Determination<br/>injury     Invector<br/>inframatic<br/>injury     Invector<br/>inframatic<br/>injury     Invector<br/>inframation<br/>injury     Exosome<br/>of or of societing<br/>injury     Invector<br/>inframation<br/>inframation<br/>inframation<br/>inframation     Invector<br/>inframation<br/>inframation     Invector<br/>inframation<br/>inframation     Invector<br/>inframation<br/>inframation     Invector<br/>inframation     Invector<br/>inframation     Invector<br/>inframation     Invector<br/>inframation     Invector<br/>inframation     Invector<br/>inframation     Invector<br/>inframation     Invector<br/>inframation     Invector<br/>inframati</td>   | Human     Precipitation (So-<br>overstream gene<br>concentration)     Term nation<br>from hibbition of<br>concentration (SP),<br>cyclin D1) in both<br>concentration (SC)     Intervenuely value     ND     Exosome concentration<br>concentration<br>from human BM,<br>from human human BM,<br>from human human human human human human human  | Human Pecipitation (Exo-<br>bereariser) (MST, Cyclin D)) in both concentration (MST, Cyclin D) in concentrati   | Human     Precipitation (Exo     Determination     Traumatic brain     Controllege     controllege       Human     Precipitation (Exo     Determination     Traumatic brain     Controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1) in both       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1       Quick exosome     of tatal potein     injury     Mata controllege     Cycin D1       SS page (CD9, CD8), controllege     of traumatic brain     Mata controllege     Cycin D1       Mata controllege     of traumatic brain     Mata controllege     Cycin D1     Cycin D1       Mata controllege     of traumatic brain     Mata controllege     Cycin D1     Cycin D1       Mata controllege     Of traumatic brain     Mata
controllege     Cycin D2     Cycin D1       Mata controllege     Of traumatic br   | Human Precipitation (Exc. Determination Industries of total impact industries of controllated industri  | Human     Precipitation (Exo     Determination     Traumatic brain     Controllate     Matcrontrollate     Matcrontrollate       Human     Precipitation (Exo     Determination     Traumatic brain     Cortical impact.     Intravenously via the ND     Exosmose     Exosmose       Rolation)     Concentration     Traumatic brain     Cortical impact.     Intravenously via the ND     Exosmose     Exosmose       Rolation)     Concentration     Traumatic brain     Wistar rats model     Tal vieln     Exosmose     Exosmose       Solation)     Concentration     Mistar rats model     Tal vieln     Mistar rats     Exosmose     Exosmose       Solation     Concentration     Mistar rats     Mistar rats     Mistar rats     Exosmose     Exosmose       Solation     Concentration     Mistar rats     Mistar rats     Mistar rats     Exosmose     Exosmose       Solation     Concentration     Mistar rats     Mistar rats     Mistar rats     Exosmose     Exosmose       Solation     Concentration     Mistar rats     Mistar rats     Mistar rats     Exosmose     Exosmose       Concentration     Concentration     Mistar rats     Mistar rats     Mistar rats     Mistar rats     Mistar rats       Human     Grotal protein     Detertion     Sorad   | Human     Precipitation (Evo-<br>outic exosome<br>solation)     Termination<br>receptation (Evo-<br>outic exosome<br>solation)     Termination<br>receptation (Evo-<br>outic exosome<br>of total protein<br>solation)     Termination<br>receptation<br>outic exosome<br>of traumatic bain<br>of traumatic bain<br>injury     Termeously value<br>value<br>injury     N/S     Exosome<br>of traumatic<br>protein<br>solation)     Termination<br>receptation<br>of traumatic bain<br>injury     Termeously value<br>value<br>injury     N/S     Exosome<br>of traumatic<br>protein<br>solation)     Termination<br>receptation<br>or of traumatic<br>protein<br>solation)     Termination<br>recetoring<br>of traumatic bain<br>injury     Termeously value<br>value<br>injury     N/S     Exosome<br>of traumatic<br>protein<br>solation     Termination<br>receptation       Human     Gadient uftracentri-<br>toring concentration<br>(Coal)     Determination<br>injury     Determination<br>injury     Invector<br>inframatic<br>injury     Invector<br>inframatic<br>injury     Invector<br>inframation<br>injury     Exosome<br>of or of societing<br>injury     Invector<br>inframation<br>inframation<br>inframation<br>inframation     Invector<br>inframation<br>inframation     Invector<br>inframation<br>inframation     Invector<br>inframation<br>inframation     Invector<br>inframation     Invector<br>inframation     Invector<br>inframation     Invector<br>inframation     Invector<br>inframation     Invector<br>inframation     Invector<br>inframation     Invector<br>inframation     Invector<br>inframati  |
| Protein asay, i EM, mount we set for blot-<br>NTA, western blot-<br>ting (25101, and<br>Aix markers) and β-catenin<br>treduces the expres-<br>sion of PPAR, Wrt13a, Wrt10b<br>and β-catenin,  | NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers)<br>and β-catenin,<br>wht3a, Wht10b<br>and β-catenin,   | NLA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>sion of PPARγ,<br>Wht3a, Wht10b<br>and β-catenin,  | ting (CD9, CD63, pathway CD81, TSG101, and Exosome treatment reduces the expression of PPAR, Wnt3a, Wnt10b and $\beta$ -catenin, and $\beta$ -catenin, events and the expression of PPAR, who is the   | CD81, TSG101, and Exosome treatment Alix markers) Alix markers) sion of PPAR, wht3a, Wht10b and β-catenin, eventse and β-catenin, events | Alix markers) reduces the expression of PPARy.<br>Wht3a, Wht10b<br>and β-catenin,   | sion of PPARY,<br>Wh13a, Wh10b<br>and β-catenin,   | Wint10b<br>Wint2a, Wint10b<br>and β-catenin,  | and β-catenin,  |  | to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both  | to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate  | to inhibition of<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue   | to inhibition of downstream gene expression (WSP1, Cyclin D1) in both hepatic stellate calls and liver fibrosis tissue function of the calls and liver fibrosis tissue for the calls and liver fibrosis tissue | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]   | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114] Cyclin D1) in both head liver fallate callate | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived find tail vein isolation) concentration (BCA Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived find isolation) concentration (BCA Determination Injury Wistar rats model tail vein Intravenously via the N.D Exosomes derived find isolation) concentration (BCA Determination Injury Wistar rats model tail vein Intravenously via the N.D Exosomes derived find iter isolation) concentration (BCA Determination Injury Wistar rats model tail vein Intravenously via the N.D Exosomes derived find isolation) concentration (BCA Determination Intravenously via the N.D Exosomes derived Intel Intravenously via the N.D Exosomes derived Intel Intervention (BCA Determination (BCA Determination Intervention (BCA Determination (BCA Determinat      | Human Precipitation (Exo<br>solation) concentration Each and liver<br>fibrition of downstream gene<br>expression (WSP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue<br>isolation) concentration (BCA<br>isolation) concentration (BCA<br>isolation) concentration (BCA<br>injury contrantic brain<br>protein assay), protein assay), injury<br>injury contraction (BCA<br>injury con | Human       Precipitation (Exo       Determination       Traumatic brain       to inhibition of downstream gene expression (WSP1, Cyclin D1) in both hepatic stealate expressi stealate expression (W   | Human Precipitation (Exo-<br>Duck
exosome of total protein<br>isolation) concentration (BCA<br>Duck exosome of total protein<br>isolation) concentration (BCA<br>protein assay).<br>Protein assay).   | Human Precipitation (Evo-<br>Outick exosome of total protein<br>Solation) Precipitation (Evo-<br>Dutick exosome of total protein<br>injury Wistar rats model<br>isolation) Precipitation<br>Outick exosome of total protein<br>injury Wistar rats model<br>injury Wistar rats model<br>injury<br>SDS-page (CD9,<br>SDS-page (CD9,<br>SD             | Human Precipitation (BC-<br>buick exosme of total protein<br>isolation) concentration (BC-<br>protein assay),<br>protein a                            | Human Precipitation (Exo-<br>Bundation)<br>Autor Precipitation (Exo-<br>Bundation)<br>Autor assay),<br>addition<br>Autor assay),<br>addition<br>Autor assay),<br>addition<br>Autor assay),<br>addition<br>Autor assay),<br>addition<br>Autor assay,<br>addition<br>Autor and a<br>Autor and a<br>Aut  | Human Precipitation (Exo-<br>Burnan Precipitation (Exo-<br>Determination Traumatic brain Cortical impact. Intravenously via the NLD<br>Ouck exosome of total protein<br>isolation) Precipitation (Exo-<br>Determination Traumatic brain Cortical impact. Intravenously via the NLD<br>Protein assay), injury Wistar rats model tail vein MSCs in 20 or 3D<br>of traumatic brain injury injury injury<br>Displate (CD9,<br>DB3, CD81), exosome of traumatic brain injury injury<br>injury injury injury injury injury inductional recov-<br>ery, promoted recovo-<br>ery, promoted re  | Human Pecipitation (Evo<br>Ounstream gene<br>expression (WSP1,<br>Cyclin D1) in both<br>hepatic stallate<br>expression (WSP1,<br>Cyclin D1,<br>hoth<br>hepatic stallate<br>hoth<br>hepatic stall   
   
  | Human Precipitation (Evo<br>Determination<br>Human Precipitation (Evo<br>Determination<br>Human Precipitation (Evo<br>Determination<br>Human Precipitation (Evo<br>Determination<br>Duck exosome<br>of rotal protein<br>Natar rats model<br>isolation)<br>traumatic brain<br>Natar rats model<br>injury<br>traumatic brain<br>injury<br>traumatic brain<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>inj  | Human Precipitation (Evo-<br>buck exosome of total protein injury Wasta rats model tail vein (MSP1,<br>Cyclin D1) in both<br>hepatic stellane<br>expression (MSP1,<br>Cyclin D1) in both<br>hepatic stellane<br>estission (MSP1,<br>Cyclin D1,<br>hepatic stellane<br>estission (MSP1,<br>Cyclin D1,<br>hepatic stellane<br>estission (MSP1,<br>hepatic stellane<br>estission (MSP1,<br>hepatic stellane<br>estission<br>hepatic stellane<br>estission<br>hepatic stellane<br>estission<br>hepatic stellane<br>estission<br>hepatic stellane<br>estission<br>hepatic stellane<br>estission<br>hepatic stellane<br>estission<br>hepatic stellane<br>hepatic stella  | Human Pecipitation (Exo<br>Buck evosome of total protein<br>Outick evosome of total protein<br>Solation)<br>Pecipitation (Exo<br>Outick evosome of total protein<br>Outick evosome of total protein<br>Solation)<br>Protein asso),<br>Protein asso<br>Protein asso),<br>Protein asso),<br>Protein asso<br>Protein asso),<br>Protein asso),<br>Protein asso),<br>Protein asso<br>Protein asso),<br>Protein asso),<br>Protein asso<br>Protein approtein asso<br>Protein approtein asso<br>Protein approtein asso<br>Protein approtein appr   | Human     Precipitation (Exc.)     Determination     Taumatic brain     Cortical impact     Intravenously via the     ND     Exosones certification (Wight, Cyclin D1) in both heads callate expension (Wight, Cyclin D1) in both heads callate expension (Wisht, Cyclin D1) in both head callate callate callate in jury     Miscal impact     Intravenously via the     ND     Exosones cancer in proved in jury       0uck exosone     of traumatic brain     Intravenously via the     ND     Exosones cancer in proved in jury     Exosones cancer in proved in jury       0uck exosone     of traumatic brain     Intravenously via the     ND     Exosones cancer in proved in jury       0uck exosone     of traumatic brain     Unitravenously via the     ND     Exosones cancer in proved in travenously via the       0uck exosone     of traumatic brain     Unitravenously via the     ND     Exosones cancer existsue       0uck exosone     of traumatic brain     Unitravenously via the     ND     Exosones cancer existsue       0uck exosone     of traumatic brain     Unitravenously via the     ND     Exosones cancer existsue       0uck exosone     Dorestore     Dorestore     Dorestore     Exosones cancer existsue       0uck exosone     Dorestore     Dorestore     Dorestore     Exosones cancer existsue       0uck exosone     Dorestore     Dorestore     Dorestore     Exosones cancer existsue <tr< td=""><td>Human Precipitation (Exo<br/>Buck exosome of rotal protein<br/>ouck exosome of rotal protein<br/>ouck exosome of rotal protein<br/>solation)<br/>protein assayl<br/>protein assayl<br/>p</td><td>Human Pecipitation (Exo-<br/>budic exosome of total protein<br/>ould exosome of total protein<br/>solation) correntation<br/>noverstation<br/>Solation) correntation<br/>ased detection<br/>SS-page (CD3)<br/>human Gadient ultracentrif<br/>human Gadient ultracentrif<br/>betweetechase<br/>chromatography<br/>Human Gadient ultracentrif<br/>potein assay), else<br/>chromatography<br/>human Gadient ultracentrif<br/>potein assay),
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| Protein assay, i EM,<br>NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>ison of PPAR,<br>Wrn13a, Wrn10b<br>and β-catenin,<br>what contributed   | NTA, western blot-<br>ing (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers)<br>and β-catenin, what contributed  | NLA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Sion of PPARγ,<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed  | ting (CD9, CD63, pathway CD81, TSG101, and CD81, TSG101, and Alix markers) sion of PPARγ, Wnt3a, Wnt10b and β-catenin, what contributed  | CD81, TSG 101, and Exosome treatment Alix markers) alix markers) sion of PPARγ, Wht3a, Wht10b and β-catenin, what contributed   | Alix markers) reduces the expression of PPARγ Wnt3a, Wnt10b and β-catenin, what contributed   | sion of PPARγ.<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed  | what contributed what contributed   | and β-catenin, what contributed   | and p-caterinit, what contributed  | downstream gene<br>expression (WISP1,<br>Cyclin D1) in both  | downstream gene<br>expression (WISP1,<br>Cyclin D71) in both<br>hepatic stellate   | downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue   | downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>finosis tissue<br>downstream gene<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>finosis tissue  
  | Human       Precipitation (Exo-       Determination       Traumatic brain       Mispatic       Mispatic         Muman       Precipitation (Exo-       Determination       Traumatic brain       Mispatic       Mispatic         Muman       Precipitation (Exo-       Determination       Traumatic brain       Mispatic       Mispatic         Muman       Precipitation (Exo-       Determination       Traumatic brain       Mispatic       Mispatic  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114] Cyclin D1) in both hepatic stellate expression (WISP1,  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114] Cyclin D1) in both hepatic stellate expression (WISP1,       | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114] Quick exosome of total protein injury Wistar rats model tail vein isolation) concentration (BCA injury Wistar rats model tail vein fibrosis tissue fibrosis tissue injury of traumatic brain injury injury injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury Wistar rats model tail vein injury concentration (BCA injury with injury transmotel tail vein injury concentration (BCA injury with with with with with with with with  | Human Precipitation (Exo-<br>biolation) (Exo-<br>biolation (Exo-<br>biolation) (Exo | Human Precipitation (Evo-<br>Quick exosome of total protein<br>Solation) concentration (BCA<br>isolation) concentration (BCA<br>isolation) concentration (BCA<br>protein assay),<br>protein assay,<br>protein ass                                     | Human Precipitation (Evo-<br>Duck exosome of total protein<br>ouck exosome of total protein<br>isolation) Evo-<br>based detection,<br>SDS-page (CD9,<br>SDS-page (CD9,<br>SDS-pag | Human Precipitation (Exo<br>Outick exosome of total protein<br>Outick exosome of total protein<br>injury<br>protein assay),<br>protein assay,<br>protein as                         | Human Precipitation (Exo-<br>Duck exosome of total protein<br>solation) concentration (BCA<br>isolation)  | Human Precipitation (Evo Determination<br>Numan Precipitation (Evo Determination<br>Cyclin Dut) in both<br>hepatic stellate<br>Cyclin Dut) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue<br>injury<br>Dotein assay),<br>S5-page (CD9,<br>S55-page (C | Human Precipitation (KPF), Gyclin D1) in both<br>hepatic stellate<br>downstream gene<br>ereasion (WFP1,<br>Cyclin D1) in both<br>hepatic stellate<br>eella and liver<br>fibrosis stesue<br>of total protein<br>audic exosome of the audic exosome of total protein audic audic exosome of total protein audic audic exosome of total protein audic audic audic exosome of total protein audic au   
   
  | Human Precipitation (Exo-<br>Burnan Decipitation (Exo-<br>Burnantic brain Contical impact Intravenously via the ND<br>Ouck exosome of fotal protein<br>injury Wistar rats model tail vein<br>solation) protein assay),<br>protein assay,<br>protein approtein appr  | Human Precipitation (Exo-<br>Budick exosome of rotal protein<br>Quick exosome of rotal protein<br>alloring and<br>solation) concentration (BCA<br>injury<br>solation) receptation (BCA<br>injury<br>Human Garlient (BCA<br>injury<br>Human Garli | Human     Precipitation (Exo-<br>loadition)     Determination<br>means<br>Concentration<br>(MSP1,<br>Cyclin D) in both<br>Cyclin D (Cyclin D (C   | Human Precipitation (Exo-<br>Perension (WSP), Cyclin D) in both<br>Cyclin D) in both<br>Cyclin D) in both<br>Cyclin D) in both<br>Cyclin D) in both<br>Precipitation (Exo-<br>Determination<br>Concentration (Exo-<br>Distribution)<br>Concentration (Exo-<br>Distribution)<br>Concentra  
   
   | Human Precipitation (Exc<br>build be activity of transmoted<br>build b  | Human       Pecipitation (Exo-<br>ouck exosome<br>oucentration)       Determination<br>injury       Traumatic brain<br>wistar rats model<br>injury       Intravenously via the<br>visitar rats model<br>injury       ND       Exosomes derived<br>fibres fibres<br>fibres fibres<br>fibres fibres<br>fibres fibres fibres fibres<br>fibres fibres fibres fibres<br>fibres fibres fibres<br>fibres fibres fibres<br>fibres fibres fibres fibres<br>fibres fibres fibres fibres<br>fibres fibres fibres<br>fibres fibres fibres<br>fibres fibres fibres fibres<br>fibres fibres fibres<br>fibres fibres fibres fibres<br>fibres fibres fibres fibres<br>fibres fibres fibres fibres<br>fibres fibres<br>fibres fibres   | Human     Precipitation (Exo.     Determination     Traumatic brain     Cortical impact     Repart cellstate       Under exonance     of rotal protein     injury     injury     intravenously varthe     ND     Exosomes expersion (WSP1,<br>Cyclin D1) in both       Ould evosome     of rotal protein     injury     injury     intravenously varthe     ND     Exosomes expersion (WSP1,<br>Cyclin D1) in both       Solation)     concentration (BcA     of reatmatic brain     Cortical impact     Intravenously varthe     ND     Exosomes expersion and level<br>for on stand prection.       Solation)     concentration (BCA     of reatmatic brain     of reatmatic brain     of reatmatic brain     Intravenously varthe     ND     Exosomes expersion strate<br>for on stand prection.       Solation)     concentration (BCA     injury     Wistar rats model     tail vein     Misci in 20 or 3D       Nisci in 20 or 3D     Oricial impact     injury     injury     injury     injury       Solation, Utanfire-     concentration (BCA     of reatmatic brain     injury     injury       Def exotic     Solation     Solation     intravenuel (BCA     injury       Def exotic     Solation     of reatmatic brain     injury     injury       Def exotic     Solation     Solation     injury     injury       Def exolation   | Human     Precipitation (Exo-<br>based detection)     Determination<br>notice eosome<br>of creatingtion (Exo-<br>based detection)     Determination<br>notice and meter<br>notice and me  | Human       Precipitation (Exo       Determination       Tarumatic brain       Control impact       Control im   | Human         Precipitation (Bc-<br>diation)         Data<br>Laumatic brain<br>(Scient D1) in both<br>Contral impact         Contral impact         Intravenously via the<br>Misar rats model         ND         Exoanne advised<br>ration         Contral impact           Human         Precipitation (Bc-<br>diation)         Date         Date         Misar rats model         Intravenously via the<br>Misar rats model         ND         Exoanne advised<br>ration         Exoanne advised<br>ration         Exoanne advised<br>ration         [114]           Misar rats model         Date         Misar rats model         Iail vein         ND         Exoanne advised<br>ration         [114]           Misar rats model         Date         Date         Misar rats model         Iail vein       
 ND         Exoanne advised<br>ration         [114]           Misar rats model         Date         Misar rats model         Iail vein         ND         Exoanne advised<br>ration         [114]           Misar rats model         Date         Misar rats model         Iail vein         ND         Exoanne advised<br>ration         [114]           Misar rats model         Date         Misar rats model         Iail vein         [114]         [114]           Misar ration misary recording ration         Date         Date         [114]         [114]         [114]         [114]         [114]         [114] </td   |
| Protein assay, itm,<br>NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers)<br>is no of PAR,<br>Wrn3a, Wrn10b<br>and β-catenin,<br>what contributed<br>to inhibition of                          | NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers)<br>Alix markers<br>Alix markers<br>A | NLA, western blot-<br>ting (CD9, CD63,<br>CD81, TGG101, and<br>Alix markers)<br>Sion of PPAR,<br>Wht3a, Wht10b<br>and β-catenin,<br>what contributed<br>to inhibition of   | ting (CD9, CD63, pathway CD81, TSG 101, and CD81, TSG 101, and Aix markers) Exosome treatment reduces the expression of PPARY, Wnt3a, Wnt10b and β-catenin, what contributed to inhibition of to inhibition of   | CD81, TSG 101, and Exosome treatment reduces the expression of PPARγ Sion of PPARγ Wrt3a, Wnt Ob and β-catenin, what contributed to inhibition of to inhibition of  | Alix markers)<br>sion of PPARγ,<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of  | sion of PPARy,<br>Whr3a, Whr10b<br>and β-catenin,<br>what contributed<br>to inhibition of  | Wrt3a, Wrt10b<br>Wrt3a, Wrt10b<br>and β-cartributed<br>what contributed<br>to inhibition of   | and B-contributed what contributed to inhibition of   | and p-caterinit,<br>what contributed<br>to inhibition of   | expression (WISP1,<br>Cyclin D1) in both   | expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate   | expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue  | expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue   | Human Precipitation (Exo- Determination initive with rate and invertigation (Wish control in both head in the secone of total induce and initive for the secone of total initive with the secone of total initive with the secone of total initive with the secone of total initive matching initive with the secone of total matchi | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Quick exosome of total protein injury Wistar rats model tail vein for from human BM-<br>isolarion) concentration (RCA of the model tail vein MCCs in 20 or 20)  
  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114] Cuick exosome of total protein injury Wristar rats model tail vein isolation) concentration (BCA of traumatic brain contract brain isolation) (WIST)   | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived fibrosis tissue isolation) concentration (BCA injury Wistar rats model tail vein isolation) protein assay), injury injury concentration (114)   | Human Precipitation (Exo- Determination Traumatic brain Ortical impact Intravenously via the N.D Exosomes derived fibrosis tissue isolation) concentration (BCA Distribution) of traumatic brain of traumatic brain injury Wistar rats model tail vein MSCs in 2D or 3D cultures improved functional recov-   | Human Precipitation (Exo-<br>Ouick exosome of total protein<br>isolation) Exosomes derived<br>isolation) Precipitation (Exo-<br>of total protein<br>isolation) Cortical impact<br>Nistar rats model<br>injury<br>protein assay,<br>expression (WISP1,<br>Cyclin D1) in both<br>hepatic stellate<br>cyclin D1) in both<br>hepatic stellate<br>cyclin D1) in both<br>hepatic stellate<br>cortical impact<br>injury<br>from human BM-<br>Mistar rats model<br>tail vein<br>Mistar rats model<br>tail vein<br>t | Human Precipitation (Exo-<br>Outick exosome of total protein<br>Siolation) etermination<br>Mistar rats model<br>isolation) etermination<br>Mistar rats model<br>isolation) etermination<br>Mistar rats model<br>Minum SDS-page (CD9,<br>SDS-page  | Human Precipitation (Exo-<br>Determination (Fxo-<br>Determination (Fxo-<br>Determinatio (Fxo-<br>Determination (Fxo-<br>Determination (Fxo-<br>D   | Human Precipitation (Exo-<br>But and liver<br>fibrosis tissue<br>Human Precipitation (Exo-<br>But espatic stellate<br>cypromoted<br>isolation)<br>Cuick exosome<br>of total protein<br>injury<br>protein assay,<br>and nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD83, CD81,<br>reversed-phase<br>concentration
(BCA<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injur | Human Precipitation (Exo-<br>Butan Precipitation (Exo-<br>Duck exosome of total protein<br>isolation) concentration (BCA<br>Duck exosome of transistic brain<br>isolation) (BCA<br>Duck exosome of transistic brain<br>isolation (BCA<br>Duck exosome of trans   | Human Precipitation (Exo. Determination<br>Unick exosome of total protein<br>Solation) concentration (Exo. Determination<br>Duick exosome of total protein<br>injury Wistar rats model<br>injury Wistar rats model<br>injury Mistar rats model<br>tail vein<br>Divide assay,<br>protein approtein approtei  
   
   | Human Precipitation (Exo- Determination<br>Numeric Prince Signal Wight, Special S   | Human Pecipitation (Exo- Determination Traumatic brain Outs exosome of total protein injury Vistar rats model tail vein Cortical impact Intravenously via the N.D. Exosomes derived [114] ecells and liver fibrosis tissue cells and liver fibrosis tissue and liver fibrosis tissue cals and liver fibrosis tissue and liver fibrosis and liver   | Human       Precipitation (Exo       Determination       Traumatic brain       Cortical impact       Intravenously via the       ND       Expension (WSP1, cyclin D) in both hepatic statuse         Human       Precipitation (Exo       Determination       Traumatic brain       Cortical impact       Intravenously via the       ND       Exosones derived       [114]         Quick exosome       of traumatic brain       Cortical impact       Intravenously via the       ND       Exosones derived       [114]         Quick exosome       of traumatic brain       Cortical impact       Intravenously via the       ND       Exosones derived       [114]         Robit on anopore-       based detection,       SD-spage (CD9,       of traumatic brain       Nists in 20 or 3D   | Human       Precipitation (Exo-<br>location)       Determination<br>(WSP1,<br>Cyclin D1) in both<br>period static<br>Cyclin D1) in both<br>period static<br>(Solation)       Respection<br>(WSP1,<br>Cyclin D1) in both<br>period static<br>(Solation)         Human       Precipitation (Exo-<br>location)       Contral protein<br>(NSP1,<br>Cyclin D1)       Intravenously via the<br>injury       N.D.       Exosomes derived<br>(Intravenously via the<br>of traumatic brain<br>(NSC in 2) or 3D         Note       Solation)       concentration (BCA<br>phano nanopore-<br>pased detection,<br>DS-page (Cb9,<br>DS-page (C   
  | Human       Precipitation (Kso-<br>concentration)      
Taumatic brain<br>(visition)       Taumatic brain<br>(visition)       Taumatic state<br>concentration (Kso-<br>concentration)       Experision (WSp),<br>contral protein<br>(Solation)         Human       Precipitation (Kso-<br>concentration) (Ks  | Human       Precipitation (Exo-<br>based detection)       Intumatic brain<br>injury       Contral impact<br>injury       Intravenously via the<br>visit and liver<br>injury       ND       Exosense evened<br>from human B/M<br>from human B/M<br>(SC sin 2D or 3D<br>MSCs in 2   | Human       Precipitation (Exo-<br>concentration)       Determination       Traumatic brain       Exoremestion (WSP),<br>Found (SP),<br>Found (SP),<br>Foun  | Human       Precipitation (Sc.       Determination       Traumatic brain       Control 10) in both heads callerer close of total protein       minus       Cyclin D) in both heads callerer close of total protein       minus       Cyclin D) in both heads callerer close of total protein       minus       Cyclin D) in both heads callerer close of total protein       minus       Cyclin D) in both heads close of total protein       minus       Cyclin D) in both heads close of total protein       minus       Cyclin D) in both heads close of total protein       minus       Cyclin D) in both heads close of total protein       minus       Cyclin D) in both heads close of total protein       minus       Cyclin D) in both heads close of total monologies       Cyclin D) in both heads close of total protein       minus       Cyclin D) in both heads close of total protein       minus       Concentration (WSP), close of total protein       minus       Cyclin D) in both heads close of total protein       minus       Cyclin D) in both heads close of total protein       minus       Cyclin D) in both heads close of total protein       Missin D or side close of  | Human     Precipitation (Exo.     Determination     Traumatic brain     Intravenously via the ND     Econes of treat protein       Ouick exosome     of traat protein     njuyr     Wistar rats model     Intravenously via the ND     Econes derived       Ouick exosome     of traat natic brain     Nistar rats model     Intravenously via the ND     Econes derived       Ouick exosome     of traat natic brain     Nistar rats model     Intravenously via the ND     Econes derived       Ouick exosome     of traat natic brain     Nistar rats model     Intravenously via the ND     Econes derived       Orest of traat natic brain     orict aumatic brain     Nistar rats model     Intravenously via the ND     Econes derived       Obsis (DB)     Deset deticion     Deset deticion     Deset deticion     Dor 3D     Dor 3D       Obsis (DB)     Deset deticion     Deset deticion     Dor 3D     Dor 3D     Dor 3D       Obsis (DB)     Deset deticion     Dor 3D     Dor 3D     Dor 3D     Dor 3D       Obsis (DB)     Deset deticion     Deset deticion     Dor 3D     Dor 3D     Dor 3D       Obsis (DB)     Deset deticion     Deset deticion     Dor 3D     Dor 3D     Dor 3D       Human     Gradient ultracentrif     Deset deticion     Dor 3D     Dor 3D     Dor 3D       Human </td <td>Human       Precipitation (Eo-<br/>outde exosome<br/>outde exosome<br/>o</td> | Human       Precipitation (Eo-<br>outde exosome<br>outde exosome<br>o |
| Protein asay, i EM,<br>NTA, western blot-<br>tring (CD9, CD63,<br>CD91, T5G101, and<br>Alix markers)<br>Alix markers)<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene  | NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alx markers)     Wnt/β-catenin<br>pathway       Korsome treatment<br>reduces the expres-<br>sion of PARR,<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream opene  | NLA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Sion of PPARγ,<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene   | ting (CD9, CD63,<br>CD81, TSG 101, and<br>CD81, TSG 101, and<br>Alix markers)<br>Alix markers<br>Alix markers      | CD81, TSG 101, and Exosome treatment educes the expression of PPARγ, witta, Wint30, Witta, Wint30, Witta, Wint30, Witta, Wint30, Witta, Wint30, Witta, Wint30, Wint30 | Aix markers)<br>Aix markers)<br>Aix markers)<br>Ant 10b<br>and 3-catenin,<br>what contributed<br>to inhibition of<br>downstream cone                | sion of PPARy,<br>wht3a, Wht10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene                     | wht3a, Wht10b<br>wht3a, Wht10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene   | and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene   | and p-caterim,<br>what contributed<br>to inhibition of<br>downstream cane  | Cyclin D1) in both   | Cyclin D11) in both hepatic  | Cyclin D1) in both<br>hepatic stellate<br>cells and liver<br>fibrosis tisue   | Cyclin Divertion of the contract of the contra | Human Precipitation (Exo- Determination Traumatic brain Ortical impact Intravenously via the N.D Exosomes derived [114]  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Quick exosome of total protein injury Wistar rats model tail vein form man BM-<br>isolarion) concentration (RCA of traumatic brain   | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Quick exosome of total protein injury Wistar rats model tail vein fibrosis tissue isolation) concentration (BCA  
  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Ouick exosome of total protein injury Wistar rats model tail vein form human BM-<br>isolation) concentration (BCA injury of traumatic brain injury contranant brain injury contrain inju   | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114] from human BM- isolation) concentration (BCA injury Wistar rats model tail vein MCS in 2D or 3D protein assay), injury of traumatic brain injury dynames derived injury transmosed in travenous via the N.D from human BM- isolation assay), injury of traumatic brain injury from human Exosomes derived functional recov-  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114] Couck exosome of total protein injury Wristar rats model tail vein injury of traumatic brain protein assay), of traumatic brain protein assay), and nanopore-based detection, based detection, evy, promoted   | Human Precipitation (Exo- Determination Traumatic brain Ortical impact Intravenously via the N.D Precipitation (Exo- Determination Injury Wristar rats model tail vein for traumatic brain injury of traumatic brain injury of traumatic brain protein assay), and nanopore-based detection. SDS-page (CD9, SDS-pa  | Human Precipitation (Exo- Determination Traumatic brain Outick exosome of total protein injury Wistar rats model tail vein N.D. Exosomes derived [114] from human BM- outick exosome of total protein injury Wistar rats model tail vein N.D. Exosomes derived [114] from human BM- protein assay), injury of traumatic brain of traumatic brain based detection, SDS-page (CD9, CD81), CD63, CD81), CD63, CD81, C   | Human Precipitation (Evo-<br>Determination Traumatic brain<br>Quick exosome of total protein<br>isolation) concentration (BCA<br>protein assay),<br>protein arcov-<br>tein assay),<br>protein arcov-<br>tein assay),<br>protein arcov-<br>tein assay),<br>protein arcov-<br>tein arcov-<br>te   | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the NLD Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the NLD Exosomes derived finding isolation) correntation (BCA of traumatic brain injury Wistar rats model tail vein man BM- protein assay), injury injury injury injury injury injury injury injury cortector, SDS-page (CD9, CD63, CD81), reversed-phase detection, corrested-phase detection, corrested-phase detection, corrested-phase chromatography, injury injury injury injury injury injury induced and incompare injury induced and induced neuro- enviored injury induced induced neuro- enviored injury induced neuro- enviored neuro- inflammation in   
   | Human Precipitation (Exo-<br>Determination Traumatic brain Cortical impact Intravenously via the ND Precipitation (Exo-<br>Ouck exosome of total protein injury Wistar rats model tail vein fibrosis tissue<br>Siolation) concentration (BCA of traumatic brain<br>protein assoyne<br>SIS-page (CD9,<br>SIS-page (CD9   
   
   | Human Precipitation (Evo Determination Traumatic brain Outick exosome of total protein injury Outick exosome of total protein injury Outick exosome of total protein injury Mistar rats model tail vein injury of traumatic brain   | Human Precipitation (Evo Determination Traumatic brain Cortical impact Intravenously via the ND Focal seral liver fibrosis tissue concentration (Evo Determination Traumatic brain Ouick evosome of total protein injury Wistar rats model tail vein Stores derived (114) from human BM from human from human BM from human BM from human from human BM from human BM from human BM from human BM from human from huma   | Human       Precipitation (Exo-<br>concentration (Exo-<br>based detection)       Traumatic brain<br>injury       Contical impact<br>traumatic brain<br>of traumatic brain       Intravenously via the<br>traumatic brain       N.D.       Exosones<br>fibrosis tissue<br>fibrosis tissue         Human       Precipitation (Exo-<br>based detection)       Traumatic brain<br>injury       Intravenously via the<br>injury       N.D.       Exosones derived<br>fibrosis tissue         So rabin       Ouck exosome<br>of contentration (BCA<br>isolation)       Injury       Wistar ans model<br>tail vein<br>injury       Intravenously via the<br>injury       N.D.       Exosones derived<br>fibrosis tissue         So rabin       Ouck exosome<br>dramatic brain<br>injury       Vistar ans model<br>tail vein<br>injury       Iniviny       Nistar and<br>travenously via the<br>injury       N.D.       Exosones derived<br>fibrosis tissue         Promosore-<br>chromatography       Dost and<br>traversed chaeterion,<br>chromatography       Exosones derived<br>fibrosis tissue       Iniviny         Human       Gradient ultracentrif       Determination       Bone defects in<br>solution in<br>traversed meuno-<br>ditoral proven       Defects traated with       Infi-196a, mit27a,<br>mitamation in<br>tratis determination in<br>tratin determinatin<br>tratin determination in<br>tratin determination in<br>trat   | Human       Precipitation (Exo-<br>beta created<br>and created<br>and created<br>biolation)       Traumatic brain<br>injury       Traumatic brain<br>injury       Traumatic brain<br>injury       Cyclin D) in both<br>hepatic stellare<br>fibrosis itsue         Human       Precipitation (Exo-<br>ouck exosome<br>of rotal protein<br>isolation)       Tearumatic brain<br>injury       Traumatic brain<br>injury       Exosome serviced<br>injury       Fraumatic brain<br>injury         Namo<br>brased detection-<br>sed detect   
   | Human       Precipitation (Exo-<br>solation)       Determination<br>transmission       Tranmatic brain<br>injury       Control impact<br>injury       Intravenously via the<br>visit ratumatic brain<br>protein assay).       ND       Exosomes derived<br>fibrosi sissue<br>fibrosi sissue         Human       Precipitation (Exo-<br>biolick eosome       Determination       Traumatic brain<br>injury       Intravenously via the<br>onternation (BCA       ND       Exosomes derived<br>fibrosi sissue         Visit ratumatic brain       Duick eosome       onteration (BCA       Nyistir ratumatic brain       Exosomes derived<br>fibrosi sissue         Solation)       protein assay).       onteration (BCA       Nyistir ratumatic brain       Nyistir ratumatic brain         Solation)       protein assay).       onteration (BCA       Nyistir ratumatic brain       Injury       Exosomes derived<br>functional recov-<br>ery promoted       Industriane         Minan       Gadient Ultracentif       Determination in<br>retrose       Exosomes derived<br>functional recov-<br>ery promoted       Industriane         Human       Gradient Ultracentif       Determination in<br>retrose       Exosomes derived<br>functional recov-<br>ery promoted       Promoted<br>functional recov-<br>ery promoted         Human       Gradi   
   | Human       Precipitation (Exo-<br>outck exosome       Determination       Taumatic brain       Material model       Concentratione       Concentratione         Human       Precipitation (Exo-<br>outck exosome       of total protein       Taumatic brain       Intravenously via the       ND       Exosomes derived       [114]         Outick exosome       of total protein       injury       Wistar rats model       tail vein       Exosomes derived       [114]         Namo nanopore-<br>based detection,<br>Sociation       Distration (Exo-<br>onternation (Exo-<br>detection,<br>Sociation)       Taumatic brain       Wistar rats model       tail vein       Exosomes derived       [114]         Funna       Color, CD81,<br>CD81, CD8  | Human Pecipitation (Exo-<br>Determination Traumatic brain Carical impact<br>Natar rats model tail vein for state<br>and live<br>Duck evosome of rotal protein assay).<br>Duck evosome of rotal protein assay,<br>notein assay,<br>protein assay,<br>Sols page (CD9,<br>notein assay),<br>protein assay,<br>protein assay,<br>protein assay,<br>human Gradient ultracentif<br>Human Gradient ultracentif<br>Human Gradient ultracentif<br>Human Gradient ultracentif<br>Human Gradient ultracentif<br>Determination in<br>option assay, elec-<br>tion microscopy,<br>protein assay and the protein assay and the p   | Human     Precipitation (Exo-<br>load latent)     Determination<br>of total impact.     Traumatic brain<br>injury     Intravenously via the<br>visitant mation     ND     Exosones derived<br>lorigitation<br>for munuma BM-<br>for munuma BM-<br>fo  | Human       Precipitation (Exo.       Determination       Traumatic brain       Contral impact       Contrastilitie       Contrastilitie         Under exosome       Outcle exosome       Contral impact       Intravenously via the       ND       Exosomes derived       [114]         Outcle exosome       Contral impact       Intravenously via the       ND       Exosomes derived       [114]         Concentration (Bco       Determination       Intravenously via the       ND       Exosomes derived       [114]         Concentration (Bco       Determination       Intravenously via the       ND       Exosomes derived       [114]         Concentration (Bco       Determination       Intravenously via the       ND       Exosomes derived       [114]         Concentration (Bco       Determination       Intravenously via the       ND       Exosomes derived       [114]         Concentration (Bco       Determination       Concentration (Bco       Intravenously via the       ND       Exosomes derived       [114]         Funded neuro       Determination       Determination       Intravenously via the       ND       Exosomes derived       [114]         Funde       Exosomes derived       Distribution       Exosomes derived       [114]       [114]       [114]       [114]   | Human       Precipitation (Exo       Determination<br>for and its and line<br>biolation)       Trannatic brain<br>for and mark<br>for any order and<br>protein and protein<br>posten and protein<br>protein protein protein protein<br>protein protein protein<br>protein protein protein<br>protein protein protein<br>protein protein protein<br>protein protein protein<br>protein protein<br>protein protein protein<br>protein protein<br>protein protein<br>protein protein<br>protein protein<br>protein protein<br>protein protein<br>protein protein<br>protein protein protein<br>protein protein<br>protein protein<br>protein p   |
| Protein asay, i EM,<br>NTA, western blot-<br>ting (CD63,<br>CD81, TSG101, and<br>Aix markers)<br>Aix markers)<br>Aix markers)<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene                                | NTA, western blot-<br>ing (CD9, CD63,<br>CD81, TSG101, and<br>Alx markers)<br>Alx markers)<br>Alx markers)<br>and $\beta$ -catenin,<br>what contributed<br>to inhibition of<br>downstream gene   | wirky-catenin       ting (CD9, CD63,       cD81, TSG101, and       Alix markers)       cD81, TSG101, and       Alix markers)       sion of PPARy,       wnt3a, Wnt10b       and β-catenin,       what contributed       to inhibition of       downstream gene | ting (CD9, CD63,<br>CD81, TSG101, and<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers<br>Alix markers<br>Ali | CD81, TSG101, and Exosome treatment reduces the expression of PPAR, while3a, Whit10b and β-catenin, what contributed to inhibition of downstream gene expression (WIGD1   | Alix markers)<br>sion of PPARγ<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene                        | sion of PPARγ.<br>Wrt3a, Wrt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene                     | wh13a, Wh10b<br>wh3a, Wh10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene  | and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene   | and p-caterim,<br>what contributed<br>to inhibition of<br>downstream gene<br>evenescion (MICD1   |  | Cyclin U ( ) in both hepatic stellate  | Cyclin U.J.In boun<br>hepatic stellate<br>cells and liver<br>fibrosis tissue  | Cyclin U J In both<br>hepatic stellate<br>cells and liver<br>fibrosis tissue<br>ULIMA Dominiation Commission Control Innoved International Control Innoved Inter   | Cyclin U J In Dom<br>hepatic stellate<br>cells and liver<br>fibrosis tissue<br>Muman Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Ouick exosome of total incluvion Wistar arts model tail vein from human BM-<br>from human BM-   
   | Cyclin U J In Dom<br>Cyclin U J In Dom<br>hepatic stellate<br>cells and liver<br>fibrosis tissue<br>Quick exosome of total protein injury Wistar rats model tail vein<br>icolarion) concentration (RCA of Traumatic brain<br>isolarion) Concentration (RCA of Traumatic brain<br>MCCs in 20 or 30  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Quick exosome of total protein injury Wistar rats model tail vein form human BM-<br>isolation) concentration (BCA of traumatic brain form but and bm-<br>meter for traumatic brain form but and bm-<br>from human BM-<br>MSGs in 20 of traumatic brain for the N.D form human BM-<br>from human BM-<br>MSGs in 20 of traumatic brain for the N.D form human BM-<br>from human BM-<br>MSGs in 20 of 3D   | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Quick exosome of total protein injury Wistar rats model tail vein fibrosis tissue<br>isolation) concentration (BCA of traumatic brain protein assay), injury cultures improved   | Human Precipitation (Exo- Determination Traumatic brain Ortical impact Intravenously via the N.D Exosomes derived [114]<br>Quick exosome of total protein injury Wristar rats model tail vein injury of traumatic brain protein assay), protein assay), injury in   | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Quick exosome of total protein injury Wistar rats model tail vein injury of traumatic brain protein assay), injury injury exotent and protein assay injury exoten assay exoten as assay injury exoten assay exoten as assay exote   | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Ecosomes derived [114] Cuick exosome of total protein injury Wistar rats model tail vein concentration (BCA injury Vistar rats model tail vein M.D Exosomes derived [114] from human BM- Nano nanopore- based detection, SDS-page (CD9, SDS-pa  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Evasomes derived [114] Concentration (BCA Ouck exosome of total protein injury Wistar rats model tail vein concentration (BCA of traumatic brain protein assay), injury injury Costan assay injury Costan assay concentration (BCA of traumatic brain protein assay), concentration (BCA of traumatic
brain injury Wistar rats model tail vein concentration (BCA of traumatic brain protein assay), concentration (BCA of traumatic brain protein assay), concentration (BCA of traumatic brain brain assay), concentration (BCA of traumatic brain brain brain assay), concentration (BCA of traumatic brain brain brain brain brain assay), concentration (BCA of traumatic brain bra   | Human Precipitation (Evo-<br>Duris) of total protein<br>Quick exosome of total protein<br>isolation) concentration (BCA<br>isolation) concentration (BCA<br>isolation) of traumatic brain<br>protein assay),<br>of traumatic brain<br>protein assay),<br>of traumatic brain<br>protein assay),<br>of traumatic brain<br>protein assay),<br>of traumatic brain<br>protein assay),<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>injury<br>inju                               | Human Precipitation (Evo- Determination<br>Quick exosome of total protein<br>solation) concentration (BCA Determination<br>Traumatic brain Cortical impact Intravenously via the NLD Exosomes derived<br>isolation) concentration (BCA of traumatic brain<br>protein assay),<br>protein assay),   | Human Precipitation (Evo Determination Traumatic brain Contral impact Intravenously via the N.D Precipitate cells and liver fibrosis tissue injury Wistar rats model tail vein M.D Provad fibrosis tissue solution) concentration (BCA injury Wistar rats model tail vein SSS-page (CD9, SSS-page (SD9, SSS-page (SD8, SSS), SD0) SSS-page (SD9, SSS), SSS-page (SD9, SSS), SSS-page (S  
   
   | Human Pecipitation (Exo- Determination Traumatic brain Contical impact Intravenously via the NLD Exosomes derived filuation concentration (BCA injury Wistar rats model tail vein concentration (BCA isolation) concentration (BCA injury Wistar rats model tail vein monone based detection, solation) of traumatic brain of traumatic brain concentration (BCA injury Wistar rats model tail vein monone based detection, concentration (BCA injury Wistar rats model tail vein monone based detection, concentration (BCA injury Wistar rats model tail vein monone environed from human BM-from human BM-from nanopore-based detection, concentration (BCA injury Wistar rats model tail vein monone environed from human BM-from nanopore-based detection, concentration (BCA injury QExactive mass pectrometry provided injury QExactive mass pectrometry and monone provided injury definition in the mass pectrometry provided in the matter pr  | Human Precipitation (Evo- Determination Traumatic brain Cortical impact Intravenously via the N.D Evosomes derived [14]<br>Quick exosome of total protein injury Wistar rats model tail vein concentration (BCA Notation) (BCA Notation) concentration (BCA Notation) (BCA Notation  | Human Precipitation (Exo-<br>Duick exosome of total protein in jury Using the ND Precipitation (Exo-<br>Duick exosome of total protein in jury Wistar rats model tail vein Cortical impact intravenously via the ND Prosenes derived (114)<br>Solation) concentration (BCA Of traumatic brain in jury Wistar rats model tail vein MD Precipitation (BCA) of traumatic brain in jury Mistar rats model tail vein Cortical impact in jury Mistar rats model tail vein Cortical impact in travenously via the ND Prosenes derived (114)<br>Solation) concentration (BCA Of traumatic brain injury Mistar rats model tail vein MD Precipitation in travenously via the ND Prosenes derived (114)<br>Disolation) concentration (BCA Of traumatic brain injury Mistar rats model tail vein MD Precipitation in travenously via the ND Precipitation (114)<br>Disolation anopore-<br>based detection, SD-page (CD9, CD8), CD81), reversed-phase<br>CD83, CD81), reversed-phase<br>CD83, CD81, reversed-phase<br>CD81, CD81, reversed-phase<br>CD81, CD81, reversed-phase<br>CD81, reversed-phase<br>CD83, CD81, reversed-phase<br>CD83, CD81, reversed-phase<br>CD83, CD81, reversed-phase<br>CD81,   | Human       Precipitation (Exo-<br>lisolation)       Determination<br>from human (Boosis states<br>solution)       Traumatic brain<br>(Brosis states<br>oncentration (BCA<br>isolation)       Contical impact<br>injury       Intravenously via the<br>wist rats model<br>traumatic brain       ND       Exosomes derived<br>fibrosis states<br>(Brosis states<br>(Brosis states<br>(Brosis states)         Human       Precipitation (Exo-<br>potetion assay),<br>protein assay,<br>protein astater traumatic<br>protein and<br>protein assay,<br>protein assay,<br>protein and<br>protein assay,<br>protein assay,<br>protein assay,<br>protein and<br>protein and<br>pr   
   
  | Human       Precipitation (Evo-<br>cols and inverting<br>outce easome<br>isolation)       Taumatic brain<br>concentration<br>(BCA       Contical impact<br>injury       Intravenously via the<br>visibility       N.D.<br>For some defect solation<br>(BCA       Exosome defered<br>injury         Human       Precipitation (Evo-<br>solation)       Determination<br>injury       Traumatic brain<br>wisation       Intravenously via the<br>wisation       N.D.       Exosomes derived<br>for numan BN-<br>for Minan BN-<br>Mission         Date       Solation)       concentration (BCA       Wistar rais model<br>tail vein       Tail vein       Exosomes derived<br>for mana BN-<br>mingry         Solation)       concentration (BCA       Wistar rais model<br>tail vein       Tail vein       Exosomes derived<br>for mana BN-<br>mingry       [114]         Mississione       Solation,<br>divingry       Exosomes derived<br>for mana to mana to<br>motional recov-<br>ery promoted<br>for motional rec  | Human     Precipitation (Exo-<br>Culter exosome<br>Quick exosome<br>of rotal protein<br>solation)     Tarumatic train<br>injury     Contral impact<br>wistar rats model<br>injury     Intravenously via the<br>visit rate     ND     Exosome advised<br>from human B/N<br>from from from from from<br>from human B/N<br>from from from from human B/N<br>from from from from human B/N<br>from from from from human B/N<br>from human B/N<br>from from from from from from from from  | Human     Precipitation (Exc.     Determination     Traumatic brain     Contral impact     Intravenously via the     N.D.     Exosome service     Control import       Duick exosome     of total protein     injury     Wristar rats model     Intravenously via the     N.D.     Exosome service     [114]       Solation)     concentration (BCA     Wristar rats model     Intravenously via the     N.D.     Exosome service     [114]       Namo monore-     Based detection     Solation)     of traumatic brain     Intravenously via the     N.D.     Exosome service       Solation)     protein assay).     injury     Wristar rats model     Ial vein     MiSCs in 2D or 3D       Precipitation     Solation)     protein assay).     injury     Wristar rats model     Ial vein     MiSCs in 2D or 3D       Solation     Solation     Solation     Solation     injury     Wristar rats model     Ial vein       Misch     Solation     Solation     Solation     Solation     Ian vein     Miscs in 2D or 3D       Promatography.     Solation     Solation     Solation     Solation     Solation     Intravenously via the N.D.     Exosome service       Misch     Solation     Solation     Solation     Solation     Solation     Intravenously via the N.D.     Intravenously in 10   | Human Pecipitation (Exo-<br>biolicitation (Exo-<br>orieration) Pecipitation (Exo-<br>orieration) Protein assoy).<br>Duck exosome of rotal protein<br>out exosome of rotal protein<br>isolation) correntation (Exo-<br>protein assoy).<br>Duck exosome of rotal protein<br>assol detection.<br>Dispected assoc.<br>Human Pecipitation (Exo-<br>protein assoy).<br>Dispected assoc.<br>Human Pecipitation (Exo-<br>protein assoy).<br>Dispected assoc.<br>Human Pecipitation (Exo-<br>protein assoy).<br>Dispected assoc.<br>Human Gadient ultracentif-<br>bet ultracentif-<br>protein assoy.<br>Dispected assoc.<br>Human Gadient ultracentif-<br>protein assoy.<br>Detection assoy.<br>Detection assoy.<br>Human Gadient ultracentif-<br>protein assoy.<br>Detection assor.<br>Detection assor.<br>Detection assor.<br>Detection assor.<br>Detection assor.<br>Detection assor.<br>Detection assor.<br>Detection assor.<br>Detection a                            | Human       Precipitation (Exo.       Determination       Traumatic brain       Control impact<br>injury       Intravenously value       ND       Exones derived<br>fination         Unck exosome       of rotal protein       injury       Wistar rats model       Traumatic brain       Exones derived       Forein human BM   
   | Human       Precipitation (Exo-<br>buck exosome       Determination       Traumatic brain       Contral impact<br>finance       Contranonce<br>finance       Contranote<br>finance   |
| Protein assay, i tim,<br>NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>sion of PPAR,<br>Wrt3a, Wrt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WSP1, | NTA, western blot-<br>ting (CD9, CD63,<br>CD81, TSG 101, and<br>Alix markers)<br>Alix markers)<br>Alix markers<br>Alix markers     | wirky-catenin       ting (CD9, CD63,       cD81, TSG101, and       Alix markers)       sion of PPRR,       wht3a, Wht10b       and β-catenin,       what contributed       to inhibition of       downstream gene       expression (WISP1,                     | ting (CD9, CD63,<br>CD81, TSG101, and<br>Alix markers)<br>Alix markers<br>Alix mar | CD81, TSG 101, and<br>Exosome treatment<br>reduces the expres-<br>sion of PPARY,<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,  | Alix markers)<br>sion of PPARγ.<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1, | ion of PPAR,<br>Wnt3a, Wnt10b<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1, | whita, writiob<br>and β-catenin,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,                                       | and β-carenity<br>and β-carenity<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WSP1,  | and p-caterim,<br>what contributed<br>to inhibition of<br>downstream gene<br>expression (WISP1,  |  | hepatic stellate   | hepatic stellate<br>cells and liver<br>fibrosis tissue  | hepatic stellate<br>cells and liver<br>fibrosis tissue   | hepatic stellate<br>cells and liver<br>fibrosis tissue<br>Muman Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Ouick exosome of total notain injury Wistar arts model tail vein from human BM-  | Human Precipitation (Exo- Determination Traumatic brain Cortical impact Intravenously via the N.D Exosomes derived [114]<br>Quick exosome of total protein injury Wistar rats model tail vein form Muman BM-<br>isolarion) concreterion (RCA of traumatic brain   
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BM- isolation) of traumatic brain protein assay), injury SDS-page (CD9, SDS-page (CD9, CD63, CD81), CD61), CD63, CD81), CD63, CD81), CD61, CD61), CD61, C   | Human       Precipitation (Exo-<br>Outek exosome       Determination       Traumatic brain       Cortical impact       Intravenously via the       N.D       Exosomes derived<br>fibrosis tissue         Human       Precipitation (Exo-<br>Outek exosome       Determination       Traumatic brain       Cortical impact       Intravenously via the       N.D       Exosomes derived<br>from human BM-<br>from human h   | Human Precipitation (Exo- Determination Iraumatic brain Cortical impact Intravenously via the N.D Precipitation (Exo- Determination injury Wistar rats model tail vein N.D Protein assay), protein assay), of traumatic brain protein assay), injury Sicher Si   | Human       Precipitation (Exo-<br>solation)       Determination       Traumatic brain       Corrical impact       Intravenously via the       N.D       Repatic stellate         Human       Precipitation (Exo-<br>guick exosome       of total protein       injury       Wistar rats model       Intravenously via the       N.D       Exosomes derived       [114]         Resolution)       concentration (BCA       of traumatic brain       Wistar rats model       tail vein       MSCs in 2 D or 3D         Protein assay),<br>and no nanopore-<br>based detection,<br>SDS-page (CD9,<br>CD63, CD81),<br>reversed-phase       injury       MSCs in 2 D or 3D       D or 3D         Cube3, CD81),<br>reversed-phase       injury       injury       injury       MSCs in 2 D or 3D         Cube3, CD81),<br>reversed-phase       injury       injury       injury       injury         Cube3, CD81),<br>reversed-phase       injury       injury       injury       injury <tr< td=""><td>Human Precipitation (Exo-<br/>Duck exosome of total protein<br/>20 vick exosome of total protein<br/>injury concentration (BCA<br/>isolation) concentration (BCA<br/>isolation) concentration (BCA<br/>isolation) concentration (BCA<br/>isolation) concentration (BCA<br/>injury Wistar rats model<br/>protein assay),<br/>protein assay,<br/>protein astart arumiter,<br/>protein and<br/>protein and<br/>protei</td><td>Human     Precipitation (Exo-<br/>cals and liver<br/>fibrosistissue     hepatic stellate<br/>cals and liver<br/>fibrosistissue       Human     Precipitation (Exo-<br/>outick exosome<br/>of total protein<br/>isolation)     Traumatic brain<br/>of traumatic brain     Corrical impact<br/>injury     Intravenously via the<br/>visitar rats model<br/>injury     N.D     Exosomes derived<br/>fibrosistissue<br/>fibrosistissue       Namo<br/>observed     Solation)     Corrical impact<br/>injury     Intravenously via the<br/>visitar rats model<br/>injury     N.D     Exosomes derived<br/>fibrosistissue       Solation)     concentration (BCA<br/>isolation)     Wistar rats model<br/>injury     Intravenously via the<br/>visitar rats model<br/>injury     Intravenously via the<br/>visitar rats model<br/>injury     N.D     Exosomes derived<br/>fibrosistissue       Cold3, CD81)     Solation     Of traumatic brain<br/>injury     Intravenously via the<br/>visitar rats model<br/>injury     N.D     Exosomes derived<br/>fibrosistissue       Human     Gradiant ultracentrif     Deferts in     Ordical fibrosi     N.D     Fibrosistissue       Human     Gradiant ultracentrif     Deferts fibrosi     Deferts fibrosi     Intraversitival<br/>fibrosistissue     Intraversitival<br/>fibrosistissue</td><td>Human     Precipitation (Exo-<br/>lice activation)     Determination<br/>from individual intravenously via the<br/>solation)     ND     Exosones derived<br/>from human BM-<br/>from human hu</td><td>Human Precipitation (Exo-<br/>Bulation) Concentration (Exo-<br/>Doticel impact Intravenously via the ND<br/>Siolation) concentration (BCA<br/>isolation) concentration (BCA<br/>protein assay),<br/>protein assay,<br/>protein as</td><td>Human       Precipitation (Exo-<br/>concentration (Exo-<br/>based detection)       Traumatic brain<br/>injury       Contical impact<br/>injury       Intravenously via the<br/>trai vein       N.D.<br/>from human BM-<br/>from human Human<br/>from human BM-<br/>from human BM-<br/>from human BM-<br/>from human Human Human<br/>from human Human Human<br/>from human Human Human<br/>from human Human Human<br/>from human Human</td><td>Human     Precipitation (Exo-<br/>solation)     Determination<br/>cortical impact     Traumatic brain<br/>injury     Cortical impact     Intravenously via the<br/>tail vein     N.D.     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    Human       Gadient ultracentrif       Determination<br/>(Indon)       Exosomes derived<br/>(I</td><td>Human       Precipition (Sro-<br/>out expiration)       Determination<br/>injury       Trannatic brain<br/>of trantation (BCA       Annatic brain<br/>injury       Contral impact<br/>injury       Mean impact<br/>injury       Repair callstate<br/>for and inverticial<br/>for minuma BM-<br/>monstation         Human       Quick exosome<br/>out exists       of trantation (BCA       Trannatic brain<br/>injury       Contral impact<br/>injury       Intravenously varte       ND       Exosomes derived<br/>from human BM-<br/>monstation       [114]         Solation)       concentration (BCA       injury       Viratumatic brain<br/>injury       Intravenously varte       ND       Exosomes derived<br/>from human BM-<br/>monstation       [114]         Row in station       concentration (BCA       injury       Viratumatic brain<br/>injury       Intravenusly varte       ND       Exosomes derived<br/>from human BM-<br/>monstation       [114]         Human       Gradient Urbacentrif       Deriver mass<br/>from addreed neuro-<br/>from exosophic       Exosomes derived<br/>from addreed neuro-<br/>from addr</td></tr<> | Human Precipitation (Exo-<br>Duck exosome of total protein<br>20 vick exosome of total protein<br>injury concentration (BCA<br>isolation) concentration (BCA<br>isolation) concentration (BCA<br>isolation) concentration (BCA<br>isolation) concentration (BCA<br>injury Wistar rats model<br>protein assay),<br>protein assay,<br>protein astart arumiter,<br>protein and<br>protein and<br>protei  | Human     Precipitation (Exo-<br>cals and liver<br>fibrosistissue     hepatic stellate<br>cals and liver<br>fibrosistissue       Human     Precipitation (Exo-<br>outick exosome<br>of total protein<br>isolation)     Traumatic brain<br>of traumatic brain     Corrical impact<br>injury     Intravenously via the<br>visitar rats model<br>injury     N.D     Exosomes derived<br>fibrosistissue<br>fibrosistissue       Namo<br>observed     Solation)     Corrical impact<br>injury     Intravenously via the<br>visitar rats model<br>injury     N.D     Exosomes derived<br>fibrosistissue       Solation)     concentration (BCA<br>isolation)     Wistar rats model<br>injury     Intravenously via the<br>visitar rats model<br>injury     Intravenously via the<br>visitar rats model<br>injury     N.D     Exosomes derived<br>fibrosistissue       Cold3, CD81)     Solation     Of traumatic brain<br>injury     Intravenously via the<br>visitar rats model<br>injury     N.D     Exosomes derived<br>fibrosistissue       Human     Gradiant ultracentrif     Deferts in     Ordical fibrosi     N.D     Fibrosistissue       Human     Gradiant ultracentrif     Deferts fibrosi     Deferts fibrosi     Intraversitival<br>fibrosistissue     Intraversitival<br>fibrosistissue  | Human     Precipitation (Exo-<br>lice activation)     Determination<br>from individual intravenously via the<br>solation)     ND     Exosones derived<br>from human BM-<br>from human hu   | Human Precipitation (Exo-<br>Bulation) Concentration (Exo-<br>Doticel impact Intravenously via the ND<br>Siolation) concentration (BCA<br>isolation) concentration (BCA<br>protein assay),<br>protein assay,<br>protein as   
   | Human       Precipitation (Exo-<br>concentration (Exo-<br>based detection)       Traumatic brain<br>injury       Contical impact<br>injury       Intravenously via the<br>trai vein       N.D.<br>from human BM-<br>from human Human<br>from human BM-<br>from human BM-<br>from human BM-<br>from human Human Human<br>from human Human Human<br>from human Human Human<br>from human Human Human<br>from human  | Human     Precipitation (Exo-<br>solation)     Determination<br>cortical impact     Traumatic brain<br>injury     Cortical impact     Intravenously via the<br>tail vein     N.D.     Exosomes derived<br>flores fissue<br>flores instand       Human     Precipitation (Exo-<br>ouck exosome     Tetraumatic brain<br>ouck exosome     Traumatic brain<br>of traumatic brain     Intravenously via the<br>vistar rats model<br>and involve     N.D.     Exosomes derived<br>floren human BM-<br>MSCs in 2D or 3D<br>or | Human     Precipitation (Exo-<br>concentration (Exo-<br>concentration (BCA     Contral impact<br>injury     Intravenously via the<br>Misar rats model<br>injury     Intravenously via the<br>Misar rats model<br>inform model<br>inform model     Intravenously via the<br>Misar rats model<br>inform model     Intravenously via the<br>Misar rats model<br>inform model     Intravenously via the<br>Misar rats modelever-<br>min modelever     Intravenously via the<br>Misar rats   | Human     Precipitation (Exo-<br>Outic exosome     Determination     Traumatic brain     Contral protein<br>injury     Contral protein<br>wistancis     Repatic stellate       Human     Precipitation (Exo-<br>Outic exosome     of trad protein<br>of traumatic brain     Intravenously via the<br>Nistancis     N.D.     Exosomes derived<br>finosis tisue       Outic exosome     of trad protein<br>solation)     more<br>oncentration (Exo-<br>protein
assay).     Traumatic brain<br>of traumatic brain     Intravenously via the<br>Nistancis     N.D.     Exosomes derived<br>finosis tisue       Name     Outic exosome     of trad protein<br>of traumatic brain     Intravenously via the<br>Nistancis     N.D.     Exosomes derived<br>finorial recov-<br>ery promored       Human     Gradient ultracentrif-<br>terored recov-<br>onometration (Exo-<br>tron     Deredects     Defects treated with     miR-196a, miR-206,<br>findiamaticn in<br>transactilation       Human     Gradient ultracentrif-<br>terored recov-<br>tron     Deredects     Defects treated with     miR-206,<br>findiamaticn in<br>transactilation       Human     Gradient ultracentrific     Deremination<br>findiamaticn in<br>transactilation     Defects treated with     miR-206,<br>findiamaticn in<br>transactilation       Human     Gradient ultracentrific     Deremination<br>findiamaticn in<br>transactilation     Defects treated with     miR-206,<br>findiamaticn in<br>transactilation       Human     Gradient ultracentrific     Deremination in<br>transactilation     Defects     Defects     Defects    <   | Human       Precipitation (Evo-<br>concentration)       Terumatic brain<br>brand incentration<br>outic exosome       Terumatic stelate<br>celes and ince-<br>brand incentration       Repetic stelate<br>celes and ince-<br>brand incentration         Human       Precipitation (Evo-<br>concentration (Bro-<br>brand incentration)       Determination<br>(Bro-<br>concentration (Bro-<br>brand incentration)       Terumatic brain<br>(Indon)       Intravenously via the<br>of reammatic brain<br>(Indon)       ND       Exosomes derived<br>(Indon)       Evosomes derived<br>(Indon)         Duck exosome       concentration<br>(Bro-<br>brased detection)       Terumatic brain<br>(Injury)       Intravenously via the<br>(Indon)       ND       Exosomes derived<br>(Indon)       [114]         Concentration (Bro-<br>brased detection)       concentration (Bro-<br>injury)       Intravenously via the<br>(Indon)       ND       Exosomes derived<br>(Indon)       [114]         Human       Gadient ultracentrif       Concentration<br>(Bro-<br>torentation (Bro-<br>brand decides)       Exosomes derived<br>(Indon)       Exosomes derived<br>(Indon)       Exosomes derived<br>(Indon)       [114]         Human       Gadient ultracentrif       Determination (Bro-<br>brand decides)       Exosomes derived<br>(Indon)       Exosomes derived<br>(Indon)       [114]         Human       Gadient ultracentrif       Determination (Bro-<br>brand decides)       Exosomes derived<br>(Indon)       [114]       [114]         Human       Gadient ultracentrif       Determination<br>(Indon)       Exosomes derived<br>(I  | Human       Precipition (Sro-<br>out expiration)       Determination<br>injury       Trannatic brain<br>of trantation (BCA       Annatic brain<br>injury       Contral impact<br>injury       Mean impact<br>injury       Repair callstate<br>for and inverticial<br>for minuma BM-<br>monstation         Human       Quick exosome<br>out exists       of trantation (BCA       Trannatic brain<br>injury       Contral impact<br>injury       Intravenously varte       ND       Exosomes derived<br>from human BM-<br>monstation       [114]         Solation)       concentration (BCA       injury       Viratumatic brain<br>injury       Intravenously varte       ND       Exosomes derived<br>from human BM-<br>monstation       [114]         Row in station       concentration (BCA       injury       Viratumatic brain<br>injury       Intravenusly varte       ND       Exosomes derived<br>from human BM-<br>monstation       [114]         Human       Gradient Urbacentrif       Deriver mass<br>from addreed neuro-<br>from exosophic       Exosomes derived<br>from addreed neuro-<br>from addr   |

Table 1 (coi	ntinued)								
Tissue type	MSC origin	Method of exosome isolation	Exosome characterization	Disease focus	Animal type and model	Exosome administration	Related exosome cargo/pathway	Outcome	Refs
	Porcine	Ultrafiltration	Determination of total protein con- centration (Brad- ford assay), NTA, flow cytometry (CD44 and CD90)	Synovitis	Porcine model of antigen-triggered synovitis	Intra-articular injec- tions	C. Z	Exosomes decreased synovial lym- phocytes, the downregulated TNF-a transcripts and improved the impulse in exosome-treated joints	[116]
	Rat	Ultracentrifugation	Determination of total protein concentration (BCA protein assay), TEM, RT-PCR	Acute kidney injury	Acute kidney injury induced by gen- tamicin in Wistar rats	Injection into caudal vein	RNAase, RNA carried by the exosomes/ microvesicles	BM conditioned media increased the renal function recovery. Protec- tive effects were mediated by the exosome ' RNA in the conditioned media	[86]
	Rat	Differential centrifu- gation	Determination of total protein concentration (BCA protein assay), DLS, confocal micros- copy, SEM, TEM, ELISA (CD9), flow cytometry (CD63), western blotting (CD81)	Acute liver injury	Ischemic/reperfusion liver injury and CCI <sub>4</sub> induced acute liver injury in rats	Injection through hepatic portal vein	Exosome-rich fractionated secretome	In vitro – exosomes showed antiapop- totic and prosur- vival effect, better HepG2 cells recov- ery and reduced cytotoxicity In vivo – exosomes improved liver regeneration and recovery from liver iniury	[601]

Befe		mes improved [111] iac function ischemic	oved the oved the formation of EC cells and tined T-cell feration inhibi- eccel infarct and retained olic perfor- cel
Belated evocome Outro	cargo/pathway	N.D Exoso card after injur in vitr	HUDE HUDE Function Thore in vive card diars
Evocome	administration	Intramyocardial injection	
Animal two and	model	Acute myocardial infarction in SD rats	
		Myocardial infarction	
	characterization	Determination of total protein concentration (BCA protein assay), flow cytometry (CD63), TEM	
	isolation	Precipitation (ExoQuick-TC exo- some isolation)	
MSC origin		Rat	
	addiansei		

Table 1 (coi	ntinued)								
Tissue type	MSC origin	Method of exosome isolation	Exosome characterization	Disease focus	Animal type and model	Exosome administration	Related exosome cargo/pathway	Outcome	Refs
	Rat	Multistep centrifuga- tion	Determination of total protein con- centration (micro BCA protein assay)	Stroke	Middle cerebral artery occlusion Wistar rats model	Injection into the tail vein	Q. Z	Exosomes improved neurologic out- come by functional recovery and enhanced neurite remodeling, neuro- genesis. Exosomes systemic treatment improves neuro- logic outcome, sig- nificantly increased the synaptophysin immunoreactive area in ischemic boundary zone	[11]
	Mouse	Filtration, differential centrifugation ultracentrifugation	Determination of total protein concentration (BCA protein assay), DLS, electron micros- copy	Cardiac hypertrophy	Transverse aortic constriction mouse model	Intramyocardial injection	Q.Z	In vitro—exosomes inhibited cell hypertrophy stimulated with angiotensin II in cultured myocytes In vivo—exosomes significantly protected myo- cardiac hyper- trophy, inhibited myocardial apop- tosis and fibrosis and retained heart function when the pressure was overloaded	

Table 1 (con	itinued)								
Tissue type	MSC origin	Method of exosome isolation	Exosome characterization	Disease focus	Animal type and model	Exosome administration	Related exosome cargo/pathway	Outcome	Refs
	Mouse (ischemic precondi- tioned)	Precipitation (Exo- Quick exosome isolation)	Determination of total protein concentration (BCA protein assay), western blotting (CD9, CD63)	Alzheimer's disease	Transgenic APP/PS1 mouse model	Injection through lateral caudal vein	miR-21, miR-181c	Exosomes improved memory functions and learning capabilities in mice. Hypoxic MSC- derived exosomes reduced effectively AB accumula- tion, increased the expression of synaptic proteins and enhanced the level of miR-21 in the brains of APP/ PS1 mice PS1 mice	[115]
Umbilical cord	Human (Wharton's jelly) and mouse BM	Precipitation, column size exclusion chromatography, ultracentrifugation	Electron microscopic analysis, deter- mination of total protein concen- tration (Bradford assay) western blotting (CD63, ALIX, TSG101, CD81, CD9, hsp90, flotillin-1, Dicer), isolation and quantification of microRNAs	Hypoxic pulmonary hypertension	Hypoxia induced pulmonary hyper- tension in FVB strain mice	Q	miR-204, miR-17	MSC-derived exosomes were able to inhibit pul- monary hyperten- sion by inihition of hyperproliferative pathways, iclud- ing suppression of the hypoxic activation of STAT3 signaling and the upregulation of the miR-17, whereas it increased lung levels of miR-204	[82]

Refs	87]	d [122] ere ام ام ام ا	[123] 2E 3f 3n
Outcome	MSC-derived exosomes inhibit EMT and improv- CCl <sub>4</sub> induced live fibrosis In vivo—exosome transplantation reduced TGF-81 expression, inactivated Smac phosphorylation and inverted live EMT In vitro – Exo- some treatment of HL7702 cells after EMT causec reversed spindle shaped cells and EMT associated marker expressio	Exosomes enriched in miR-455-3p w capable to inhib- ited the overactiv tion of monocyte maccophages an reduced acute liv injury by inhibitir IL-6-related signa ing pathways	Exosomes sup- pressed kidney injury and NRK-5 cell injury by improvement of oxidative stress and cell apoptos and promotion c cell proliferation through activatic of ERK1/2 in vivo and in vitro
Related exosome cargo/pathway	(TGF)-b1/Smad sign- aling pathway	miR455-3p	p38MAPK pathway, ERK 1/2 pathway
Exosome administration	Injection into the left and right lobes of livers	Injection	Renal capsule injection
Animal type and model	CCI <sub>4</sub> -induced liver fibrosis in mice	CCI <sub>4</sub> -induced acute liver injury and endotoxemia in C57BL/6 mice	Gisplatin-induced acute kidney injury in SD rats
Disease focus	liver fibrosis	Acute liver injury	Acute kidney injury
Exosome characterization	Determination of total protein concentration (BCA protein assay), TEM, western blotting (CD9, CD81)	Electron microscopy, NTA, western blotting (TSG101, CD63, CD81), qPCR analysis, sequenc- ing of miRNAs	TEM, western blot- ting (CD9, CD63, CD81)
Method of exosome isolation	Ultracentrifugation	Precipitation (Exo- Quick ULTRA EV isolation)	Ultracentrifugation
MSC origin	Human	Human	Human
Tissue type			

ble 1 (coi	ntinued)								
ue type	MSC origin	Method of exosome isolation	Exosome characterization	Disease focus	Animal type and model	Exosome administration	Related exosome cargo/pathway	Outcome	Refs
	Human	Ultracentrifugation	Determination of total protein con- centration (Brad- ford assay), TEM, flow cytometry	Acute kidney injury	Acute kidney injury model induced by ischemia-reperfu- sion injury in rats	Intravenous adminis- tration	Q.	Exosomes reduced cell apoptosis and improved proliferation 24 h after kidney injury, promoted angiogenesis by inducing VEGF elevation through HIF- Ia independ- ent manner	[124]
	Human	Differential centrifu- gation, ultracen- trifugation	Determination of total protein concentration (BCA protein assay), western blotting (CD9, HSP70), TEM, NTA	Wound healing and angiogenesis	Skin burn wound model in rats	Subcutaneous injec- tion	Wnt4	In vitro—exosomes elevated endothe- lial cell prolifera- tion, migration and tube formation In vivo—exosomes improved angiogenesis in the repair of skin burn injury by delivering Wrt4 to activate Wrt/β-catenin signaling (tissue repair mechanism)	[125]
	Human	Ultracentrifugation	Determination of total protein concentration (BCA protein assay), TEM, western blotting (CD9, CD63, CD81, β-catenin, Wnt3a, β-actin)	Fracture healing	Model of femorale fracture in SD rats	Injection of the mix of hydrogel and exosomes into the fracture	Q.	Exosomes partici- pated in the repair of fracture in rats through the Wnt signaling pathway by increasing of β-catenin and Wnt3a protein expressions	[126]

Table 1 (coi	ntinued)								
Tissue type	MSC origin	Method of exosome isolation	Exosome characterization	Disease focus	Animal type and model	Exosome administration	Related exosome cargo/pathway	Outcome	Refs
	Human	Ultracentrifugation	Determination of total protein concentration (BCA protein assay), NTA, western blotting (CD81) (CD81)	Wound healing	Skin-defect model in ICR and BALB/c-u mice	Injection of the mix of hydrogel and exosomes around the wound the wound	miR-125b, miR-145 miR-125b, miR-145	Exosomes enriched in specific microR- NAs (miR-21, -23a, -125b, and - 145) inhibited myofi- broblast formation, inhibited TGF-82, TGF-8R2 and SMAD2 pathway and accordingly suppressed the expression of c-SMA gene and reduced col- lagen I deposition. Significant role of exosomes for anti-scarring ability and the myofibro- blast-suppressing was showed both in vitro and in vivo by blocking miRNAs inside the exosomes	[127]
	Human	Ultracentrifugation	TEM, determination of total protein concentration (BCA protein assay), NTA, western blotting (CD9, CD63, CD81)	Inflammatory bowel disease	DSS-induced inflam- matory bowel disease mouse model	Injection through the tail vein	Q	Exosomes could improve inflamma- tory bowel disease In vitro – coculture with exosomes suppression of iNOS and IL-7 in mouse enterocelia mac- rophages in vivo – exosomes reduced the expression of pro-inflammatory cytokines TNF-a, IL-1β, IL-6) and increased the expression of anti-inflammatory cytokine (II 10)	[128]

Table 1 (coi	ntinued)								
Tissue type	MSC origin	Method of exosome isolation	Exosome characterization	Disease focus	Animal type and model	Exosome administration	Related exosome cargo/pathway	Outcome	Refs
	Human	Ultracentrifugation	Determination of total protein con- centration, TEM, Zetasizer, westerm blotting (CD9, CD63, CD81)	Colitis	Colitis induction in C57BL/6 mice	Intraperitoneal injection	Q	In vitro – exosomes decreased pro- inflammatory cytokines (IFN-Y, TNF-a, IL-1 $\beta$ ) concentration and enhanced the secretion of anti-inflammatory cytokines (TGF- $\beta$ 1, IL-10) In vivo – exosomes showed thera- peutic activity in experimental colitis via suppressing inflammation machinery, improved clinical symptoms and his- tological severity	[06]
Adipose	Human	Ultracentrifugation	Determination of total protein concentration (Bradford assay), TEM, NTA, SIOS,	Alzheimer's disease	Q.N	QN	Neprilysin	Exosomes secrete enzymatically active neprily- sin. Transfer of exosomes to N2a cells significantly decreased both the intracellular and extracellular and and A342 levels	[133]
	6 I	Ultracentrifugation	NTA, TEM, western blotting (CD9, CD29, CD63), RT PCR (mRNA con- tent of IL-10)	Renal inflammation	Metabolic syndrome and renal artery stenosis model in domestic pigs	Intrarenal delivery	IL- 10	Exosomes reduced renal inflamma- tion, enhanced the reparative mac- rophages number and increased expression of IL-10. Exosomes were able to reduce renal fibrosis and to improve stenotic kidney function	[130]

Refs	
Outcome	Exosomes pro- tected ischemic myocardium fron ischemia/reperfu sion injury throu the Wnt/β-caten signaling pathwi activation In vitro – exosome reduced cell apoptosis and the expression of Bcl apoptosis and the expression of Bcl and Cyclin D1 in hypoxia/reoxy- genation-induce H9c2 cells In vivo – exosome: significantly reduced ischemi reperfusion- induced aptoor- induced aptoor- induced attenu ation of ischemiz reperfusion- induced attenu atton of ischemiz reperfusion- induced attenu reperfusion- induced attenu reperfusion- in
Related exosome cargo/pathway	Q
Exosome administration	Infusion through the tail vein
Animal type and model	Myocardial ischemia/ reperfusion model in SD rats
Disease focus	lschemic heart disease
Exosome characterization	Determination of total protein concentration (BCA protein assay), TEM, western blotting (CD9, CD63, HSP70, CD81) CD81)
Method of exosome isolation	Ultrafiltration, ultra- centrifugation
MSC origin	Rat
Tissue type	

Table 1 (continued)

Tissue type	MSC origin	Method of exosome isolation	Exosome characterization	Disease focus	Animal type and model	Exosome administration	Related exosome cargo/pathway	Outcome	Refs
	Mouse	Precipitation and magnetic beads purification (Mag- Capture Exosome Isolation)	Determination of total protein concentration (BCA protein assay), NTA, TEM, western blot- ting (CD29, CD63)	Acute myocardial infarction	QN	QN	Q.N.	Exosomes reduced apoptosis in myocardial cells subjected to oxida- tive stress in vitro	(132)

N.D. not defined in the given reference; TEM, transmission electron microscopy; NTA, nanoparticle tracking analysis; SIOS, scanning ion occlusion sensing; EMT, epithelial-mesenchymal transition; DLS, Dynamic light scattering; SEM, scanning electron microscopy

heart model of acute myocardial ischemia/reperfusion injury in mice, where their cardioprotective effect was identified by myocardial infarct size reducing [88]. In this study, authors identified exosomes as cardioprotective elements in the MSCs' paracrine secretion [88].

Several preclinical studies compared the beneficial effects of cell therapy based on MSCs and cell-free therapy based on MSC-derived EVs/exosomes and showed that they had similar therapeutic outcomes. Comparative analyses of MSCs and their EVs demonstrated different genetic cargo and protein content that play a significant role in biological processes, including angiogenesis, adipogenesis, apoptosis, regulation of inflammation, blood coagulation and extracellular matrix remodeling. Application of mice adipose MSCs in comparison with its conditioned medium had the same effect on sympotms of chronic colitis mouse model. Clinical symptoms and tissue damages were suppressed in treated mice [89]. Zhi et al. indicated that the application of umbilical cord MSC-derived exosomes (200 µg) resulted in amelioration of clinical symptoms, reduction of colonic damage and decrease of the inflammatory state in mice colitis when compared with MSCs  $(1 \times 10^6 \text{ cells})$  administration [90]. Shao et al. compared activity of rat bone marrow MSCs and MSC-derived exosomes in a rat acute myocardial infarction model. It was showed a superior beneficial effects of MSC-derived exosomes in contrast to MSCs in cardiac repair. There were observed differences in expression profiles of several miRNAs from that of MSCs detected through miRNA sequence analysis [91]. A recent cutaneous wound model study in rabbits reported that intradermal injection of EVs derived from adipose and bone marrow MSCs were superior to MSCs injection in vivo. Furthermore, adipose MSC-derived EVs enhanced wound healing better than EVs from bone marrow [92]. In the study by Gatti et al. intravenous administration of human bone marrow MSC-derived EVs had the same efficacy as MSCs on the treatment of acute kidney injury in rats by inhibiting apoptosis and stimulating tubular cell proliferation [93]. In an induced experimental autoimmune encephalomyelitis murine model of multiple sclerosis, both human placental MSCs and its MSC-derived EVs showed regenerative effects and prevented oligodendroglia degradation and demyelination [94]. Another preclinical study showed that MSC-derived exosomes could be a promising cell-free therapeutic strategy for the treatment of Alzheimer's disease. It was demonstrated that 28 days after intervention of mice groups with 10  $\mu$ g exosomes and 1  $\times$  10<sup>6</sup> MSCs separately had similar beneficial effects in improvement of neurogenesis and cognitive functions [95].

From the preclinical studies of MSC-derived exosomes therapy to the clinical application, many critical parameters should be resolved and determined, including clarification of important factors and conditions, defining optimal MSC culture conditions and protocols for precise monitoring of exosome formation, isolation, its characterization and storage. The biological effect of MCS-derived exosomes is mainly affected by the source of MSCs. The ideal source would be a high-exosomeyielding cell with a high expansion capacity [96, 97]. Further relevant requirement is the age of the donor tissue considering the exosome production might be indirectly connected with mentioned factor. Isolated exosomes are routinely identified by vesicle size and expression of typically tetraspanin markers CD63, CD9 and CD81. Production of exosomes could be enhanced by changing of several cell cultivation conditions, like increasing of intracellular calcium, or serum starvation. The long lasting donor HEK293 cell cultivation and maintaining cells at acidic pH could results in considerably increased production of exosomes [98]. Pre-conditioning of MSCs with hypoxia [99, 100], cytokines [101, 102] and another biomoleculs or chemicals (e.g. LPS [103], thrombin [104], NO [105],  $H_2O_2$  [106]) also evoked the increase of exosomes activity, directly or indirectly by increasing MSCs function. Further important requirements for exosome preservation is an adequate storage. Sokolova et al. detected that the exosomes diameter decreased within 4 days at 4 °C and 2 days at 37 °C, indicating a structural change or degradation of exosomes, but storage at -20 °C did not affect their size [107]. Extensive questions concerning of clinical grade exosomes production in sufficient quantity and of influence of different strategies on exosome potency are still under examination.

### Bone marrow MSC-derived exosomes Improvement of liver regeneration by BM MSC-derived exosomes

The potential of bone marrow (BM) MSC-derived exosomes for the treatment of various disease pathologies seems to be obvious. Rong et al. demonstrated the ability of human BM MSC-derived exosomes to reduce liver fibrosis in a carbon tetrachloride (CCl<sub>4</sub>)-induced liver fibrosis model of Sprague Dawley (SD) rats through the Wnt/ $\beta$ -catenin pathway. They also indicated the recovery of markers related to improved liver features, increasing hepatocyte regeneration and inhibition of inflammation process (significantly decreased inflammatory cytokines) [108]. Damania et al. studied the capability of rat BM MSC-derived exosomes present in fractionated MSC secretome to reduce liver injury in vitro in both 2D and 3D culture conditions of HepG2 cells and in in vivo rat models of acute liver injury caused by CCl<sub>4</sub>. Anti-apoptotic, anti-oxidative and prosurvival effects were shown in in vitro models of liver injury. In addition, the exosome rich fraction of conditioned media improved liver regeneration and recovery in vivo [109].

#### Cardioprotection by BM MSC-derived exosomes

The multiple therapeutic effects of BM MSC-derived exosomes have also been detected in cardiovascular, ischemic and reperfusion diseases. Currently, Chen et al. established significant protection of myocardium against hypertrophy, inhibition of myocardial apoptosis and reduction of cardiac fibrosis by using mice BM MSC-derived exosomes in the murine pressure overload induced cardiac hypertrophy model [110]. Teng et al. in their study hypothesized about a significant role of rat BM MSC-derived exosomes in the cardioprotection through angiogenesis and anti-inflammation in SD rats with acute myocardial infarction. They shown an efficacious action of exosomes in cardiac remodeling post-myocardial infarction in vivo. Accordingly, obtained results indicated that exosomes supported angiogesesis in vitro in human umbilical vein endothelial cell line (HUVEC). Furthermore, the proliferation of CD3 stimulated T-cells was reduced after exosome treatment, which means decrease in proliferation of spleen lymphocytes [111]. The rat myoblast cell line H9c2 was used to study myocardial pathogenic processes as cellular hypoxia-reoxygenation model. Inhibition effect of cell proliferation, migration and also of suppresion of cardiomyocyte apoptosis during hypoxia-reoxygenation was revealed after rat BM MSCderived exosome treatment [112]. In addition, quantity of both apoptosis- and autophagy-competent functional proteins and Apaf1 (apoptotic protease activating factor 1) and ATG13 (autophagy-related protein 13) gene expression in these treated H9c2 cells exhibited modulations in accordance with SD rat myocardial ischemia/ reperfusion model. Apaf1 expression was considerably suppressed and ATG13 expression was significantly increased in vivo after exosome treatment. Authors concluded, that myocardial injury associated with myocardial infarction could be inhibited with BM MSC-derived exosomes, alternatively throught regulation of autophagy mechanism [112].

# BM MSC-derived exosomes and recovery after stroke and traumatic brain injury

In a stroke model (middle cerebral artery occlusion model) in Wistar rats, Xin et al. indicated that systemic administration of rat BM MSC-derived exosomes significantly enhanced functional recovery and improved neurite remodeling, neurogenesis and angiogenesis [113]. Therefore, exosomes could be effectively used for stroke treatment. Zhang et al. used human BM MSC-derived exosomes for the treatment of experimental traumatic brain injury in controlled cortical impact model in Wistar rats. Similarly, the improvement of functional recovery and promotion of neurovascular remodeling were demonstrated [114]. Administration of BM MSC-derived exosomes could regenerate cognition functions and memory impairment in neurological and neurodegenerative diseases. Exosomes derived from MSCs preconditioned by hypoxia supressed amyloid  $\beta$  accumulation and enhanced the synaptic protein expression in the brains of transgenic APP/PS1 mice (Alzheimer's disease mice). Furthermore, reduced activation of astrocytes and microglia and changes in levels of inflammatory factors (increase of anti-inflammatoty cytokines IL-4, IL-10 and decrease of pro-inflammatory cytokines TNF $\alpha$  and IL-1 $\beta$ ) were observed [115].

# Anti-inflammation mediated by BM MSC-derived exosomes

Another promising therapeutic feature of porcine BM MSC-derived exosomes was evaluated by Casado et al. They showed the anti-inflammatory effect of exosomes in porcine model (large white pigs) of antigen-triggered synovitis. The local inflammation in animals caused by intra-articular injection of BSA leads to an elevated level of white blood cells in synovial fluid. Interestingly, there were found no differences of white blood cells in joints after exosome administration, but significant decrease in the lymphocytes accompanied by a noteworthy decline of only one (TNF $\alpha$ ) from eight tested inflammatory cytokines in synovial fluid was revealed [116]. It is interesting, that TNF $\alpha$  antagonists (e.g. infliximab, golimumab, etanercept) are generally used for the treatment of rheumatoid arthritis [117].

# Influence of BM MSC-derived exosomes on bone regeneration

Osteogenically differentiated human BM MSCs and subsequently derived EVs were used in the study of Martins et al.. They demonstrated, that human BM MSC-derived vesicles have osteoinductive potential characterized by early activation of alkaline phosphatase, early overexpression of the activator bone morphogenetic protein 2, transient increase in expression of Sp7 transcription factor (osterix) and secretion of phosphoprotein 1 (osteopontin) and integrin-binding sialoprotein (bone sialoprotein) [118]. Qin et al. tested the BM MSC-derived exosomes in the regulation of osteoblast activity in vitro and bone regeneration in vivo. Osteoblasts treated with miR-196a exhibited the best osteogenic activity in comparison with miR-27a and miR-206 treatment. Mentioned miR-NAs are typical osteogenic related RNAs and are highly enriched in BM MSC-derived exosomes [119]. They also generated calvarial bone defects in SD rats and then applied hydrogel with EVs, which resulted in accelerated bone regeneration and indicated obvious improvement of the defect repair in comparison with hydrogel without EVs [119]. Narayanan et al. confirmed that exosomes from osteogenic human marrow MSCs are able to trigger lineage-specific differentiation of undifferentiated human BM MSCs [120]. Moreover, Shimbo et al. showed that the introduction of synthetic miR-143 into BM MSCs leads to an increase in not only the extracellular miR-143 but also increased secretion of exosomes. Such exosomeformed miR-143 was transferred to human osteosarcoma cell line 143B and caused suppression of their migration. It seems, that BM MSC-derived exosomes are also able to act as effective delivery system [121].

## **Umbilical cord MSC-derived exosomes** Reduction of liver fibrosis and liver injury by UC MSC-derived exosomes

Umbilical cord (UC) MSCs and their exosomes have also extensive potential in regenerative medicine, but their fundamental mechanism of action is still unknown. Li et al. used UC MSC-derived exosomes to treat CCl<sub>4</sub>-induced mouse liver fibrosis on Kunmingbai strains mice. It was shown that transplantation of human UC MSC-derived exosomes caused successful decrease of the serum fibrotic marker hyaluronic acid, TGF-B1 and serum aspartate aminotransferase and reduced hepatic inflammation and collagen deposition. Entire improvement after liver injury was confirmed [87]. Likewise, Jiang et al. identified hepatoprotective activities of human UC MSC-derived exosomes throught antioxidant defenses in mouse models (BALB/c female mice) of acute and chronic liver injury and liver tumor induced by CCl<sub>4</sub> injection. They detected suppression of the liver tumor development, inhibition of oxidative stress in liver tumor, reduction of oxidative stress, inhibition of apoptosis in liver fibrosis and accordingly, reduction of oxidative stress and inhibition of apoptosis in acute liver injury after human UC MSC-derived exosome administration [71]. Shao et al. described large production of miR-455-3p enriched exosomes by human UC MSCs and their ability to suppress macrofage activation and reduce acute liver injury in mice model by inhibiting IL-6 signaling pathway [122].

#### Influence of UC MSC-derived exosomes on treatment of kidney injury

Furthermore, Zhou et al. studied the influence of human UC MSC-derived exosomes in SD rat model of kidney injury induced by cisplatin and in rat NRK-52E cells treated with or without cisplatin in vitro. There was indicated activation of the p38MAPK pathway followed by the increase of caspase 3 in NRK-52E cells after cisplatina treatment. Increase of apoptotic cells and oxidative stress were also observed. By contrast, these parameters were significantly reduced after human UC MSC-derived exosome administration. Accordingly, human UC MSC-derived exosomes moderated tubular oxidative damage, suppressed renal cell apoptosis and promoted renal cell proliferation in vivo in rats [123]. The major reason of acute kidney injury is ischemia/reperfusion injury in hospitalized patients. Therefore, Zou et al. in other study showed, that a single intravenous administration of human UC MSCderived exosomes in rats with acute kidney injury induced by ischemia/reperfusion injury elevated renal capillary vessel density and alleviated renal fibrosis by increase of proangiogenic vascular endothelial growth factor (VEGF). In this process, reduction of HIF-1 $\alpha$ (hypoxia inducible factor) was also observed. Exosomes were able to reduce cell apoptosis and improve proliferation after kidney injury [124].

# Enhancement of fracture healing and wound healing by UC MSC-derived exosomes

Zhang et al. demonstrated intensive support of cutaneous wound healing and angiogenesis in vivo in a rat model of skin-deep second degree burn wound by human UC MSC-derived exosomes [125]. The Wnt signaling pathway plays an important role in angiogenesis mediated with the endothelial cell proliferation modulation, migration, vascular sprouting and remodeling, and vascular system maturation. UC-MSC-derived exosomes promote the tube formation, proliferation and migration of endothelial cells in vitro. In addition to that, applied exosomes improved angiogenesis by delivering Wnt4 to activation of Wnt/βcatenin in endothelial cells which could be one of the possible mechanism for tissue repair [125]. Likewise, Zhou et al. investigated the role of human UC MSCderived exosomes in the Wnt signaling and their influence on femoral fracture healing in SD rats. Increase of β-catenin and Wnt3 expression indicating presumed participation of injected exosomes in repairing of the fracture was identified [126]. An important knowledge in this area is the study of Fang et al., in which they found that UC MSC-derived exosomes, especially exosomal microRNAs, decreased scar formation and myofibroblast accumulation in a skin-defect ICR mouse (Swiss-Hauschka mice) and nude mouse (BALB/c-v) model. Myofibroblast formation can generally result in abnormal scarring. It was shown, that specific exosomal microRNAs (miR-21, miR-23a, miR-125b, and miR-145) inhibited redundant  $\alpha$ -smooth muscle actin  $(\alpha$ -SMA) and collagen I deposition and also suppressed TGF- $\beta$ /SMAD2 signaling pathway [127].

#### UC MSC-derived exosomes relieve bowel diseases

UC MSC-derived exosomes have high potential in the treatment of inflammatory bowel diseases involving chronic inflammation of the gastrointestinal tract, both Crohn's disease and ulcerative colitis in the future. Mao et al. demonstrated decrease of pro-inflammatory cytokines IL-6, IL-1 $\beta$ , TNF- $\alpha$  expression and increase of anti-inflammatory cytokine IL-10 expression after UC MSC-derived exosomes treatment in inflammatory bowel disease in a mice model. Interestingly, significant inhibition of IL-7 expression was also observed in the colon mucosa tissues and spleens in a mice model [128]. The serum cytokine level of IL-7 is normally increased in inflammatory bowel disease patients [129]. Similarly, single intraperitoneal injection of UC MSC-derived exosomes resulted in a significant reduction of the clinical symptoms and colonic damages in the mouse model of dextran sodium sulfate-induced colitis through suppression of inflammation mechanism [90].

#### Adipose MSC-derived exosomes

# Attenuation of kidney inflammation by AD MSC-derived exosomes

Adipose (AD) MSC-derived exosomes as well as exosomes derived from BM and UC MSCs present a multipotent and rich therapeutic role in the improvement of the injury repair of many tissues. AD MSCderived exosomes are more abundant and have lower risk of side effects. A single intrarenal delivery of pig AD MSC-derived exosomes in a porcine model of metabolic syndrome and renal artery stenosis resulted in reduction of renal inflammation, enhancement of the reparative macrophages number and elevation of anti-inflammatory cytokine IL-10 expression. Furthermore, exosome administration lowered renal vein level of pro-inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$  and IL-6 [130]. Results in the study of Eirin et al., established attenuation of renal fibrosis and improvement of stenotic kidney function after AD MSC-derived exosome treatment [130].

#### Cardioprotection by AD MSC-derived exosomes

It was observed, that AD MSC-derived exosomes are able to protect myocardium against acute ischemia/reperfusion induced necrosis and apoptosis in SD rat myocardial ischemia/reperfusion model. Ischemia/reperfusion injury in rats was accompanied with a remarkable decrease of Bcl-2 and an obvious increase in Bax expression. Both were eliminated after exosome administration. It was also observed, that AD MSC-derived exosomes attenuated hypoxia/reoxygenation induced apoptosis and promoted cell survival in H9c2 cell line [131]. In addition, Cui et al. hypothesized that AD MSC-derived exosome administration could protect ischemic myocardium through activation of Wnt/ $\beta$ -catenin signaling in vivo [131]. Liu et al. determined the protective influence of mouse AD MSC-derived exosomes on cardiomyocytes under oxidative stress in vitro [132].

# Potential of AD MSC-derived exosomes for Alzheimer's disease treatment

Interestingly, Katsuda et al. demonstrated remarkable potential of AD MSC-derived exosomes for Alzheimer's disease therapy [133]. They showed that AD MSCderived exosomes exhibited neprilysin specific enzyme activity. Neprilysin is the most essential enzyme that degrade amyloid beta peptide in the brain. In addition, transfer of mentioned exosomes to neuroblastoma N2a cells resulted in a decrease of both intracellular and extracellular amyloid beta peptide grades, suggesting a promising therapeutic approach for exosome-based Alzheimer's disease treatment [133].

#### Role of AD MSC-derived exosomes in tumor progression

Recently, the influence of MSC-derived exosomes on tumor progression in both inhibiting and supporting mode was intensively described. Reza et al. indicated that human AD MSC-derived exosomal miRNAs have significant inhibitory influence on the regulation of different ovarian cancer cells [134]. Exosomes collected from human AD MSC-derived conditioned medium inhibited the growth and proliferation of ovarian cancer cells A2780 and SKOV-3. Decreased cell viability and wound healing of cancer cells were also observed after exosome treatment. Furthermore, collected exosomes caused apoptosis by increasing of pro-apoptotic signalling molecules Bax, caspase 3 and caspase 9 and by decreasing of anti-apoptotic bcl-2 protein [134].

#### **Clinical perspectives**

Clinical applications using exosome technology as cellfree therapy has become an important field of research over the last years. Currently, 91 clinical trials involving exosomes are listed on www.clinicaltrials.gov. Exosomes used in these trials are mainly derived from several body fluids and are used as early diagnostic tools in prediction of various diseases.

The clinical use of human MSC-derived exosomes is limited due to rigorous resolution of critical parameters involved in the translation process of preclinical studies to the clinical ones. These paramaters include the optimal MSC culture conditions and protocols for exosome production, isolation, and storage with a considerable effect on the uniformity of optimal dose, exosome administration and efficacy evaluation [2, 24]. Various approaches to optimize the therapeutic efficacy of exosomes are being developed. In general, the substantial requirement 
 Table 2
 List of clinical trials of MSC-derived exosomes-based therapies (source: www.clinicaltrials.gov)

NCT number	Study title	Study start	Condition	Intervention	Phase	Status
NCT04602104	A Clinical Study of Mesenchymal Stem Cell Exosomes Nebulizer for the Treatment of ARDS	October 2020	Acute Respiratory Distress Syndrome	Allogenic human MSC-Exos	Phase 1 Phase 2	Not yet recruiting
NCT04602442	Safety and Efficiency of Method of Exo- some Inhalation in COVID-19 Associated Pneumonia (COVID- 19EXO2)	October 1, 2020	Covid19; SARS-CoV-2 PNEU- MONIA	MSC-Exos	Phase 2	Enrolling by invitation
NCT04173650	MSC EVs in Dystrophic Epidermolysis Bul- Iosa	September 2020	Dystrophic Epider- molysis Bullosa	AGLE 102	Phase 1 Phase 2	Not yet recruiting
NCT04356300	Exosome of Mesenchy- mal Stem Cells for Multiple Organ Dys- funtion Syndrome After Surgical Repaire of Acute Type A Aortic Dissection	September 1, 2020	Multiple Organ Failure	UC MSC-Exos	Not Applicable	Not yet recruiting
NCT04491240	Evaluation of Safety and Efficiency of Method of Exosome Inhalation in SARS- CoV-2 Associated Pneumonia	July 20, 2020	Covid19; SARS-CoV-2 PNEU- MONIA	MSC-Exos	Phase 1 Phase 2	Completed has results
NCT04544215	A Clinical Study of Mesenchymal Progenitor Cell Exosomes Nebulizer for the Treatment of Pulmonary Infection	July 1, 2020	Drug-resistant	Human AD MS progenitor cell- Exos	Phase 1 Phase 2	Recruiting
NCT04388982	the Safety and the Efficacy Evaluation of Allogenic Adipose MSC-Exos in Patients With Alzheimer's Disease	July 1, 2020	Alzheimer´s Disease	allogenic AD MSC-Exos	Phase 1 Phase 2	Recruiting
NCT03608631	iExosomes in Treating Participants With Metastatic Pancreas Cancer With KrasG12D Mutation	March 2020	Pancreatic cancer with KrasG12D mutation; Metastatic Pancreatic Adenocarcinoma; Pancreatic Ductal Adenocarcinoma; Stage IV Pancreatic Cancer AJCC v8	MSC-Exos with KRAS G12D siRNA	Phase 1	Not yet recruiting
NCT04313647	A Tolerance Clinical Study on Aerosol Inhalation of Mesen- chymal Stem Cells Exosomes In Healthy Volunteers	March 16, 2020	Healthy	Allogenic AD MSC-Exos	Phase 1	Recruiting
NCT04213248	Effect of UMSCs Derived Exosomes on Dry Eye in Patients With cGVHD	February 18, 2020	Dry Eye	UC MSC-Exos	Phase 1 Phase 2	Recruiting
NCT04276987	A Pilot Clinical Study on Inhalation of Mes- enchymal Stem Cells Exosomes Treating Severe Novel Coro- navirus Pneumonia	February 15, 2020	Coronavirus	Allogenic AD MSC-Exos	Phase 1	Completed

#### Table 2 (continued)

NCT number	Study title	Study start	Condition	Intervention	Phase	Status
NCT03384433	Allogenic Mesen- chymal Stem Cell Derived Exosome in Patients With Acute Ischemic Stroke	April 17, 2019	Cerebrovascular Disorders	Allogenic MSC-Exos enriched by miR-124	Phase 1 Phase 2	Recruiting
NCT03437759	MSC-Exos Promote Healing of MHs	March 1, 2017	Macular Holes	MSC-Exos	Early Phase 1	Recruiting
NCT03562715	microRNAs Role in Pre- eclampsia Diagnosis	November 28, 2016	Pre-eclampsia			Completed
NCT02138331	Effect of Microvesi- cles and Exosomes Therapy on β-cell Mass in Type I Diabe- tes Mellitus (T1DM)	April 2014	Diabetes Mellitus Type 1	UC blood MSC-Exos	Phase 2 Phase 3	Unknown

NCT number, ClinicalTrials.gov identifier; MSC-Exos, mesenchymal stem cells-derived exosomes

is a standardization of the classification and extraction method of exosomes from various body fluids, including definition of using of lower biofluid volume, higher purity and yield. Also the identification and better characterization of specific EVs subgroups is needed because different EVs could involve different biological effects. Whereas actual extraction methods of exosomes are too diverse for confirmation of its purity, it is necessary to standardize the protocols and characterization methods before application of exosomes in clinical trials. In addition, determination of the optimal dose, adequate time and appropriate method for exosome administration with maximal targeted efficacy, biological safety and without adverse effects must be confirmed before their clinical use.

Up to date, there are 15 clinical trials related to MSCderived exosomes, registered on Clinicaltrials.gov, which are summarized in Table 2. Some of these studies have been completed or are recruiting/about to open to accrual. The trial NCT04491240 is focused on the evaluation of safe and effective method of MSC-derived exosomes aerosol inhalation in SARS-CoV-2 associated pneumonia and is only one trial which has been posted the results. Similar issue is performed in the completed pilot clinical trial NCT04276987 where the safety and efficiency of allogenic AD MSC-derived exosomes inhalation in the treatment of patients hospitalized with new coronavirus pneumonia is investigated. In completed trial NCT03562715 peripheral blood exosomes' miRNA136, miRNA494 and miRNA495 genes expression in comparison to UC MSC conditioned media exosomes in patients with pre-eclampsia (pregnancy complication) was indentified. Based on the received and published data, MSC-derived exosomes are going to be great biological tools for diabetes, stroke, Alzheimer's Disease and cancer therapy. Actually, it is hopeful to delve deeper into the potential of MSC-exosomes among SARS-CoV-2 pneumonia therapy and provide effective treatments with the highest safety.

#### Conclusion

MSCs mainly exert their therapeutic effects through the secretion of paracrine factors to reduce inflammation, cellular injury and enhance cell and tissue repair. MSCderived exosomes probably work in a similar manner and have the capacity to interact with multiple cell types, enabling the cells to recover, repair and regenerate within the tissue. Due to their ability to deliver genetic material, immunomodulatory proteins, enzymes, and growth factors directly to the recipient cells, they also represent an ideal multifunctional delivery system. MSC-derived exosome therapy may be an emerging and a promising tool for the treatment of various diseases, mainly of those with an inflammatory component. Whats more, encouraging results of preclinical and clinical data predicted that MSC-derived exosome treatment could be superior to cell-based therapy in the meaning of safety and versatility.

#### Abbreviations

MSCs: Mesenchymal stem cells; EVs: Extracellular vesicles; MVBs: Multivesicular bodies; ILVs: Intraluminal vesicles; BM: Bone marrow; UC: Umbilical cord; AD: Adipose; ESCRT: The endosomal sorting complex required for transport; SD rats: Sprague Dawley rats.

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#### Authors' contributions

JJ drafted, directed and finalized the manuscript. LS and DH participated in editing the manuscrift. TS gave suggestions during preparations, contributed to collecting information and editing manuscript. JR made critical revisions. All authors read and approved the final manuscript.

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#### **Competing interests**

The authors declare that they have no competing interests.

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#### References

- 1. Galipeau J, Sensebe L. Mesenchymal stromal cells: clinical challenges and therapeutic opportunities. Cell Stem Cell. 2018;22(6):824–33.
- 2. Squillaro T, Peluso G, Galderisi U. Clinical trials with mesenchymal stem cells: an update. Cell Transplant. 2016;25(5):829–48.
- Tanna T, Sachan V. Mesenchymal stem cells: potential in treatment of neurodegenerative diseases. Curr Stem Cell Res Ther. 2014;9(6):513–21.
- Chen XD, Wang SJ, Cao W. Mesenchymal stem cell-mediated immunomodulation in cell therapy of neurodegenerative diseases. Cell Immunol. 2018;326:8–14.
- Staff NP, Jones DT, Singer W. Mesenchymal stromal cell therapies for neurodegenerative diseases. Mayo Clin Proc. 2019;94(5):892–905.
- Shi YF, Wang Y, Li Q, Liu KL, Hou JQ, Shao CS, et al. Immunoregulatory mechanisms of mesenchymal stem and stromal cells in inflammatory diseases. Nat Rev Nephrol. 2018;14(8):493–507.
- Wang LT, Ting CH, Yen ML, Liu KJ, Sytwu HK, Wu KK, et al. Human mesenchymal stem cells (MSCs) for treatment towards immune- and inflammation-mediated diseases: review of current clinical trials. J Biomed Sci. 2016. https://doi.org/10.1186/s12929-016-0289-5.
- Katuchova J, Harvanova D, Spakova T, Kalanin R, Farkas D, Durny P, et al. Mesenchymal stem cells in the treatment of Type 1 diabetes mellitus. Endocr Pathol. 2015;26(2):95–103.
- Katuchova J, Tothova T, Iannaccone SF, Toporcer T, Harvanova D, Hildebrand T, et al. Impact of different pancreatic microenvironments on improvement in hyperglycemia and insulin deficiency in diabetic rats after transplantation of allogeneic mesenchymal stromal cells. J Surg Res. 2012;178(1):188–95.
- Haynesworth SE, Goshima J, Goldberg VM, Caplan Al. Characterization of cells with osteogenic potential from human marrow. Bone. 1992;13(1):81–8.
- Lazarus HM, Haynesworth SE, Gerson SL, Rosenthal NS, Caplan AI. Ex vivo expansion and subsequent infusion of human bone marrowderived stromal progenitor cells (mesenchymal progenitor cells): implications for therapeutic use. Bone Marrow Transplant. 1995;16(4):557–64.
- Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999;284(5411):143–7.

- Caplan Al. Mesenchymal stem cells. J Orthopaedic Res. 1991;9(5):641–50.
- Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini FC, Krause DS, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315–7.
- Harvanová D, Tóthová T, Sarišský M, Amrichová J, Rosocha J. Isolation and characterization of synovial mesenchymal stem cells. Folia Biol. 2011;57(3):119–24.
- Romanov YA, Svintsitskaya VA, Smirnov VN. Searching for alternative sources of postnatal human mesenchymal stem cells: candidate MSClike cells from umbilical cord. Stem Cells. 2003;21(1):105–10.
- He S, Gleason J, Fik-Rymarkiewicz E, Difiglia A, Bharathan M, Morschauser A, et al. Human placenta-derived mesenchymal stromallike cells enhance angiogenesis via T cell-dependent reprogramming of macrophage differentiation. Stem Cells. 2017;35(6):1603–13.
- Bacenkova D, Rosocha J, Tothova T, Rosocha L, Sarissky M. Isolation and basic characterization of human term amnion and chorion mesenchymal stromal cells. Cytotherapy. 2011;13(9):1047–56.
- Kern S, Eichler H, Stoeve J, Kluter H, Bieback K. Comparative analysis of mesenchymal stem cells from bone marrow, umbilical cord blood, or adipose tissue. Stem Cells. 2006;24(5):1294–301.
- Fitzsimmons REB, Mazurek MS, Soos A, Simmons CA. Mesenchymal Stromal/Stem Cells in Regenerative Medicine and Tissue Engineering. Stem Cells International. 2018;2018.
- 21. Saeedi P, Halabian R, Imani Fooladi AA. A revealing review of mesenchymal stem cells therapy, clinical perspectives and Modification strategies. Stem cell Investigation. 2019;6:34.
- 22. Shao H, Im H. New technologies for analysis of extracellular vesicles. Chem Rev. 2018;118(4):1917–50.
- Heldring N, Mager I, Wood MJA, Le Blanc K, Andaloussi SEL. Therapeutic potential of multipotent mesenchymal stromal cells and their extracellular vesicles. Hum Gene Ther. 2015;26(8):506–17.
- 24. Mendt M, Rezvani K, Shpall E. Mesenchymal stem cell-derived exosomes for clinical use. Bone Marrow Transplant. 2019;54:789–92.
- Lou GH, Chen Z, Zheng M, Liu YN. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. Exp Mol Med. 2017;49:e346.
- 26. Liew LC, Katsuda T, Gailhouste L, Nakagama H, Ochiya T. Mesenchymal stem cell-derived extracellular vesicles: a glimmer of hope in treating Alzheimer's disease. Int Immunol. 2017;29(1):11–9.
- Haynesworth SE, Baber MA, Caplan AI. Cytokine expression by human marrow-derived mesenchymal progenitor cells in vitro: effects of dexamethasone and IL-1 alpha. J Cell Physiol. 1996;166(3):585–92.
- Min JY, Sullivan MF, Yang Y, Zhang JP, Converso KL, Morgan JP, et al. Significant improvement of heart function by cotransplantation of human mesenchymal stem cells and fetal cardiomyocytes in postinfarcted pigs. Ann Thorac Surg. 2002;74(5):1568–75.
- 29. Patschan D, Plotkin M, Goligorsky MS. Therapeutic use of stem and endothelial progenitor cells in acute renal injury: ca ira. Curr Opin Pharmacol. 2006;6(2):176–83.
- Kinnaird T, Stabile E, Burnett MS, Lee CW, Barr S, Fuchs S, et al. Marrowderived stromal cells express genes encoding a broad spectrum of arteriogenic cytokines and promote in vitro and in vivo arteriogenesis through paracrine mechanisms. Circ Res. 2004;94(5):678–85.
- Miyahara Y, Nagaya N, Kataoka M, Yanagawa B, Tanaka K, Hao H, et al. Monolayered mesenchymal stem cells repair scarred myocardium after myocardial infarction. Nat Med. 2006;12(4):459–65.
- Akyurekli C, Le Y, Richardson RB, Fergusson D, Tay J, Allan DS. A systematic review of preclinical studies on the therapeutic potential of mesenchymal stromal cell-derived microvesicles. Stem Cell Rev Rep. 2015;11(1):150–60.
- Thery C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. Nat Rev Immunol. 2009;9(8):581–93.
- 34. Caruso S, Poon IKH. Apoptotic cell-derived extracellular vesicles: more than just debris. Front Immunol. 2018;9:1486.
- Pap E, Pallinger E, Pasztoi M, Falus A. Highlights of a new type of intercellular communication: microvesicle-based information transfer. Inflamm Res. 2009;58(1):1–8.

- Camussi G, Deregibus MC, Bruno S, Grange C, Fonsato V, Tetta C. Exosome/microvesicle-mediated epigenetic reprogramming of cells. Am J Cancer Res. 2011;1(1):98–110.
- Jy W, Horstman LL, Jimenez JJ, Ahn YS. Measuring circulating cellderived microparticles. J Thromb Haemost. 2004;2(10):1842–51.
- Heijnen HFG, Schiel AE, Fijnheer R, Geuze HJ, Sixma JJ. Activated platelets release two types of membrane vesicles: microvesicles by surface shedding and exosomes derived from exocytosis of multivesicular bodies and alpha-granules. Blood. 1999;94(11):3791–9.
- Bjorge IM, Kim SY, Mano JF, Kalionis B, Chrzanowski W. Extracellular vesicles, exosomes and shedding vesicles in regenerative medicine—a new paradigm for tissue repair. Biomater Sci. 2017;6(1):60–78.
- Hu P, Yang QX, Wang Q, Shi CS, Wang DL, Armato U, et al. Mesenchymal stromal cells-exosomes: a promising cell-free therapeutic tool for wound healing and cutaneous regeneration (vol 7, 38, 2019). Burns & Trauma. 2020;8.
- Herrera MB, Fonsato V, Gatti S, Deregibus MC, Sordi A, Cantarella D, et al. Human liver stem cell-derived microvesicles accelerate hepatic regeneration in hepatectomized rats. J Cell Mol Med. 2010;14(6B):1605–18.
- Bruno S, Grange C, Deregibus MC, Calogero RA, Saviozzi S, Collino F, et al. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. J Am Soc Nephrol. 2009;20(5):1053–67.
- Johnstone RM, Adam M, Hammond JR, Orr L, Turbide C. Vesicle formation during reticulocyte maturation—association of plasmamembrane activities with released vesicles (exosomes). J Biol Chem. 1987;262(19):9412–20.
- Harding C, Heuser J, Stahl P. Receptor-mediated endocytosis of transferrin and recycling of the transferrin receptor in rat reticulocytes. J Cell Biol. 1983;97(2):329–39.
- 45. Pan BT, Teng K, Wu C, Adam M, Johnstone RM. Electron-microscopic evidence for externalization of the transferrin receptor in vesicular form in sheep reticulocytes. J Cell Biol. 1985;101(3):942–8.
- Greening DW, Gopal SK, Xu R, Simpson RJ, Chen WS. Exosomes and their roles in immune regulation and cancer. Semin Cell Dev Biol. 2015;40:72–81.
- Mittelbrunn M, Gutierrez-Vazquez C, Villarroya-Beltri C, Gonzalez S, Sanchez-Cabo F, Gonzalez MA, et al. Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells. Nat Commun. 2011. https://doi.org/10.1038/ncomms1285.
- Gangoda L, Boukouris S, Liem M, Kalra H, Mathivanan S. Extracellular vesicles including exosomes are mediators of signal transduction: are they protective or pathogenic? Proteomics. 2015;15(2–3):260–71.
- 49. Isola AL, Chen SZ. Exosomes: the messengers of health and disease. Curr Neuropharmacol. 2017;15(1):157–65.
- Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;367(6478):640.
- Henne WM, Stenmark H, Emr SD. Molecular mechanisms of the membrane sculpting ESCRT pathway. Cold Spring Harbor Perspect Biol. 2013;5(9):a016766.
- 52. Piper RC, Luzio JP. Ubiquitin-dependent sorting of integral membrane proteins for degradation in lysosomes. Curr Opin Cell Biol. 2007;19(4):459–65.
- Zhang Y, Liu YF, Liu HY, Tang WH. Exosomes: biogenesis, biologic function and clinical potential. Cell Biosci. 2019. https://doi.org/10.1186/ s13578-019-0282-2.
- Urbanelli L, Magini A, Buratta S, Brozzi A, Sagini K, Polchi A, et al. Signaling pathways in exosomes biogenesis. Secretion Fate Genes. 2013;4(2):152–70.
- Colombo M, Moita C, van Niel G, Kowal J, Vigneron J, Benaroch P, et al. Analysis of ESCRT functions in exosome biogenesis, composition and secretion highlights the heterogeneity of extracellular vesicles. J Cell Sci. 2013;126(24):5553–65.
- Hoshino D, Kirkbride KC, Costello K, Clark ES, Sinha S, Grega-Larson N, et al. Exosome secretion is enhanced by invadopodia and drives invasive behavior. Cell Rep. 2013;5(5):1159–68.
- Baietti MF, Zhang Z, Mortier E, Melchior A, Degeest G, Geeraerts A, et al. Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. Nat Cell Biol. 2012;14(7):677–85.

- Trajkovic K, Hsu C, Chiantia S, Rajendran L, Wenzel D, Wieland F, et al. Ceramide triggers budding of exosome vesicles into multivesicular endosomes. Science. 2008;319(5867):1244–7.
- Chairoungdua A, Smith DL, Pochard P, Hull M, Caplan MJ. Exosome release of beta-catenin: a novel mechanism that antagonizes Wnt signaling. J Cell Biol. 2010;190(6):1079–91.
- Fang Y, Wu N, Gan X, Yan WH, Morrell JC, Gould SJ. Higher-order oligomerization targets plasma membrane proteins and HIV gag to exosomes. PLoS Biol. 2007;5(6):1267–83.
- Janowska-Wieczorek A, Wysoczynski M, Kijowski J, Marquez-Curtis L, Machalinski B, Ratajczak J, et al. Microvesicles derived from activated platelets induce metastasis and angiogenesis in lung cancer. Int J Cancer. 2005;113(5):752–60.
- 62. Ailawadi S, Wang XH, Gu HT, Fan GC. Pathologic function and therapeutic potential of exosomes in cardiovascular disease. BBA Mol Basis Dis. 2015;1852(1):1–11.
- 63. Mitchell PJ, Welton J, Staffurth J, Court J, Mason MD, Tabi Z, et al. Can urinary exosomes act as treatment response markers in prostate cancer? J Transl Med. 2009;7:4.
- 64. Atienzar-Aroca S, Flores-Bellver M, Serrano-Heras G, Martinez-Gil N, Barcia JM, Aparicio S, et al. Oxidative stress in retinal pigment epithelium cells increases exosome secretion and promotes angiogenesis in endothelial cells. J Cell Mol Med. 2016;20(8):1457–66.
- 65. Chen TS, Lai RC, Lee MM, Choo ABH, Lee CN, Lim SK. Mesenchymal stem cell secretes microparticles enriched in pre-microRNAs. Nucleic Acids Res. 2010;38(1):215–24.
- Simpson RJ, Lim JWE, Moritz RL, Mathivanan S. Exosomes: proteomic insights and diagnostic potential. Expert Rev Proteomics. 2009;6(3):267–83.
- Lai RC, Tan SS, Teh BJ, Sze SK, Arslan F, de Kleijn DP, et al. Proteolytic potential of the msc exosome proteome: implications for an exosomemediated delivery of therapeutic proteasome. Int J Proteomics. 2012;2012:971907.
- Kang DJ, Oh S, Ahn SM, Lee BH, Moon MH. Proteomic analysis of exosomes from human neural stem cells by flow field-flow fractionation and nanoflow liquid chromatography-tandem mass spectrometry. J Proteome Res. 2008;7(8):3475–80.
- 69. Arslan F, Lai RC, Smeets MB, Akeroyd L, Choo A, Aguor EN, et al. Mesenchymal stem cell-derived exosomes increase ATP levels, decrease oxidative stress and activate PI3K/Akt pathway to enhance myocardial viability and prevent adverse remodeling after myocardial ischemia/ reperfusion injury. Stem Cell Res. 2013;10(3):301–12.
- Li X, Arslan F, Ren Y, Adav SS, Poh KK, Sorokin V, et al. Metabolic adaptation to a disruption in oxygen supply during myocardial ischemia and reperfusion is underpinned by temporal and quantitative changes in the cardiac proteome. J Proteome Res. 2012;11(4):2331–46.
- Deng H, Sun C, Sun YX, Li HH, Yang L, Wu DB, et al. Lipid, protein, and MicroRNA composition within mesenchymal stem cell-derived exosomes. Cell Reprogram. 2018;20(3):178–86.
- Ratajczak J, Miekus K, Kucia M, Zhang J, Reca R, Dvorak P, et al. Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery. Leukemia. 2006;20(5):847–56.
- Valadi H, Ekstrom K, Bossios A, Sjostrand M, Lee JJ, Lotvall JO. Exosomemediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. Nat Cell Biol. 2007;9(6):654-U72.
- Alvarez-Garcia I, Miska EA. MicroRNA functions in animal development and human disease. Development. 2005;132(21):4653.
- Ono M, Kosaka N, Tominaga N, Yoshioka Y, Takeshita F, Takahashi RU, et al. Exosomes from bone marrow mesenchymal stem cells contain a microRNA that promotes dormancy in metastatic breast cancer cells. Sci Signal. 2014;7(332):ra63.
- Qian X, Xu C, Fang S, Zhao P, Wang Y, Liu H, et al. Exosomal MicroRNAs derived from umbilical mesenchymal stem cells inhibit Hepatitis C virus infection. Stem Cells Transl Med. 2016;5(9):1190–203.
- Li M, Zeringer E, Barta T, Schageman J, Cheng AG, Vlassov AV. Analysis of the RNA content of the exosomes derived from blood serum and urine and its potential as biomarkers. Philos Trans R Soc B-Biol Sci. 2014;369(1652):20130502.
- 78. Wang K, Jiang Z, Webster KA, Chen JH, Hu HX, Zhou Y, et al. Enhanced cardioprotection by human endometrium mesenchymal stem

cells driven by exosomal MicroRNA-21. Stem Cells Transl Med. 2017;6(1):209–22.

- Rana S, Yue SJ, Stadel D, Zoller M. Toward tailored exosomes: the exosomal tetraspanin web contributes to target cell selection. Int J Biochem Cell Biol. 2012;44(9):1574–84.
- Nazarenko I, Rana S, Baumann A, McAlear J, Hellwig A, Trendelenburg M, et al. Cell surface tetraspanin Tspan8 contributes to molecular pathways of exosome-induced endothelial cell activation. Can Res. 2010;70(4):1668–78.
- Williams C, Rodriguez-Barrueco R, Silva JM, Zhang WJ, Hearn S, Elemento O, et al. Double-stranded DNA in exosomes: a novel biomarker in cancer detection. Cell Res. 2014;24(6):766–9.
- Liang GF, Zhu YL, Ali DJ, Tian T, Xu HT, Si K, et al. Engineered exosomes for targeted co-delivery of miR-21 inhibitor and chemotherapeutics to reverse drug resistance in colon cancer. J Nanobiotechnol. 2020. https://doi.org/10.1186/s12951-019-0563-2.
- Yang TZ, Fogarty B, LaForge B, Aziz S, Pham T, Lai LN, et al. Delivery of small interfering Rna to inhibit vascular endothelial growth factor in Zebrafish using natural brain endothelia cell-secreted exosome nanovesicles for the treatment of brain cancer. Aaps J. 2017;19(2):475–86.
- Raposo G, Nijman HW, Stoorvogel W, Leijendekker R, Harding CV, Melief CJM, et al. B lymphocytes secrete antigen-presenting vesicles. J Exp Med. 1996;183(3):1161–72.
- Lee C, Mitsialis SA, Aslam M, Vitali SH, Vergadi E, Konstantinou G, et al. Exosomes mediate the cytoprotective action of mesenchymal stromal cells on hypoxia-induced pulmonary hypertension. Circulation. 2012;126(22):2601.
- Reis LA, Borges FT, Simões MJ, Borges AA, Sinigaglia-Coimbra R, Schor N. Bone marrow-derived mesenchymal stem cells repaired but did not prevent gentamicin-induced acute kidney injury through paracrine effects in rats. PLoS ONE. 2012;7(9):e44092.
- Li TF, Yan YM, Wang BY, Qian H, Zhang X, Shen L, et al. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. Stem Cells Dev. 2013;22(6):845–54.
- Lai RC, Arslan F, Lee MM, Sze NSK, Choo A, Chen TS, et al. Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. Stem Cell Res. 2010;4(3):214–22.
- Heidari M, Pouya S, Baghaei K, Aghdaei HA, Namaki S, Zali MR, et al. The immunomodulatory effects of adipose-derived mesenchymal stem cells and mesenchymal stem cells-conditioned medium in chronic colitis. J Cell Physiol. 2018;233(11):8754–66.
- Jie Z, Wang YH, Li ZG, Wang Y, Li BY, Kang HY, et al. Immunosuppressive effect of exosomes from mesenchymal stromal cells in defined medium on experimental colitis. Int J Stem Cells. 2019;12(3):440–8.
- Shao LB, Zhang Y, Lan BB, Wang JJ, Zhang ZW, Zhang LL, et al. MiRNAsequence indicates that mesenchymal stem cells and exosomes have similar mechanism to enhance cardiac repair. Biomed Res Int. 2017. https://doi.org/10.1155/2017/4150705.
- 92. Pelizzo G, Avanzini MA, Cornaglia AI, De Silvestri A, Mantelli M, Travaglino P, et al. Extracellular vesicles derived from mesenchymal cells: perspective treatment for cutaneous wound healing in pediatrics. Regen Med. 2018;13(4):385–94.
- Gatti S, Bruno S, Deregibus MC, Sordi A, Cantaluppi V, Tetta C, et al. Microvesicles derived from human adult mesenchymal stem cells protect against ischaemia-reperfusion-induced acute and chronic kidney injury. Nephrol Dial Transplant. 2011;26(5):1474–83.
- Clark K, Zhang S, Barthe S, Kumar P, Pivetti C, Kreutzberg N, et al. Placental mesenchymal stem cell-derived extracellular vesicles promote myelin regeneration in an animal model of multiple sclerosis. Cells. 2019;8(12):1497.
- Reza-Zaldivar EE, Hernandez-Sapiens MA, Gutierrez-Mercado YK, Sandoval-Avila S, Gomez-Pinedo U, Marquez-Aguirre AL, et al. Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease. Neural Regen Res. 2019;14(9):1626–34.
- Vakhshiteh F, Atyabi F, Ostad SN. Mesenchymal stem cell exosomes: a two-edged sword in cancer therapy. Int J Nanomed. 2019;14:2847–59.
- Yeo RWY, Lai RC, Zhang B, Tan SS, Yin YJ, Teh BJ, et al. Mesenchymal stem cell: an efficient mass producer of exosomes for drug delivery. Adv Drug Deliv Rev. 2013;65(3):336–41.

- 98. Ban JJ, Lee M, Im W, Kim M. Low pH increases the yield of exosome isolation. Biochem Biophys Res Commun. 2015;461(1):76–9.
- 99. Zhang HC, Liu XB, Huang S, Bi XY, Wang HX, Xie LX, et al. Microvesicles derived from human umbilical cord mesenchymal stem cells stimulated by hypoxia promote angiogenesis both in vitro and in vivo. Stem Cells Dev. 2012;21(18):3289–97.
- Lee SC, Jeong HJ, Lee SK, Kim SJ. Hypoxic conditioned medium from human adipose-derived stem cells promotes mouse liver regeneration through JAK/STAT3 signaling. Stem Cells Transl Med. 2016;5(6):816–25.
- Domenis R, Cifu A, Quaglia S, Pistis C, Moretti M, Vicario A, et al. Pro inflammatory stimuli enhance the immunosuppressive functions of adipose mesenchymal stem cells derived exosomes. Sci Rep. 2018. https://doi.org/10.1038/s41598-018-31707-9.
- Zhang Q, Fu L, Liang Y, Guo Z, Wang L, Ma C, et al. Exosomes originating from MSCs stimulated with TGF-β and IFN-γ promote Treg differentiation. J Cell Physiol. 2018;233(9):6832–40.
- Lee SC, Jeong HJ, Lee SK, Kim SJ. Lipopolysaccharide preconditioning of adipose-derived stem cells improves liver-regenerating activity of the secretome. Stem Cell Res Therapy. 2015. https://doi.org/10.1186/ s13287-015-0072-7.
- 104. Kim YE, Sung SI, Chang YS, Ahn SY, Sung DK, Park WS. Thrombin preconditioning enhances therapeutic efficacy of human wharton's jellyderived mesenchymal stem cells in severe neonatal hypoxic ischemic encephalopathy. Int J Mol Sci. 2019;20(10):2477.
- Du W, Zhang KY, Zhang SQ, Wang R, Nie Y, Tao HY, et al. Enhanced proangiogenic potential of mesenchymal stem cell-derived exosomes stimulated by a nitric oxide releasing polymer. Biomaterials. 2017;133:70–81.
- 106. Bai Y, Han YD, Yan XL, Ren J, Zeng Q, Li XD, et al. Adipose mesenchymal stem cell-derived exosomes stimulated by hydrogen peroxide enhanced skin flap recovery in ischemia-reperfusion injury. Biochem Biophys Res Commun. 2018;500(2):310–7.
- 107. Sokolova V, Ludwig AK, Hornung S, Rotan O, Horn PA, Epple M, et al. Characterisation of exosomes derived from human cells by nanoparticle tracking analysis and scanning electron microscopy. Colloids and Surfaces B-Biointerfaces. 2011;87(1):146–50.
- Rong X, Liu J, Yao X, Jiang T, Wang Y, Xie F. Human bone marrow mesenchymal stem cells-derived exosomes alleviate liver fibrosis through the Wnt/β-catenin pathway. Stem Cell Res Therapy. 2019;10(1):98.
- Damania A, Jaiman D, Teotia AK, Kumar A. Mesenchymal stromal cellderived exosome-rich fractionated secretome confers a hepatoprotective effect in liver injury. Stem Cell Res Therapy. 2018. https://doi.org/10. 1186/s13287-017-0752-6.
- Chen F, Li XL, Zhao JX, Geng J, Xie J, Xu B. Bone marrow mesenchymal stem cell-derived exosomes attenuate cardiac hypertrophy and fibrosis in pressure overload induced remodeling. Vitro Cellular Dev Biol Animal. 2020;56(7):567–76.
- 111. Teng XM, Chen L, Chen WQ, Yang JJ, Yang ZY, Shen ZY. Mesenchymal stem cell-derived exosomes improve the microenvironment of infarcted myocardium contributing to angiogenesis and anti-inflammation. Cell Physiol Biochem. 2015;37(6):2415–24.
- 112. Zou LY, Ma XK, Lin S, Wu BY, Chen Y, Peng CQ. Bone marrow mesenchymal stem cell-derived exosomes protect against myocardial infarction by promoting autophagy. Exp Ther Med. 2019;18(4):2574–82.
- Xin HQ, Li Y, Cui YS, Yang JJ, Zhang ZG, Chopp M. Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. J Cereb Blood Flow Metab. 2013;33(11):1711–5.
- 114. Zhang YL, Chopp M, Zhang ZG, Katakowski M, Xin HQ, Qu CS, et al. Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury. Neurochem Int. 2017;111:69–81.
- 115. Cui GH, Wu J, Mou FF, Xie WH, Wang FB, Wang QL, et al. Exosomes derived from hypoxia-preconditioned mesenchymal stromal cells ameliorate cognitive decline by rescuing synaptic dysfunction and regulating inflammatory responses in APP/PS1 mice. FASEB J. 2018;32(2):654–68.
- 116. Casado JG, Blazquez R, Vela FJ, Alvarez V, Tarazona R, Sanchez-Margallo FM. Mesenchymal stem cell-derived exosomes: immunomodulatory

evaluation in an antigen-induced synovitis porcine model. Front Veterinary Sci. 2017;4:39.

- 117. Ma XX, Xu SQ. TNF inhibitor therapy for rheumatoid arthritis (Review). Biomedical Rep. 2013;1(2):177–84.
- Martins M, Ribeiro D, Martins A, Reis RL, Neves NM. Extracellular vesicles derived from osteogenically induced human bone marrow mesenchymal stem cells can modulate lineage commitment. Stem Cell Rep. 2016;6(3):284–91.
- Qin Y, Wang L, Gao Z, Chen G, Zhang C. Bone marrow stromal/stem cell-derived extracellular vesicles regulate osteoblast activity and differentiation in vitro and promote bone regeneration in vivo. Sci Rep. 2016;6(1):21961.
- 120. Narayanan R, Huang C-C, Ravindran S. Hijacking the cellular mail: exosome mediated differentiation of mesenchymal stem cells. Stem Cells Int. 2016;2016:3808674.
- 121. Shimbo K, Miyaki S, Ishitobi H, Kato Y, Kubo T, Shimose S, et al. Exosomeformed synthetic microRNA-143 is transferred to osteosarcoma cells and inhibits their migration. Biochem Biophys Res Commun. 2014;445(2):381–7.
- 122. Shao M, Xu Q, Wu Z, Chen Y, Shu Y, Cao X, et al. Exosomes derived from human umbilical cord mesenchymal stem cells ameliorate IL-6-induced acute liver injury through miR-455-3p. Stem Cell Res Ther. 2020;11(1):37.
- 123. Zhou Y, Xu HT, Xu WR, Wang BY, Wu HY, Tao Y, et al. Exosomes released by human umbilical cord mesenchymal stem cells protect against cisplatin-induced renal oxidative stress and apoptosis in vivo and in vitro. Stem Cell Res Therapy. 2013;4:34.
- 124. Zou XY, Gu D, Xing XY, Cheng ZL, Gong DL, Zhang GY, et al. Human mesenchymal stromal cell-derived extracellular vesicles alleviate renal ischemic reperfusion injury and enhance angiogenesis in rats. Am J Transl Res. 2016;8(10):4289–99.
- Zhang B, Wu X, Zhang X, Sun Y, Yan Y, Shi H, et al. Human umbilical cord mesenchymal stem cell exosomes enhance angiogenesis through the Wnt4/β-catenin pathway. Stem Cells Transl Med. 2015;4(5):513–22.
- 126. Zhou J, Liu HX, Li SH, Gong YS, Zhou MW, Zhang JH, et al. Effects of human umbilical cord mesenchymal stem cells-derived exosomes on fracture healing in rats through the Wnt signaling pathway. Eur Rev Med Pharmacol Sci. 2019;23(11):4954–60.
- 127. Fang S, Xu C, Zhang Y, Xue C, Yang C, Bi H, et al. Umbilical cord-derived mesenchymal stem cell-derived exosomal micrornas suppress

myofibroblast differentiation by inhibiting the transforming growth Factor- $\beta$ /SMAD2 pathway during wound healing. Stem Cells Transl Med. 2016;5(10):1425–39.

- 128. Mao F, Wu YB, Tang XD, Kang JJ, Zhang B, Yan YM, et al. Exosomes derived from human umbilical cord mesenchymal stem cells relieve inflammatory bowel disease in mice. Biomed Res Int. 2017;2017:1.
- 129. Korolkova OY, Myers JN, Pellom ST, Wang L, M'Koma AE. Characterization of serum cytokine profile in predominantly colonic inflammatory bowel disease to delineate ulcerative and crohn's colitides. Clin Med Insights Gastroenterol. 2015;8:29–44.
- Eirin A, Zhu XY, Puranik AS, Tang H, McGurren KA, van Wijnen AJ, et al. Mesenchymal stem cell-derived extracellular vesicles attenuate kidney inflammation. Kidney Int. 2017;92(1):114–24.
- 131. Cui X, He Z, Liang Z, Chen Z, Wang H, Zhang J. Exosomes from adiposederived mesenchymal stem cells protect the myocardium against ischemia/reperfusion injury through Wnt/β-catenin signaling pathway. J Cardiovasc Pharmacol. 2017;70(4):225–31.
- Liu Z, Xu YD, Wan YG, Gao J, Chu YY, Li J. Exosomes from adiposederived mesenchymal stem cells prevent cardiomyocyte apoptosis induced by oxidative stress. Cell Death Discov. 2019. https://doi.org/10. 1038/s41420-019-0159-5.
- Katsuda T, Tsuchiya R, Kosaka N, Yoshioka Y, Takagaki K, Oki K, et al. Human adipose tissue-derived mesenchymal stem cells secrete functional neprilysin-bound exosomes. Sci Rep. 2013. https://doi.org/10. 1038/srep01197.
- Reza A, Choi YJ, Yasuda H, Kim JH. Human adipose mesenchymal stem cell-derived exosomal-miRNAs are critical factors for inducing antiproliferation signalling to A2780 and SKOV-3 ovarian cancer cells. Sci Rep. 2016. https://doi.org/10.1038/srep38498.

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