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I have just re-revised the article "Mesenchymal stem cells from different sources and their derived exosomes: A pre-clinical perspective." by Alvarez-Viejo et al. submitted to your journal. Having corrected some small errors introduced by the authors during the review process, I hope you now find the manuscript suitable for publication. I attach a new version of the text with the changes tracked for your inspection. Please do not hesitate to contact me if you would like me to make any further changes or introduce any new information.

Sincerely yours,

Ana Burton

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**Mesenchymal stem cells from different sources and their derived exosomes: A pre-clinical perspective**

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Álvarez-Viejo M *et al.* MSC and their derived exosomes

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## Abstract

Since the introduction of cell therapy as a strategy for the treatment of many diseases several decades ago, cell therapy emerged as a promising strategy for the treatment of many diseases. Since then, mesenchymal stem cells have been identified emerged as ideal candidates, producing beneficial effects in several tissues, yet the underlying mechanisms for these their beneficial effects effects are only partially understood. At the start of the 21st century, a paracrine effect was proposed as a mechanism of tissue repair by these cells. In addition, a role was suggested for a heterogeneous population of extracellular vesicles in cell-to-cell communication. Some of these vesicles including exosomes ese extracelullar vesicles, a heterogeneous population including exosomes, have been isolated from most fluids and cells, as well as from supernatants of *in vitro* cell cultures. Recent research in the field of regenerative medicine suggests that exosomes exosomes derived from mesenchymal stem cells could be a powerful new therapeutic tool. This review examines the therapeutic potential of these exosomes derived from mesenchymal cells obtained from the sources most used in cell therapy: bone marrow, adipose tissue, and umbilical cord.

**Key words:** Mesenchymal stem cells; Exosomes; Cellular therapy

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**Core tip:** This article reviews~~We review~~ the latest data on the use of exosomes derived from mesenchymal stem cells in to treat various disease states and discusses their possible clinical applicationsat the translational level. Cell therapy “without cells”, is an emerging field, many researchers direct their efforts to transfer these results to the clinic.

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## **INTRODUCTION**

At the start of the ~~21th-21st~~ century, cell therapy, defined as a series of strategies based on the use of living cells for therapeutic purposes, emerged as a promising tool in the field of biomedicine. ~~Cell therapy has been defined as a series of strategies based on the use of living cells for therapeutic purposes.~~ The aim of cell therapy is to repair, replace or restore the biological functions of an organ or of damaged tissue. Research efforts in regenerative medicine have mainly focused on the use of mesenchymal stem cells (MSC).

Friedenstein and co-workers were the first to discover MSC. These authors showed that bone marrow (BM) contains a population of cells, with a high proliferative capacity that adheres to plastic in culture<sup>[1]</sup>. Since this observation ~~of MSC in BM~~ in the 1970s, many studies have focused on this type of adult stem cell. However, there was no defined approach to characterize MSC and different methods of isolation, expansion and characterization were reported. This made it difficult to compare findings between independent laboratories. To resolve this issue, in 2006, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy proposed minimal criteria to define human MSC: they should be plastic-adherent when maintained in standard culture conditions; they must express specific surface antigens; and they should also show multipotent cell differentiation potential *in vitro*<sup>[2]</sup>. These criteria facilitated the work of many groups which continued their research with this cell type. MSC have been successfully obtained from many sources including adipose tissue, Wharton Jelly, placenta, dental pulp or amniotic fluid among others<sup>[3]</sup>. Further, throughout the years, the regenerative capacity of MSC and their immunoregulatory properties ~~has~~ have been ~~suitably~~ well documented ~~as well as their immunoregulatory properties~~<sup>[4]</sup>.

Because of their characteristics, MSC offer great therapeutic potential and many ~~cell-based~~ therapies based on these cells have been developed to treat a wide range of disorders. However, despite good results, the underlying mechanisms for their beneficial impacts are only partially understood. One hypothesis is that MSC induce tissue regenerations through their capacity to

migrate to the site of injury and then to differentiate into the corresponding cells in the damaged tissue. In 2005, Gnecchi *et al*<sup>[5]</sup> were among the first ~~researchers~~ to propose a paracrine effect of MSC in tissue regeneration<sup>[5]</sup>. Since then, many studies have shown the ~~se paracrine~~ effects of MSC<sup>[6,7]</sup> ~~and Today~~, it is recognized today that, besides releasing cytokines and growth factors, MSC also secrete extracellular vesicles (EV), which are thought to play an important role in tissue regeneration and immunomodulation<sup>[4]</sup>. Based on these data, recent research has focused on EV derived from MSC as a form of non-cellular therapy<sup>[8]</sup>.

The term EV refers to a heterogeneous population of vesicles<sup>[9]</sup>. For several decades, the presence of membrane-enclosed vesicles outside solid tissue cells, as well as biological fluids such as blood or semen, was described<sup>[10]</sup>. ~~For a long time, t~~ these vesicles were considered a vehicle for the cell to discard unwanted proteins<sup>[11]</sup>. In the first decade of the 21st century, two independent research groups demonstrated the presence of RNA, including miRNA in EV. This finding has rekindled interest in EVs as possible mediators of cell-to-cell communication<sup>[12,13]</sup>. The International Society for ~~Extracelular~~Extracellular Vesicles proposed minimum criteria for their definition: EV is the generic term for particles naturally released from the cell that are delimited by a lipid bilayer and cannot replicate, *i.e.* they do not contain a functional nucleus<sup>[14]</sup>. To date, EV ~~has~~have been isolated from most fluids and cells<sup>[15]</sup> and from supernatants of *in vitro* cell cultures<sup>[16]</sup>. It has also been established that the release of EV is an evolutionarily well-conserved mechanism that the cells exploit for the exchange of bioactive proteins, lipids and nucleic acids<sup>[17]</sup>.

The term EV ~~includes~~encompasses microvesicles/nanoparticles/vesicles, apoptotic bodies and exosomes<sup>[16]</sup>. Exosomes are small EV generated through inward budding of endosomal membranes. While the definition of exosomes is not completely clear, they are negatively charged lipid-bilayer vesicles of diameter 30-100 nm and density 1.13-1.19 g/mL. Exosomes are secreted by fusion of the multivesicular body containing exosomes with the plasma membrane<sup>[18]</sup>. The protein content of exosomes has been extensively studied

since their initial description. So far, it is known that the composition of exosomal proteins varies among cell types. However, proteins such as Alix, Tsg101 and tetraspanins including CD9, CD63 or CD81 are frequent components and are often used as exosome markers<sup>[19]</sup>.

Several studies have suggested that exosomes derived from MSC could serve as a novel therapeutic tool in the field of regenerative medicine. A main benefit proposed is that as no cells are introduced, mutated or damaged genetic material that could negatively affect the recipient is avoided. Another advantage is that exosomes lack immunogenicity<sup>[20]</sup>. As a shortcoming, exosomes are static and do not reproduce *in vivo*<sup>[21]</sup>.

While MSC can be found in most adult tissues, the major sources of MSC for therapeutic use have been bone marrow, adipose tissue and umbilical cord<sup>[22]</sup>. This review updates research addressing the therapeutic potential of exosomes derived from MSC ~~exosomes obtained derived from MSC from~~ these tissues.

### **EXOSOMES DERIVED FROM BONE MARROW MESENCHYMAL STEM CELLS**

MSC derived from bone marrow are probably the most commonly used stem cells in clinical trials. The use of bone marrow MSC derived exosomes (BM MSC-Ex) as a promising tool for future therapies has been examined in experimental models of various pathologies. In a model of liver disease, Damania *et al*<sup>[23]</sup> employed rat BM MSC conditioned medium in *in vitro* and *in vivo* experiments. The rich exosome fraction obtained through ultracentrifugation of this medium was found to have antiapoptotic and ~~antioxidative~~ antioxidant effects in *in vitro* models of liver injury and to improve liver regeneration and recovery from liver injury *in vivo*. These results are in accordance with those reported by Rong *et al*<sup>[24]</sup> who, using a rat model of liver fibrosis, observed that the administration of BM MSC-Ex improved this fibrosis. Further, these authors proposed that the beneficial effects of these exosomes consisted of inhibition of the Wnt/ $\beta$ -catenin signaling pathway and suggested their use to treat liver disease in a clinical setting<sup>[24]</sup>. The therapeutic

potential of BM MSC-Ex in degenerative diseases, such as intervertebral disc degeneration (IDD), has been advocated by several researchers. IDD is a cause of lower back pain related to degenerative musculoskeletal disorders ~~that~~ affecting a large number of patients. Liao *et al*<sup>[25]</sup>, using human BM MSC-Ex in a rat tail model proposed that exosomes ~~could may prevent delay or prevent~~ disc degeneration ~~—progression~~. Exosomes could modulate endoplasmic reticulum stress and protect against nucleus pulposus cell death. The therapeutic effects of BM MSC-Ex on IDD are supported by the findings of another study conducted in an IDD model in rabbits. In this work, Xia *et al*<sup>[26]</sup> proposed that the use of BM MSC-Ex significantly prevents the progression of degeneration *via* anti-oxidant and anti-inflammatory effects. The use of BM MSC-Ex for the treatment of cancer has also been explored by several groups. Recently, BM MSC-Ex overexpressing (exogenous) miR-34a, a recognized tumor suppressor, were reported to ameliorate glioblastoma in a mouse model<sup>[27]</sup>. In another experimental study on pancreatic cancer, Wu *et al*<sup>[28]</sup> observed that BM MSC-Ex-derived miRNA-126-3p ~~prevented—blocked~~ the progression of this cancer.

Zhu *et al*<sup>[29]</sup> found that exosomes derived from different cells types had different therapeutic effects. This hypothesis is consistent with recently published data by the same group. When comparing the effects of exosomes obtained from healthy or diabetic rats in a rat calvarial defect, these authors observed a more positive effect when exosomes from rats without type-1 diabetes were used. Accordingly, they proposed that for patients with type-1 diabetes, the autologous transplantation of BM MSC-Ex to promote regeneration could be inappropriate<sup>[30]</sup>.

According to the literature, the potential of BM MSC-Ex for the treatment of various pathologies seems evident. However, in terms of clinical applications we have only found a letter to the Editor in which their use to treat graft *vs* host disease (GvHD) is described. BM-MSC have been employed in the treatment of GvHD in clinical practice since Blanc *et al*<sup>[31]</sup> published their encouraging results for the treatment of refractory GvHD. In one patient, Kordelas *et al*<sup>[32]</sup> used an

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exosome-enriched fraction processed from collected MSC supernatants instead of administering the MSC themselves. The patient was stable for several months post-exosome application. Although the patient died of pneumonia 7 months after treatment, the authors concluded that BM MSC-Ex could be a ~~potential~~-new ~~and~~-safe tool to treat therapy-refractory GvHD and most likely other inflammation-associated diseases<sup>[32]</sup>. The improvement observed in this patient is supported by work ~~done~~-conducted in mouse models<sup>[33,34]</sup>.

### **EXOSOMES DERIVED FROM ADIPOSE MESENCHYMAL STEM CELLS**

As with BM MSC-Ex, there are many literature descriptions of the use of exosomes derived from adipose MSC (AMSC-Ex), in which a paracrine effect is produced both *in vivo* and *in vitro*. Several research groups have reported positive effects of AMSC-Ex in various skin disorders. Cho *et al*<sup>[35]</sup> ~~was~~-were the first to investigate the therapeutic effect of AMSC-Ex in an atopic dermatitis mouse model. Taken together, results suggested that AMSC-Ex could be a novel cell-free treatment for atopic dermatitis. The limitations reported by these authors were that AMSC donor age seemed to affect their immunomodulatory properties. Accordingly, they proposed to continue working on this issue to determine whether the potential of AMSC-Ex could be influenced by age<sup>[35]</sup>. Treatment ~~for~~-of cutaneous wound healing has also been explored using exosomes derived from AMSC. ~~According to~~To-~~a need for~~ improve ~~the~~enhanced retention of exosomes in the target area, Liu *et al*<sup>[36]</sup> proposed the use of hyaluronic acid ~~for this purpose~~ and examined the effect of AMSC-Ex combined with hyaluronic acid for acute cutaneous wound healing in nude mice. These authors concluded that this preparation of exosomes combined with appropriate scaffolds was effective. Their results showed that AMSC-Ex could markedly promote fibroblast activities, re-epithelialization and vascularization in wound healing<sup>[36]</sup>. Other studies have shown that AMSC-Ex accelerate wound healing *via* optimizing fibroblast function and collagen deposition<sup>[37]</sup>. Further, Shen *et al*<sup>[38]</sup> detected a role of AMSC-Ex in corneal stromal cell and extracellular matrix remodeling.

Other disease states such as heart and neural conditions or cancer have also been examined as targets of AMSC-Ex therapy. The results of *in vitro* experiments by Liu *et al*<sup>[39]</sup> indicated that apoptosis induced by oxidative stress in the cardiomyocyte was blocked by AMSC-Ex. Others have reported the inhibition of ovarian cancer cell proliferation by exosomes collected from AMSC conditioned medium<sup>[40]</sup>. Feng *et al*<sup>[41]</sup> also argued that the use of AMSC-Ex to inhibit the activation of microglia cells and prevent neuroinflammation could be a promising therapeutic strategy for nerve injury.

### **EXOSOMES DERIVED FROM UMBILICAL CORD MESENCHYMAL STEM CELLS**

Umbilical cord mesenchymal stem cells and their exosomes have been also examined as potential therapeutic tools in regenerative medicine. However, as for exosomes derived from other sources, the underlying mechanisms are still not well understood. Zhang *et al*<sup>[42]</sup> suggested that exosomes derived from umbilical cord MSC (UcMSC-Ex) enhanced angiogenesis through the Wnt4/ $\beta$ -catenin pathway, which could be an important mechanism responsible for cutaneous wound healing. This positive effect on angiogenesis has also been reported by another group. Hence, [the](#) authors of a recent study reported that transplantation of UcMSC-Ex markedly enhanced angiogenesis and bone healing in a rat model of femoral fracture. Their results unveiled a novel role of exosomes in accelerating fracture healing *via* the promotion of angiogenesis<sup>[43]</sup>. The results of both these studies are in accordance with the data reported by Zhou *et al*<sup>[44]</sup>. These last authors explored the impacts of human UcMSC-Ex on fracture healing by acting on the Wnt signaling pathway. They concluded that UcMSC-Ex could participate in repairing fractures in rats through this pathway.

Mao *et al*<sup>[45]</sup> investigated the effects of UcMSC-Ex in a model of induced inflammatory bowel disease. According to their findings, UcMSC-Ex are able to substantially alleviate induced inflammatory bowel disease in mice and may exert their impact through IL-7 expression modulation in macrophages. Other authors have assessed the immunosuppression and therapeutic effects of

UcMSC-Ex used to treat colitis in a mouse model. Exosomes were obtained from MSC cultures in defined medium thus avoiding the use of fetal bovine serum. Results indicated that UcMSC-Ex alleviate colon damage in animal disease model and have ~~immunosuppressive~~immunosuppressive effects *in vitro*<sup>[46]</sup>. These results have interesting ~~possible~~ implications for the clinical use of this type of therapy. Because of their immunosuppressive activity, autoimmune diseases have been a popular target of MSC therapy. This activity has been related to the secretion of soluble factors. Bai *et al*<sup>[47]</sup> analyzed the effect of UcMSC-Ex in an experimental model of autoimmune uveitis. Results revealed the therapeutic potential of exosomes for this condition. Bearing in mind that this is a major cause of visual impairment worldwide, these are promising results. Zhang *et al*<sup>[48]</sup> in 2018 addressed the clinical treatment of another common cause of visual impairment, idiopathic macular hole. This work is interesting because, as previously mentioned, the translation of exosome-based therapies to clinical practice is still very limited. Five patients with large, long-standing idiopathic macular holes were treated ~~by~~with an intravitreal UcMSC-Ex ~~intravitreal~~ injection. The authors proposed that ~~UcMSC-Ex~~these exosomes may ~~could~~ improve ~~the~~ anatomic and visual outcomes of surgery for that disease, and suggested the need for a clinical trial with a greater number of patients<sup>[48]</sup>. In a mouse model of acute liver failure, Jiang *et al*<sup>[49]</sup> observed that UcMSC-Ex decreased the expression of the NLRP3 inflammasome and improved acute liver failure in that model. Animal models have ~~also~~ also been used to examine the treatment of ischemic heart disease using exosomes. In a recent study, Han *et al*<sup>[50]</sup> encapsulated UcMSC-Ex in a functional peptide hydrogel designed to increase the retention and stability of exosomes. The hydrogel containing UcMSC-Ex was then used in a rat myocardial infarction model, injecting it into the infarcted border of the heart. The authors concluded that this is an effective way of harnessing exosomes for cardiac regeneration<sup>[50]</sup>.

The data available in the literature related to the use of exosomes derived from different MSC to treat various pathologies are practically all at the

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experimental ~~level~~stage. These data supporting their therapeutic potential are summarized in Tables 1, 2 and 3. Although many studies have interesting clinical implications, there are still few data on the clinical use of exosomes including very few registered trials (in [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov)).

There is still much work to do. The optimization and standardization of obtaining exosomes is an important goal. Some authors advocate inducing hypoxia or stress in exosome-producing cells to increase exosome production<sup>[18]</sup>. This could be an interesting way of ~~to~~ generateing exosomes for clinical applications. Another interesting issue is related to adjusting ~~the~~ doses to ~~the~~ treatment. Further questions that need to be addressed are: which is the ideal time to administer exosomes? Will scaffolds be necessary in some applications? The different laboratories are presently working on these issues to standardize how exosomes are obtained.

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## **CONCLUSION**

In summary, cell therapy “without cells”, is an emerging field. While still at the experimental level, recent research efforts are starting to explore its translation to clinical practice. In the meantime, research into MSC cell therapy continues and there are hundreds of registered trials at different stages. We envisage that clinical trials in the near future will compare the benefits and shortcomings of cell therapy with and without cells.

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## Footnotes

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**Table 1. Exosomes derived from bone marrow mesenchymal stem cells  
(bone marrow mesenchymal stem cell derived exosomes)**

| Condition                        | <i>In vitro</i> study | <i>In vivo</i> study (animal model / clinical use) | Results  | Ref.  |
|----------------------------------|-----------------------|--|--|---|
| Liver disease                    | +                     | Liver injury model (Rat)                           | Improves liver regeneration and recovery   | Damania <i>et al</i> <sup>[23]</sup> , 2018 |
| Liver disease                    | +                     | Liver fibrosis model (Rat)                         | Reduces liver fibrosis   | Rong <i>et al</i> <sup>[24]</sup> , 2019    |
| Intervertebral disc degeneration | -                     | Tail model (Rat)                                   | Prevents disc degeneration progression   | Liao <i>et al</i> <sup>[25]</sup> , 2019    |
| Intervertebral disc degeneration | +                     | IDD model (Rabbit)                                 | Prevents the progression of degeneration <i>via</i> anti-oxidant and anti-inflammatory effects | Xia <i>et al</i> <sup>[26]</sup> , 2109     |
| Cancer                           | +                     | Xenografted with glioblastoma cells (Nude mice)    | Improves glioblastoma  | Wang <i>et al</i> <sup>[27]</sup> , 2019    |
| Cancer                           | +                     | Pancreatic cancer cells xenografted (Nude mice)    | Inhibits <del>cancer the</del> development <del>of</del> <del>that cancer</del>                | Wu <i>et al</i> <sup>[28]</sup> , 2019      |
| Bone regeneration                | +                     | Calvarian defect (Rat)                             | Promotes bone regeneration and neovascularization  | Zhu <i>et al</i> <sup>[30]</sup> , 2019     |
| Graft vs host disease            | +                     | GvHD model (Mouse)                                 | Enhances Treg production <i>in vitro</i> and <i>in vivo</i>                                    | Zhang <i>et al</i> <sup>[34]</sup> , 2018   |
| Graft vs host                    | +                     | GvHD model (Mouse)                                 | Ameliorates  | Fuji <i>et al</i> <sup>[33]</sup> , 2018    |

|   |                    |   |  |
|---|--------------------|---|--|
| disease   |                    | aGvHD <del>by</del> <u>via the</u><br>therapeutic<br>infusion of BM<br>MSC- <del>EV</del> <u>Ex</u><br>Patient stable for<br>several months |  |
| Graft <i>vs</i> host<br>disease   | - Clinical patient | <del>post</del> <u>after</u><br>exosome<br>application  | Kordelas <i>et al</i> <sup>[32]</sup> , 2014 |
| GvHD: <u>Graft-graft</u> <i>vs</i> host disease; BM MSC- <del>EV</del> <u>Ex</u> : Bone marrow mesenchymal stem cells derived exosomes; IDD: <del>Intervertebral</del> <u>intervertebral</u> disc degeneration. |                    |   |  |

**Table 2. Exosomes derived from adipose mesenchymal stem cells**  
~~(exosomes derived from adipose mesenchymal stem cell)~~

| Condition   | <i>In vitro</i> study | <i>In vivo</i> study (animal model / clinical use)  | Results  | Ref.                                      |
|---|-----------------------|---|--|---|
| Atopic dermatitis                                     | -                     | Atopic dermatitis model (Mouse)   | Reduces <del>pathological-clinical</del> symptoms                                      | Cho <i>et al</i> <sup>[35]</sup> , 2018   |
| Acute cutaneous wound healing                         | -                     | Acute cutaneous wound healing (Nude mice) Mouse <del>full-thickness incision wound model of a full-thickness incision wound</del> | Promotes fibroblast activities, re-epithelialization, vascularization in wound healing | Liu <i>et al</i> <sup>[36]</sup> , 2019   |
| Wound healing   | +                     | Mouse <del>full-thickness incision wound model of a full-thickness incision wound</del>   | Accelerates wound healing <del>via-by</del> optimizing fibroblast function             | Zhang <i>et al</i> <sup>[37]</sup> , 2018 |
| Corneal stromal cells                                 | +                     | -   | Role of ASC-Ex in corneal stromal cell and extra cellular matrix remodeling            | Shen <i>et al</i> <sup>[38]</sup> , 2018  |
| Apoptosis in cardiomyocyte caused by oxidative stress | +                     | -   | Prevents apoptosis   | Liu <i>et al</i> <sup>[39]</sup> , 2019   |
| Ovarian cancer  | +                     | -   | Ovarian cancer cells inhibited by exosomes   | Reza <i>et al</i> <sup>[40]</sup> , 2016  |
| Neural injury   | +                     | -   | Could inhibit the activation of microglia cells and prevent neuroinflammation          | Feng <i>et al</i> <sup>[41]</sup> , 2019  |

ASC-Ex: ~~exosomes Dd~~ derived from adipose mesenchymal stem cells.

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**Table 3. Exosomes derived from umbilical cord mesenchymal stem cells**  
~~(exosomes derived from umbilical cord mesenchymal stem cell)~~

| Condition                  | <i>In vitro</i> study | <i>In vivo</i> study (animal model / clinical use)             | Results  | Ref.                                      |
|----------------------------|-----------------------|--|--|---|
| Cutaneous wound healing    | +                     | Wound model (Rat)  | Proangiogenic effect   | Zhang <i>et al</i> <sup>[42]</sup> , 2015 |
| Bone healing               | +                     | Femoral fracture model (Rat)                                   | Accelerated fracture healing via the promotion of angiogenesis                                     | Zhang <i>et al</i> <sup>[43]</sup> , 2018 |
| Bone healing               | -                     | Fracture model (Rat)   | Repairs fractures in rats through the Wnt signaling pathway  | Zhou <i>et al</i> <sup>[44]</sup> , 2019  |
| Inflammatory bowel disease | +                     | Inflammatory bowel disease model (Mouse)                       | Alleviates induced inflammatory bowel disease  | Mao <i>et al</i> <sup>[45]</sup> , 2017   |
| Acute liver failure        | +                     | Liver injury model (Mouse)                                     | Decreases acute liver failure in that model  | Jiang <i>et al</i> <sup>[49]</sup> , 2018 |
| Colitis                    | +                     | Colitis model (Mouse)  | Improves colon damage in an animal disease model and has immunosuppressive effects <i>in vitro</i> | Ma <i>et al</i> <sup>[46]</sup> , 2019    |
| Autoimmune uveitis         | +                     | <del>Autoimmune</del><br><u>Autoimmune</u> uveitis model (Rat) | Ameliorates autoimmune uveitis by inhibiting the migration of                                      | Bai <i>et al</i> <sup>[47]</sup> , 2017   |

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|                         |   |                                   |   |   |
|-------------------------|---|-----------------------------------|---|---|
| Idiopathic macular hole | - | Clinical patients (5)             | inflammatory cells<br>May improve <del>the</del> anatomic and visual outcomes of surgery for that disease | Zhang <i>et al</i> <sup>[48]</sup> , 2018 |
| Myocardial infarction   | + | Myocardial infarction model (Rat) | UcMSC-Ex encapsulated in <u>a</u> functional peptide hydrogel could be effective for cardiac regeneration | Han <i>et al</i> <sup>[50]</sup> , 2019   |

UcMSC-Ex: ~~Exosomes~~ exosomes derived from umbilical cord mesenchymal stem cells;

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