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Subject: U.S. Trademark Application Serial No. 79209128 - EVOX THERAPEUTICS
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Attachments

**United States Patent and Trademark Office (USPTO)
Office Action (Official Letter) About Applicant's Trademark Application**

U.S. Application Serial No. 79209128

Mark: EVOX THERAPEUTICS

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Applicant: Evox Therapeutics Limited

Reference/Docket No. N/A

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**REQUEST FOR RECONSIDERATION
AFTER FINAL ACTION
DENIED**

International Registration No. 1348112

Issue date: December 08, 2021

Applicant's Request for Reconsideration is denied. *See* 37 C.F.R. §2.63(b)(3). The Trademark Examining Attorney has carefully reviewed Applicant's request and determined the request did not: (1) raise a new issue, (2) resolve the outstanding issue, (3) provide any new or compelling evidence with regard to the outstanding issue, or (4) present analysis and arguments that were persuasive or shed new light on the outstanding issue. TMEP §§715.03(a)(ii)(B), 715.04(a).

Accordingly, the following refusal made final in the Office action dated April 19, 2021 is **maintained and continued**:

- Section 2(d) Refusal - Likelihood of Confusion

See TMEP §§715.03(a)(ii)(B), 715.04(a).

Section 2(d) Refusal - Likelihood of Confusion

Introduction. Registration of the applied-for mark is refused because of a likelihood of confusion with the mark in U.S. Registration No. 6110326. Trademark Act Section 2(d), 15 U.S.C. §1052(d); *see* TMEP §§1207.01 *et seq.* *See* the previously attached registration.

Applicant's mark is **EVOX THERAPEUTICS** (standard characters) for “**Drug delivery agents in the form of exosomes that facilitate the delivery of pharmaceutical preparations; biological preparations comprising exosome for medical use; biological reagents comprising exosome for medical use; mixed biological preparations comprising exosome for pharmaceutical and medical use; diagnostic reagents comprising exosome for medicinal use in the fields of biology, genetic engineering and pharmaceuticals; diagnostic kits comprised of medical diagnostic reagents and assays for testing of exosomes for use in the detection of infectious diseases, cancer, diabetes, obesity, metabolic syndrome, dementia, mitochondrial disease, neuromuscular disease, inflammatory diseases and autoimmune disorders**” in International Class 005 and “**Scientific, medical and pharmaceutical research and development services; pharmaceutical drug development services; research and development of pharmaceutical preparations; biological research; clinical research in the field of transformational therapeutics; providing medical and scientific research information in the field of filtration of exosomes from blood; scientific investigations for medical purposes; scientific laboratory services; medical research laboratory services; laboratory research services relating to pharmaceuticals; research and development in the field of biotherapeutics for the treatment of infectious diseases and metabolic disorders; consulting services in the fields of biotechnology, pharmaceutical research and development and genetic science**” in International Class 042.

Registrant's mark is **EVOXX** (standard characters) for “**Chemicals used in industry; Chemical, biochemical and biotechnological preparations used in science, namely, in the chemical industry; Chemical, biochemical and biotechnological preparations used in photography; Chemical, biochemical and biotechnological preparations used in agriculture; Chemical, biochemical and biotechnological preparations used in horticulture; Chemical, biochemical and biotechnological preparations used in forestry; Chemical, biochemical and biotechnological preparations for preserving foodstuffs; Chemical, biochemical and biotechnological preparations for conserving foodstuffs; Chemical, biochemical and biotechnological preparations for making foods and foodstuffs; Chemical, biochemical and biotechnological preparations for making beverages; Chemical, biochemical and biotechnological preparations for cosmetic purposes; Chemical, biochemical and biotechnological preparations for making hair and/or body care preparations; Chemical, biochemical and biotechnological preparations for making pharmaceutical preparations and/or medicines; Enzymes for industrial purposes; Enzyme preparations for industrial purposes; Biochemical catalysts; Carbonic hydrates; Starch for industrial purposes; Artificial sweeteners; Emulsifiers for industrial purposes; Unprocessed plastics; Adhesives used in industry, none of the aforementioned being fungicides, herbicides, insecticides, or parasiticides**” in International Class 001, “**Pharmaceutical and veterinary preparations for treating digestive diseases; Adjuvants for medical purposes; Appetite suppressants for medical purposes; Medical preparation for slimming purposes; Medical preparations for treating constipation; Laxatives; Dietetic preparations adapted for medical use, namely vitamins, amino acids, and**

carbohydrates for enteral or parenteral feeding; Dietetic beverages in the nature of tea, juice, lemonade, sodas, non-alcoholic beverages, soft-drinks, adapted for medical purposes; Dietetic substances in the nature of carbohydrates and sugars adapted for medical use; Dietetic foods in the nature of bread, cookies, sweets in the nature of medicated candy adapted for medical use; Nutritional supplements; Infant formula; Nutritional supplements in the nature of edible plant fibres and soluble fibres for medical purposes in the nature of cereal fibres, pectin; Additives to fodder for medical purposes, namely, dietary supplements for animals; By-products of the processing of cereals for medical purposes; Cellulose esters for pharmaceutical purposes; Starch for dietetic or pharmaceutical purposes; Medicinal preparations for the mouth to be applied in the form of capsules for medicines; Capsules sold empty for pharmaceutical purposes; Prescription and non-prescription medicines, namely, capsules for the treatment of digestive diseases; Digestives for pharmaceutical purposes; Beverages in the nature of tea, juice, lemonade, sodas, non-alcoholic beverages, soft-drinks, adapted for medicinal purposes; Healthcare preparations for medical purposes, namely powders, drinks, tablets, capsules for treatment of gastro intestinal diseases, gut health and digestive health; Disinfectants; Biotechnological preparations and products, namely proteins supplements, enzymes for medical use; Enzymes for veterinary purposes; Enzyme preparations for medical purposes; Enzyme preparations for veterinary purposes; Bacterial production strains for medical use; Bacterial production strains for veterinary use; Micro-organism cultures for medical use for use in the treatment of gastro intestinal diseases or digestive diseases; Cultures of micro-organisms for veterinary purposes for use in the treatment of gastro intestinal diseases or digestive diseases; Ferments for pharmaceutical purposes; Ferments for veterinary use; Bacteriological culture mediums; Dental impression materials” in International Class 005, and “Science and technology services and research services relating thereto, namely, scientific research in the field of food, biotechnology, bioenergy, pharmacy, chemistry; Industrial analysis and research services, namely, industrial research in the field of food, biotechnology, bioenergy, pharmacy, chemistry; Performance of chemical analyses; Biological research; Chemical, pharmaceutical, biotechnological and genetic technology laboratories; Technical and scientific consultancy and support in the field of chemistry, pharmacy, biotechnology and genetic technology, via communications media, namely the internet; Technical and scientific consultancy and support with regard to the introduction of chemical, pharmaceutical, biotechnological and genetic technology preparations and products for others; Research and development of new products for others” in International Class 042.

Trademark Act Section 2(d) bars registration of an applied-for mark that is so similar to a registered mark that it is likely consumers would be confused, mistaken, or deceived as to the commercial source of the goods and services of the parties. *See* 15 U.S.C. §1052(d). Likelihood of confusion is determined on a case-by-case basis by applying the factors set forth in *In re E. I. du Pont de Nemours & Co.*, 476 F.2d 1357, 1361, 177 USPQ 563, 567 (C.C.P.A. 1973) (called the “*du Pont* factors”). *In re i.am.symbolic, llc*, 866 F.3d 1315, 1322, 123 USPQ2d 1744, 1747 (Fed. Cir. 2017). Any evidence of record related to those factors need be considered; however, “not all of the *DuPont* factors are relevant or of similar weight in every case.” *In re Guild Mortg. Co.*, 912 F.3d 1376, 1379, 129 USPQ2d 1160, 1162 (Fed. Cir. 2019) (quoting *In re Dixie Rests., Inc.*, 105 F.3d 1405, 1406, 41 USPQ2d 1531, 1533 (Fed. Cir. 1997)).

Although not all *du Pont* factors may be relevant, there are generally two key considerations in any likelihood of confusion analysis: (1) the similarities between the compared marks and (2) the relatedness of the compared goods and services. *See In re i.am.symbolic, llc*, 866 F.3d at 1322, 123 USPQ2d at 1747 (quoting *Herbko Int’l, Inc. v. Kappa Books, Inc.*, 308 F.3d 1156, 1164-65, 64 USPQ2d 1375, 1380 (Fed. Cir. 2002)); *Federated Foods, Inc. v. Fort Howard Paper Co.*, 544 F.2d

1098, 1103, 192 USPQ 24, 29 (C.C.P.A. 1976) (“The fundamental inquiry mandated by [Section] 2(d) goes to the cumulative effect of differences in the essential characteristics of the goods [or services] and differences in the marks.”); TMEP §1207.01.

The overriding concern is not only to prevent buyer confusion as to the source of the goods and services, but to protect Registrant from adverse commercial impact due to use of a similar mark by a newcomer. *See In re Shell Oil Co.*, 992 F.2d 1204, 1208, 26 USPQ2d 1687, 1690 (Fed. Cir. 1993). Therefore, any doubt regarding a likelihood of confusion determination is resolved in favor of Registrant. TMEP §1207.01(d)(i); *see Hewlett-Packard Co. v. Packard Press, Inc.*, 281 F.3d 1261, 1265, 62 USPQ2d 1001, 1003 (Fed. Cir. 2002); *In re Hyper Shoppes (Ohio), Inc.*, 837 F.2d 463, 464-65, 6 USPQ2d 1025, 1026 (Fed. Cir. 1988).

Comparison of the marks. Marks are compared in their entireties for similarities in appearance, sound, connotation, and commercial impression. *Stone Lion Capital Partners, LP v. Lion Capital LLP*, 746 F.3d 1317, 1321, 110 USPQ2d 1157, 1160 (Fed. Cir. 2014) (quoting *Palm Bay Imps., Inc. v. Veuve Clicquot Ponsardin Maison Fondee En 1772*, 396 F.3d 1369, 1371, 73 USPQ2d 1689, 1691 (Fed. Cir. 2005)); TMEP §1207.01(b)-(b)(v). “Similarity in any one of these elements may be sufficient to find the marks confusingly similar.” *In re Inn at St. John’s, LLC*, 126 USPQ2d 1742, 1746 (TTAB 2018) (citing *In re Davia*, 110 USPQ2d 1810, 1812 (TTAB 2014)), *aff’d per curiam*, 777 F. App’x 516, 2019 BL 343921 (Fed. Cir. 2019); TMEP §1207.01(b).

When comparing marks, “[t]he proper test is not a side-by-side comparison of the marks, but instead whether the marks are sufficiently similar in terms of their commercial impression such that [consumers] who encounter the marks would be likely to assume a connection between the parties.” *Cai v. Diamond Hong, Inc.*, 901 F.3d 1367, 1373, 127 USPQ2d 1797, 1801 (Fed. Cir. 2018) (quoting *Coach Servs., Inc. v. Triumph Learning LLC*, 668 F.3d 1356, 1368, 101 USPQ2d 1713, 1721 (Fed. Cir. 2012)); TMEP §1207.01(b). The proper focus is on the recollection of the average purchaser, who retains a general rather than specific impression of trademarks. *In re Inn at St. John’s, LLC*, 126 USPQ2d 1742, 1746 (TTAB 2018) (citing *In re St. Helena Hosp.*, 774 F.3d 747, 750-51, 113 USPQ2d 1082, 1085 (Fed. Cir. 2014); *Geigy Chem. Corp. v. Atlas Chem. Indus., Inc.*, 438 F.2d 1005, 1007, 169 USPQ 39, 40 (C.C.P.A. 1971)), *aff’d per curiam*, 777 F. App’x 516, 2019 BL 343921 (Fed. Cir. 2019); TMEP §1207.01(b).

In the present case, the compared marks are highly similar because they both contain the term "EVOX" or novel spelling "EVOXX". Marks may be confusingly similar where, as here, similar terms or phrases or similar parts of terms or phrases appear in the compared marks and create a similar overall commercial impression. *See Crocker Nat’l Bank v. Canadian Imperial Bank of Commerce*, 228 USPQ 689, 690-91 (TTAB 1986), *aff’d sub nom. Canadian Imperial Bank of Commerce v. Wells Fargo Bank, Nat’l Ass’n*, 811 F.2d 1490, 1495, 1 USPQ2d 1813, 1817 (Fed. Cir. 1987) (finding COMMCASH and COMMUNICASH confusingly similar); *In re Corning Glass Works*, 229 USPQ 65, 66 (TTAB 1985) (finding CONFIRM and CONFIRMCELLS confusingly similar); *In re Pellerin Milnor Corp.*, 221 USPQ 558, 560 (TTAB 1983) (finding MILTRON and MILLTRONICS confusingly similar); TMEP §1207.01(b)(ii)-(iii).

The additional disclaimed term, "THERAPEUTICS", in Applicant's mark fails to obviate this refusal, because "EVOX", which it shares in common with the registered mark, is the dominant feature of the applied-for mark. Although marks are compared in their entireties, one feature of a mark may be more significant or dominant in creating a commercial impression. *See In re Viterra Inc.*, 671 F.3d 1358, 1362, 101 USPQ2d 1905, 1908 (Fed. Cir. 2012); *In re Nat’l Data Corp.*, 753 F.2d 1056, 1058, 224

USPQ 749, 751 (Fed. Cir. 1985); TMEP §1207.01(b)(viii), (c)(ii). Disclaimed matter that is descriptive of or generic for a party's goods and services is typically less significant or less dominant when comparing marks. *In re Detroit Athletic Co.*, 903 F.3d 1297, 1305, 128 USPQ2d 1047, 1050 (Fed. Cir. 2018) (citing *In re Dixie Rests., Inc.*, 105 F.3d 1405, 1407, 41 USPQ2d 1531, 1533-34 (Fed. Cir. 1997)); TMEP §1207.01(b)(viii), (c)(ii).

The additional letter "X" at the end of Registrant's mark, "EVOXX", does not detract from the confusing similarity in this case. Notably, this second letter "X" merely repeats the same ending consonant sound and does not alter the overall commercial impression of the term "EVOX" in any meaningful way. Further, slight differences in the sound of similar marks will not avoid a likelihood of confusion. *In re Energy Telecomms. & Elec. Ass'n*, 222 USPQ 350, 351 (TTAB 1983); see *In re Viterra Inc.*, 671 F.3d 1358, 1367, 101 USPQ2d 1905, 1912 (Fed. Cir. 2012).

For the reasons set forth more fully above, the compared marks are confusingly similar.

Comparison of the goods and services. The goods and services are compared to determine whether they are similar, commercially related, or travel in the same trade channels. See *Coach Servs., Inc. v. Triumph Learning LLC*, 668 F.3d 1356, 1369-71, 101 USPQ2d 1713, 1722-23 (Fed. Cir. 2012); *Herbko Int'l, Inc. v. Kappa Books, Inc.*, 308 F.3d 1156, 1165, 64 USPQ2d 1375, 1381 (Fed. Cir. 2002); TMEP §§1207.01, 1207.01(a)(vi).

The compared goods and services need not be identical or even competitive to find a likelihood of confusion. See *On-line Careline Inc. v. Am. Online Inc.*, 229 F.3d 1080, 1086, 56 USPQ2d 1471, 1475 (Fed. Cir. 2000); *Recot, Inc. v. Becton*, 214 F.3d 1322, 1329, 54 USPQ2d 1894, 1898 (Fed. Cir. 2000); TMEP §1207.01(a)(i). They need only be "related in some manner and/or if the circumstances surrounding their marketing are such that they could give rise to the mistaken belief that [the goods and services] emanate from the same source." *Coach Servs., Inc. v. Triumph Learning LLC*, 668 F.3d 1356, 1369, 101 USPQ2d 1713, 1722 (Fed. Cir. 2012) (quoting *7-Eleven Inc. v. Wechsler*, 83 USPQ2d 1715, 1724 (TTAB 2007)); TMEP §1207.01(a)(i).

Determining likelihood of confusion is based on the description of the goods and services stated in the application and registration at issue, not on extrinsic evidence of actual use. See *In re Detroit Athletic Co.*, 903 F.3d 1297, 1307, 128 USPQ2d 1047, 1052 (Fed. Cir. 2018) (citing *In re i.am.symbolic, llc*, 866 F.3d 1315, 1325, 123 USPQ2d 1744, 1749 (Fed. Cir. 2017)).

Generally, the greater degree of similarity between the applied-for mark and the registered mark, the lesser the degree of similarity between the goods and services of the parties is required to support a finding of likelihood of confusion. *In re C.H. Hanson Co.*, 116 USPQ2d 1351, 1353 (TTAB 2015) (citing *In re Opus One Inc.*, 60 USPQ2d 1812, 1815 (TTAB 2001)); *In re Thor Tech, Inc.*, 90 USPQ2d 1634, 1636 (TTAB 2009).

As an initial matter, the Examining Attorney notes that the services are identical in part with respect to "biological research". Additionally, both parties' goods include pharmaceutical products. Thus, the nature of the goods and services is similar.

Notably, Applicant's goods include diagnostic products for the detection of various medical conditions and illnesses, such as obesity and metabolic syndrome and Registrant's goods include pharmaceuticals for obesity and metabolism, including appetite suppressants, medical preparations for slimming purposes, food and beverages adapted for medical and dietetic use, and more. Also, Registrant's goods include enzymes and enzyme preparations for medical purposes, which could presumably be used to

treat all types of medical conditions or illnesses and/or be used as drug delivery agents and reagents like those delineated in Applicant's identification.

Furthermore, in this case, the application uses broad wording to describe "scientific, medical and pharmaceutical research and development services", which presumably encompasses all services of the type described, including Registrant's more narrowly identified "scientific research in the field of food, biotechnology, bioenergy, pharmacy, chemistry". See, e.g., *In re Solid State Design Inc.*, 125 USPQ2d 1409, 1412-15 (TTAB 2018); *Sw. Mgmt., Inc. v. Ocinomled, Ltd.*, 115 USPQ2d 1007, 1025 (TTAB 2015). In addition, the registration uses broad wording to describe "research and development of new products for others", which presumably encompasses Applicant's more narrowly identified "pharmaceutical drug development services", "research and development of pharmaceutical preparations", and "research and development in the field of biotherapeutics for the treatment of infectious diseases and metabolic disorders". See *id.* Thus, Applicant's and Registrant's services are legally identical in part. See, e.g., *In re i.am.symbolic, llc*, 127 USPQ2d 1627, 1629 (TTAB 2018) (citing *Tuxedo Monopoly, Inc. v. Gen. Mills Fun Grp., Inc.*, 648 F.2d 1335, 1336, 209 USPQ 986, 988 (C.C.P.A. 1981); *Inter IKEA Sys. B.V. v. Akea, LLC*, 110 USPQ2d 1734, 1745 (TTAB 2014); *Baseball Am. Inc. v. Powerplay Sports Ltd.*, 71 USPQ2d 1844, 1847 n.9 (TTAB 2004)).

Additionally, the goods and services of the parties have no restrictions as to nature, type, channels of trade, or classes of purchasers and are "presumed to travel in the same channels of trade to the same class of purchasers." *In re Viterra Inc.*, 671 F.3d 1358, 1362, 101 USPQ2d 1905, 1908 (Fed. Cir. 2012) (quoting *Hewlett-Packard Co. v. Packard Press, Inc.*, 281 F.3d 1261, 1268, 62 USPQ2d 1001, 1005 (Fed. Cir. 2002)).

The previously and newly attached Internet evidence establishes that exosomes are drug delivery agents and are also known for having various potential diagnostic and therapeutic uses. Such uses include diagnosis and/or treatment of gastrointestinal disorders such as those stated in Registrant's identification. Further, the previously and newly attached Internet and dictionary evidence demonstrates that exosomes are comprised, in part, of enzymes, which are also included in Registrant's goods. This evidence demonstrates that the parties' goods are similar in purpose or function.

The Trademark Examining Attorney has attached evidence from the USPTO's X-Search database consisting of a number of third-party marks registered for use in connection with the same or similar goods as those of both Applicant and Registrant in this case. This evidence shows that the goods listed therein, namely, drug delivery agents and pharmaceutical preparations used to treat various conditions, are of a kind that may emanate from a single source under a single mark. See *In re I-Coat Co.*, 126 USPQ2d 1730, 1737 (TTAB 2018) (citing *In re Infinity Broad. Corp.*, 60 USPQ2d 1214, 1217-18 (TTAB 2001); *In re Albert Trostel & Sons Co.*, 29 USPQ2d 1783, 1785-86 (TTAB 1993); *In re Mucky Duck Mustard Co.*, 6 USPQ2d 1467, 1470 n.6 (TTAB 1988)); TMEP §1207.01(d)(iii). See attached Registration Nos. 5771628, 5956872, 6056485, 6108588, 6158772, 6170100, 6201037, 6257608, 6283602, and 6296869.

Moreover, to the extent the evidence may not address all the items in Applicant's identification, relatedness does not have to be established for every product and service. It is sufficient for a finding of likelihood of confusion if relatedness is established for any or some items encompassed by the identification within a particular class in an application. *Tuxedo Monopoly, Inc. v. General Mills Fun Group*, 648 F.2d 1335, 209 USPQ 986, 988 (CCPA 1981). In this case, relatedness has been established for many of the identified goods and services, which is enough to show a likelihood of confusion.

Therefore, the goods and services are related for likelihood of confusion purposes.

Applicant's arguments. Applicant's arguments have been carefully considered and found unpersuasive for the reasons set forth below.

First, Applicant amended its identification of goods and avers that the goods are unrelated in that Applicant's goods do not include "pharmaceutical preparations". However, despite Applicant's assertions to the contrary, its drug delivery agents, reagents, exosomes, and diagnostic kits are still considered "pharmaceutical preparations" despite that particular phrase not appearing in Class 5. In particular, the previously attached Internet evidence from *Biology Online* defines a "pharmaceutical preparation" as "drugs intended for human or veterinary use, presented in their finished dosage form" and includes "materials used in the preparation and/or formulation of the finished dosage form". See <https://www.biologyonline.com/dictionary/pharmaceutical-preparations>. See also newly attached Internet evidence defining "pharmaceutical preparations" to include "materials used in the preparation and/or formulation of the finished dosage form". See <https://connects.catalyst.harvard.edu/Profiles/display/Concept/Pharmaceutical%20Preparations>. By its definition, a "pharmaceutical preparation" includes such drugs or materials as drug delivery agents, reagents, exosomes, and diagnostic kits. Therefore, the goods remain similar in nature.

In the Request for Reconsideration, Applicant avers that the website "Biology Online" is not an authoritative source reflecting how consumers will view the term "pharmaceutical preparation". Applicant also included definitions of the word, "pharmaceutical". Notably, Applicant did not include any alternative definitions for "pharmaceutical preparations" as a whole phrase as it appears in Registrant's identification. While the Examining Attorney maintains that the previously attached evidence is sufficient, the additional attached Internet evidence reflects a similar definition of "pharmaceutical preparations" and further supports the conclusion that exosomes, reagents, and drug delivery agents are, in fact, "pharmaceutical preparations". Applicant also states that the cited registration refers to finished drugs and not ingredients thereof. While the Examining Attorney respectfully disagrees with this narrowed reading of Registrant's identification, it should be noted that Registrant's goods in International Class 1 include "chemical, biochemical and biotechnological preparations for making pharmaceutical preparations and/or medicines". Thus, even if Applicant is correct that "pharmaceutical preparations" does not refer to ingredients of medicines, which is not conceded here, it remains that Registrant's goods encompass those of Applicant by also explicitly identifying ingredients of said medicines.

Applicant further argues that Registrant's goods do not merely include "pharmaceutical preparations", but rather to pharmaceutical preparations for treating specific conditions. However, the evidence of record clearly demonstrates that exosomes and reagents are used to treat various conditions, including those conditions mentioned in Registrant's identification. Thus, the goods are highly related because they are similar in nature, purpose, and function.

Applicant also states that the goods travel in different channels of trade with Applicant's goods sold to hospitals, clinics, and medical professionals and Registrant's goods prescribed by doctors or sold over-the-counter at pharmacies and other retail outlets. However, the presumption under Trademark Act Section 7(b) is that the registrant is the owner of the mark and that their use of the mark extends to all goods and services identified in the registration. 15 U.S.C. §1057(b). In the absence of limitations as to channels of trade or classes of purchasers in the goods and services in the registration, the presumption is that the goods and services move in all trade channels normal for such goods and services and are available to all potential classes of ordinary consumers of such goods and services.

See In re I-Coat Co., 126 USPQ2d 1730, 1737 (TTAB 2018); *In re Melville Corp.*, 18 USPQ2d 1386, 1388 (TTAB 1991); TMEP §1207.01(a)(iii).

Regarding the relatedness and partially overlapping nature of the parties' respective services, Applicant argues that the confusion is unlikely because the consumers are sophisticated and the marks differ. The fact that purchasers are sophisticated or knowledgeable in a particular field, which the Examining Attorney does not concede in this case, does not necessarily mean that they are sophisticated or knowledgeable in the field of trademarks or immune from source confusion. TMEP §1207.01(d)(vii); *see, e.g., Stone Lion Capital Partners, LP v. Lion Capital LLP*, 746 F.3d 1317, 1325, 110 USPQ2d 1157, 1163-64 (Fed. Cir. 2014); *Top Tobacco LP v. N. Atl. Operating Co.*, 101 USPQ2d 1163, 1170 (TTAB 2011). Further, where the purchasers consist of both professionals and the public, as is this case, the standard of care for purchasing the goods is that of the least sophisticated potential purchaser. *In re FCA US LLC*, 126 USPQ2d 1214, 1222 (TTAB 2018) (citing *Stone Lion Capital Partners, LP v. Lion Capital LLP*, 746 F.3d at 1325, 110 USPQ2d at 1163), *aff'd per curiam*, 777 F. App'x 516, 2019 BL 375518 (Fed. Cir. 2019).

Additionally, Applicant's assertion that the extra letter "X" in "EVOXX" in Registrant's mark and the additional term "THERAPEUTICS" in Applicant's mark meaningfully differentiate the marks is not persuasive. As stated previously, the extra letter "X" fails to change the commercial impression of the term "EVOX" and the disclaimed term "THERAPEUTICS" is less significant or less dominant when comparing marks. Applicant correctly states that marks must be compared in their entireties and should not be dissected; however, a Trademark Examining Attorney may weigh the individual components of a mark to determine its overall commercial impression. *In re Detroit Athletic Co.*, 903 F.3d 1297, 1305, 128 USPQ2d 1047, 1050 (Fed. Cir. 2018) ("[Regarding the issue of confusion,] there is nothing improper in stating that . . . more or less weight has been given to a particular feature of a mark, provided the ultimate conclusion rests on consideration of the marks in their entireties." (quoting *In re Nat'l Data Corp.*, 753 F.2d 1056, 1058, 224 USPQ 749, 751 (Fed. Cir. 1985))).

Finally, Applicant's deletion of the wording "scientific, medical, and pharmaceutical research and development" is insufficient to overcome this refusal. Even without this entry, the services remain identical in part with respect to "biological research" and each parties' services encompass the other, rendering these services legally identical.

Conclusion. For the reasons set forth more fully above, the compared marks are confusingly similar and the parties' goods and services are related. Therefore, registration is refused pursuant to Trademark Act Section 2(d) and this refusal continues to be final.

What happens next. The Trademark Trial and Appeal Board will be notified to resume the appeal. *See* TMEP §715.04(a).

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Exosomal therapy—a new frontier in regenerative medicine

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Abstract

The recent advances in translational and nanomedicine have paved the way for developing the targeted drug delivery system at a greater pace among global researchers. On par with these technologies, exosomes act as a potential portal for cell-free drug delivery systems as these are bestowed with the native characteristics of the parent cell of origin. Exosomes, called extracellular vesicles (EcVs), are present in almost all cells, tissues, and body fluids. They help in intercellular signaling and maintains tissue homeostasis in the disease pathobiology. Researchers have characterized 9,769 proteins, 2,838 miRNAs, 3,408 mRNAs, and 1,116 lipids being present in exosomal cargo. The separation of exosomes from cells, tissues, and body fluids follow different patterned kinetics. Exosomes interact with the recipient cells through their surface receptor molecules and ligands and internalize within recipient cells through micropinocytosis and phagocytosis. Advancing technologies in regenerative medicine have facilitated the researchers to isolate exosomes from mesenchymal stem cells (MSCs) as these cells are blessed with supreme regenerative potentiality in targeting a disease. Exosomal cargo is a key player in establishing the diagnosis and executing therapeutic role whilst regulating a disease process. Various *in vitro* studies have exhibited the safety, efficacy, and therapeutic potentiality of exosomes in various cancers, neurodegenerative, cardiovascular, and orthopedic diseases. This article throws light on the composition, therapeutic role, and regulatory potentials of exosomes with the widening of the horizon in the field of regenerative medicine.

Keywords: Exosomes, extracellular vesicles (EcVs), cellular therapy, biological medicine

Introduction

The contemporary developments in the field of translational medicine include the development of targeted

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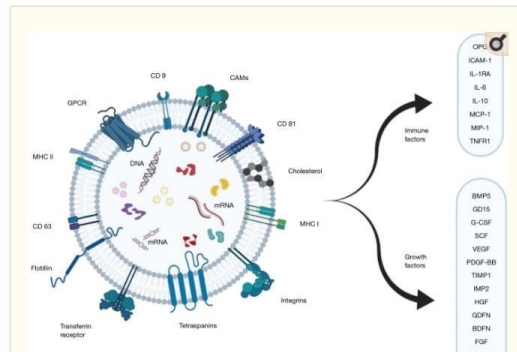
drug delivery systems for harnessing the full potentiality and utilizing the therapeutic products effectively by overcoming the limitations of the existing methods to address the pathogenesis of a disease. In that context, various polymer-based nano delivery systems have been developed (1). Utilizing extracellular vesicles (EcVs) as a drug delivery tool has been given special attention due to their native characteristics derived from the parent or host cells (2-4). Despite the normal cellular homeostasis, EcVs play a major role in intervening in the pathobiology of disease processes through the intercellular signaling cascade (5-9).

Based on the size, exosomes are subcategorized under EcVs, which are endosome derived lipid bi-layered spherical vesicles of 40-150 nm in size (2,10-12). Almost all cells, tissues, and body fluids [plasma, urine, saliva, tears, gastrointestinal (GI) secretions, semen, and breast milk] secrete exosomes (13-16). Exosomal cargo carries an array of micro-biomolecules that consists of proteins, lipids, RNA, and DNA from the secreting parent cells (2,17-19). Moreover, the characteristics and behavior of the exosomes closely relate to the parent cell of origin (20-22). On account of their appropriate size and property along with their evident role in numerous pathological processes, the potential of exosomal therapy in the management of various neurodegenerative disorders, infectious diseases, musculoskeletal disorders, and cardiovascular disorders is overwhelming. This has enabled the researchers to target the disease process at a cellular level by using natural engineered defense mechanisms.

Characterization of exosomes

Go to 

The composition of an exosome vesicle (EV) includes proteins, RNA, DNA, and other substances. Currently, 9,769 proteins, 2,838 mRNAs, 3,408 miRNAs, and 1,116 lipids have been described in their composition (23). Of these components, the exosomal proteins differ based on the nature of the primitive cells or tissues (24). Proteins like membrane transport and fusion proteins, chaperones, adhesion molecules, MHCs, cytoskeletal proteins, and lipid-related proteins are major exosomal proteins (24-28). With a pre-existing knowledge of the functioning of these proteins, ALG-2-interacting protein X (ALIX), heat shock protein 70 (HSP 70), tumor susceptibility gene 101 (TSG101), and tetraspanins (CD9, CD 63, CD 81, and CD 82) have been identified with a higher concentration in exosomes (29,30). Moreover, they serve as a biomarker for exosomal identification as shown in *Figure 1* (31). Exosomes are also rich in lipid layering molecules like glycosylphosphatidylinositol-anchored protein (LBPA) and flotillin (32,33). Apart from the metabolic enzymes and signal transduction molecules such as G protein and protein kinases, exosomes contain mRNAs, miRNAs, non-coding RNAs (ncRNAs), and mitochondrial DNA in their composition (34-35). Noteworthy, the first types of nucleic acids identified in the exosomes were mRNA and miRNA (36,37).



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ExoCarta 2012: database of exosomal proteins, RNA and lipids. [Nucleic Acids Res. 2012]

Proteomics analysis of A33 immunofluorescence-purified exosomes released from the human colon tumour [Mol Cell Proteomics. 2010]

Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandin [J Lipid Res. 2010]

Review Exosomes: current knowledge of their composition, biological functions, and diagnosis. [Biochim Biophys Acta. 2012]

Review Extracellular Vesicles in Cancer Immune Microenvironment and Cancer Immunot [Adv Sci (Weinheim). 2019]

Reassessment of Exosome Composition. [Cell. 2019]

Review Shedding light on the cell biology of extracellular vesicles. [Nat Rev Mol Cell Biol. 2018]

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Figure 1

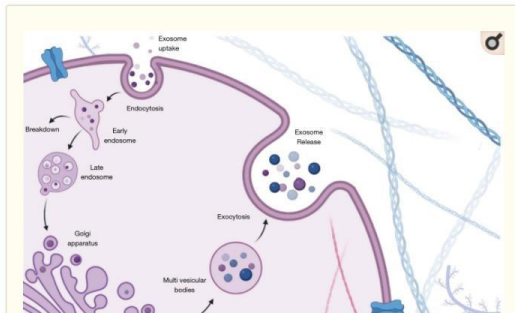
Basic structure of mesenchymal stem cell exosome depicting the surface and core proteins along with the key immune and growth factors.

Being a nanoscale vesicular component in complex body fluids, it is challenging to procure exosomes of high-yield and fineness (38). However, their isolation and characterization is an essential prerequisite to establish their therapeutic potential with a better understanding of their physiology. Exosomes are derived from the cell culture supernatants or plasma with their identification based on the physical and morphological characteristics (39,40). Although separation can be made by several methods like ultracentrifugation, ultrafiltration, gradient ultracentrifugation, precipitation, size-exclusion chromatography, immune-affinity capture, mass spectrometric immunoassay, magnetic-activated cell sorting, and microfluidics-based techniques with each having their advantages and disadvantages (41-45). Ultracentrifugation is the most commonly used method for isolating exosomes. The complex proteins in the exosomes are analyzed by processes like western blot, flow cytometry, and mass spectrometry (46). Additionally, sample analysis with high precision fluorescence is a possibility in the nanoparticle tracking method (47). Homogeneity without exosome isolation is possible with the resistance pulse sensing method (48). Profiling the miRNA content of the exosomes was made with next-generation sequencing, microarray processing, and RT-PCR. Confirmation of the isolated samples can be done by electron microscopy (49). Disparate use of various methods of isolation, confirmation, quantification, and analysis used by the researchers with their own set of advantages and disadvantages, it brings added heterogeneity in their analysis which needs standardization.

Cellular physiology of exosomes

Go to:

The formation of exosomes involves the invagination of the plasma membrane and the formation of intracellular multivesicular bodies with intraluminal vesicles. This endocytic pathway of the donor cell is followed by the transport of the transmembrane and intra-vesicular proteins from the Golgi complex resulting in the formation of early endosomes. After maturation and differentiation, they get transformed into late endosomes (50-53). They are degraded by fusing with lysosomes or plasma membrane or autophagosomes to release the intraluminal vesicles as exosomes (measuring 40–150 nm diameter) into the extracellular milieu as shown in *Figure 2* (5,32,54).



Review Extracellular Vesicle Heterogeneity: Subpopulations, Isolation Techniques, and Diverse Functions. *Front Immunol.* 2018;9:1-12.
Review Proteomic analysis of exosomes isolated from human malignant pleural effusions. *Ann J Respir Cell Mol Biol.* 2004;49:1-10.
Review Preparation of human ovarian cancer ascites-derived exosomes for a clinical trial. *Blood Cells Mol Dis.* 2005;35:1-10.
Review Progress in Exosome Isolation Techniques. *Theranostics.* 2017;7:1-12.
Review Exosomes: Small Players, Big Sound. *Bioconjug Chem.* 2018;29:1-12.
Review Analysis of antigen presenting cell derived exosomes, based on immuno-magnetic isolation and flow cytometry. *J Immunol Methods.* 2001;231:1-12.
Review Analysis of Extracellular Vesicles Using Fluorescence Nanoparticle Tracking Analysis. *Methods Mol Biol.* 2017;1471:1-12.
Review Observations of Tunable Resonant Pulse Sensing for Exosome Analysis: Improving System Sensitivity and Stability. *Langmuir.* 2015;31:1-12.
Review Visualization of distinct substrate-recruitment pathways in the yeast exosome by EM. *Nat Struct Mol Biol.* 2014;11:1-12.

Review Exosomes: from biogenesis and secretion to biological function. *Immunol Lett.* 2006;109:1-12.
Review Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. *Nat Cell Biol.* 2012;14:1-12.
Review The biology and function of exosomes and biomedical applications of exosomes. *Science.* 2020;368:1-12.
 See more ...

Review Exosomes in tumor microenvironment influence cancer progression and metastasis. *J Mol Med (Berl).* 2013;87:1-12.
Review Endocytosis, intracellular sorting, and processing of exosomes by dendritic cells. *Blood.* 2004;104:1-12.
Review Selective transfer of exosomes from oligodendrocytes to microglia by macropinocytosis. *J Cell Sci.* 2011;124:1-12.
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Figure 2

Physiology of formation and degradation of exosomes. ECM, extracellular matrix.

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Exosomes interact with the recipient cells through their surface receptor molecules and ligands. Some of the exosomes persist on the cell membranes of the donor cells after secretion while the rest of them interacts with the recipient cells (54–59). Internalization of exosomes occurs via membrane integration process mediated by raft or caveolae or clathrin dependent endocytosis. Micropinocytosis and phagocytosis have also been described as a method of internalization of the exosomes by recipient cells. This physiological integration process on the targeted recipient cells has been considered to have therapeutic potential as a targeted delivery system for effectively executing biological functions (60–64). Yet, the exosomal components in specific accounting for cell-type or organ specificity remain unclear (65).

Diagnostic role of exosomes

[Go to](#)

Exosomes are the key players of the intercellular communication portal and thereby owe the capability of determining the progression of a disease. Studies are emerging in the diagnostic and therapeutic facets of exosomes for various systemic pathologies. The detection of substances (intracellular and extracellular) carried by these nanoparticles and promoting their immune capture with surface proteins aid in the diagnosis of pathological processes. The spectrum of diseases in which exosomes play a key role in diagnosis includes cerebrovascular disease (66,67), diseases involving the central nervous system and neoplasia (8,68–70) along with disease involving kidney, liver, and lungs (70–72). Let us consider the scenario of cancer. Exosomes can protect the rapid degradation of nucleic acids and remain highly stable in plasma (73). With an exosome-based liquid biopsy, direct detection of the circulating tumor cells and their DNA or cell-free RNA from body fluids like blood, saliva can be made. This DNA or RNA (including mRNA, miRNA, ncRNA) from serum exosomes can be used for the detection of cancer-related mutations making them a promising biomarker in cancer diagnosis (74–77). Various studies have identified proteins and RNAs rich in cancer-derived exosomes which act as biomarkers that can be used in the detection and prognosticating treatment response (78–85).

Therapeutic role of exosomes

[Go to](#)

Exosomes possess a higher therapeutic potential for various disease spectra due to their ability for intracellular shuttling. Nanomedicine technologies have given rise to explore the usage of pathogenic importance of exosomal particles in various diseases. The targeted drug delivery system in nanomedicine focus on the sustained release of exosomes for exerting the biological activity in the targeted site. Exosomes are used as vectors or carrier molecules to elicit a biological response.

Under given physiological circumstances, exosomes demonstrate very low immunogenicity and the potential to circumvent the physiological blood-brain-barrier (86). With the help of a stable lipid bilayer, the cargoes loaded in the exosomal vesicles are guarded against the action of native immune cells and digestive enzymes. The engineered exosomal vesicles deliver the cargoes loaded to them to the site of



Figure 3

Methods of uptake of exosomes by the target cells.

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- Review** Characteristics and Roles of Exosomes in Cardiovascular Disease. [DNA Cell Biol. 2017]
- Review** Exosomes as Diagnostic Biomarkers in Cardiovascular Diseases. [Adv Exp Med Biol. 2017]
- Review** The biology and function of exosomes in cancer. [J Clin Invest. 2016]
- Review** Exosomes as new diagnostic tools in CNS diseases. [Biochim Biophys Acta. 2016]
- Review** Exosomes in the pathogenesis, diagnostics and therapeutics of liver diseases. [J Hepatol. 2013]
- Review** The Potential Biomarkers and Immunological Effects of Tumor-Derived Exosomes in Lung Cancer. [Front Immunol. 2016]
- Review** The function and clinical application of extracellular vesicles in innate immune regulation. [Cell Mol Immunol. 2020]

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Comparison of exosomes and ferritin protein nanocages for the delivery of membrane protein therapeutics. [J Control Release. 2018]

Review Therapeutic applications of extracellular vesicles: clinical promise and open questions. [Annu Rev Pharmacol Toxicol. 2015]

Surface functionalized exosomes as targeted drug delivery vehicles for cerebral ischemia therapy. [Biomaterials. 2018]

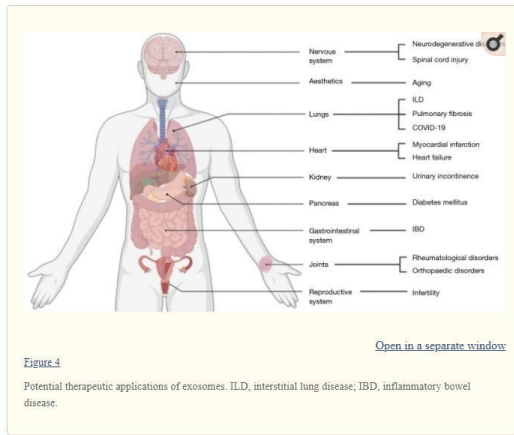
Review Mesenchymal Stem Cell-derived Extracellular Vesicles: Toward Cell-free Therapeutic Applications. [Mol Ther. 2015]

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Review The biology and biomedical applications of exosomes. [Science. 2020]

Review Extracellular Vesicles in Cancer: Cell-to-Cell Mediators of Metastasis. [Cancer Cell. 2016]

Mesenchymal Stem Cell-Derived Exosomes: A Potential



The superiority of the exosomal cargos compared to the stem cells on clinical and therapeutic potential is noted by:

Routes of delivery of exosomes

[Go to](#)

The different state of the art approaches to deliver the exosomes to their site of action and their shortcomings were analyzed and presented with their challenges encountered in them. The most common route is intravenous (IV) despite its clearance in the liver and the kidney is rapid in this method (105). This method was widely used for conditions involving orthopedic, neoplastic, and cardiovascular pathologies (106). Intramuscular (IM) has been primarily used in neuromuscular and musculoskeletal conditions while subcutaneous (SC) route in aesthetic and cosmetic indications. The IM or SC route is chosen due to the ease of injectable area and the dosing volume (97). Intrathecal is the preferred route in neurodegenerative conditions such as Alzheimer's, Parkinson's, and Creutz-Field Jakob's disease (98,99). Local aerosol sprays are used in the management of wounds and ulcers (107,108). For hair growth and rejuvenation in age-related therapies, this is the preferred route (108,109). During the time of the coronavirus disease-2019 (COVID-19) pandemic, there have been interesting studies discussing the role of exosomal therapy as a promising therapeutic candidate (110).

Global regulatory requirements

[Go to](#)

With the growing therapeutic spectrum of exosomal therapy, the International Society for Extracellular Vesicles (ISEV) and the European Network on Microvesicles and Exosomes in Health and Disease (ME-HaD) have formulated certain guidelines to foster their clinical usage (10). The regulations elaborate on the standard operative protocols to be followed in the process of collection, processing, testing, quality control, and manufacturing of exosomes for clinical usage. With the help of these policies, the potential of the EVs can be utilized at appropriate standards for therapeutic usage.

[Therapeutic Avenue in Knee Osteoarthritis](#) [Cartilage. 2020]

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[Review Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases.](#) [Exp Mol Med. 2017]

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[Review Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes](#) [Acta Pharm Sin B. 2016]

[Review Towards Therapeutic Delivery of Extracellular Vesicles: Strategies for <i>in Vivo</i> Tracking and](#) [Stem Cells Int. 2016]

[Review Recent advancements in the use of exosomes as drug delivery systems.](#) [J Nanobiotechnology. 2018]

[Review Perspective Insights of Exosomes in Neurodegenerative Diseases: A Cr](#) [Front Aging Neurosci. 2017]

[Microvesicles from human adipose stem cells promote wound healing by optimizing cellular functio](#) [Stem Cell Res Ther. 2019]

[Topical Application of Exosomes Derived from Human Umbilical Cord Mesenchymal Stem Cells in Co](#) [Int J Nanomedicine. 2020]

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[Minimal information for studies of extracellular vesicles 2018 \(MISEV2018\): a position statement o](#) [J Extracell Vesicles. 2018]

[Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper.](#) [J Extracell Vesicles. 2015]

[EBV-gp350 confers B-cell tropism to tailored exosomes and is a neo-antigen in normal and malignant B cells-](#) [PLoS One. 2011]

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Any novel therapy or a drug being developed is dependent on the strategies to standardize the process to focus on validating the proposed technology. There are currently no Food and Drug Administration (FDA)-approved exosome products for human use in the USA (2,111). According to the FDA, exosomes are classified as a 351 product that requires studies effectively showing safety and efficacy, along with the purity of the product and its potency in treating the condition (112). Therapies using the exosomes are under the Investigational New Drug (IND) developmental phase and need the approval of the regulatory agencies before initiating the clinical trial (2,113).

The regulatory framework addresses the safety standards for microbial and viral contamination and demands GxP standards (GxP = good manufacturing good laboratory good distribution good clinical good scientific practice or GMP GLP GDP GCP GSP) for the production and quality control of the corresponding therapeutics (114,115). It regulates the conduct of clinical trials (116). There remains an issue with the categorization of any emerging novel therapeutics for humans.

Pharmaceutical category of EV preparations

[Go to: ↻](#)

According to the Center for Biologics Evaluation and Research (CBER), the exosomes are regulated as biological products (117,118). Based on the individual types, the framework that was laid down for products in this category applies to the exosomes. For example, an anti-tumor vaccine that uses exosomes will be regulated under the regulations provided for therapeutic cancer vaccines (119). The functional moiety in EV-based therapy determines its medicinal type (2,120).

Hence, ISEV categorizes EV-based therapy under biological medicines with the following properties.

- I. The therapeutics acquired from unmodified cells.
- II. Therapeutics acquired from genetically manipulated cells (without trans-gene).
- III. Therapies acquired from exosomes and gene-modified cells with trans-gene classified as gene therapy products (GTP).
- IV. Native exosomal therapies, are used as drug-delivery systems, used as carriers for the biological and chemical components, and are considered as biological medicine.

As the biological medicinal products include a span of various pharmaceuticals, these were classified as Advanced Therapy Medicinal Products (ATMP's) in 2007 (2,120). It was further subgrouped to conventional biological medicinal products due to the biological properties, physicochemical and immunochemical properties (117,118). It includes somatic cell therapy, gene therapies, and tissue-engineered products.

ATMP's therapeutics involve products that have been:

- I. More than minimally manipulated such as cell expansions and cell cultures.
- II. Intended for non-homologous use. For example use of hematopoietic cells for orthopedics.
- III. Nucleated and viable cells are present in the product.
- IV. Products with therapeutically active trans-gene from genetically engineered cells are considered as ATMPs, independent of the presence of any nucleated, viable cell.
- V. EV-based therapeutics classified as ATMP's, are produced from human material by a manufacturing process comparable to the ATMP production.

Safety profile, manufacturing & standardization

[Go to: ↻](#)

The mechanism of action (MoA) is essential for the clinical translation of therapeutics based on EVs (121). The critical part of this translation is the identification of "active substances", their properties, and the essential quality controls in manufacturing a clinical-grade product (118). For phase I the hypothesis should be based on the proof of principle, reinstate the rationale based on the MoAs. Although uncertainties exist on the MoA of EV-based therapeutics on the target cells, with supportive animal models, EVs from human cells are not to be accounted as high risk in an IND (116). Commercializing a large scale

Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. [\[J Extracell Vesicles. 2015\]](#)

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Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. [\[J Extracell Vesicles. 2015\]](#)

manufacturing of EV based therapeutics requires a robust quality management system, technologically superior facility, and an updated technology complying with GxP (114,115). The endpoint of these investigational studies is to provide safety for the donor and the patient. The criteria for the therapeutic release of an investigational product is to determine efficacy based on the pre-IND studies for characterization (116).

At this moment the EV's do not have a standardized protocol for isolation and storage; and include homemade cocktails as protocols with no standardization for reagents, storage containers, and storage time for each desired EV-based product (2,19,122).

Direction for future research

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The scope of exosomal therapy among various other clinical fields remains untouched. With the global interest of the researchers towards harnessing the potential of the exosomes, making EV based therapeutics a reality is not far from reach (10). The potential of EV based therapy is established in various orthopedic conditions, neurodegenerative disorders, auto-immune diseases, cardiovascular diseases, infectious diseases, and diagnosis of rare diseases including cancers (98,99,123). However, the current domain of research in EV based therapeutics involve developing diagnostic and therapeutic applications towards patient care.

From the level of the circulating pool of EVs, early diagnosis of a complex disease could be made by using them as biomarkers in blood (74-82). Utilising the paracrine signaling property of the MSC-derived exosomes, repair, and regeneration of organs could be achieved (87-95). For use in most orthopedic conditions exosomes are deemed anti-inflammatory concerning their immunomodulatory potential (123). Understanding the role of exosomes in the disease processes have enabled us to propel our understanding of the disease and expand the scope of the therapies evolved out of them (124). As of now therapeutic applications of the EV-based therapies from defined cell sources based on their immunomodulatory capabilities include inflammatory disorders, degenerative disorders, vehicles of drug-delivery, anti-tumor therapies, and pathogen vaccination tool (98-102). Immunomodulation of exosomes may be exerted by either immune-activation or suppression. This novel platform with the above-mentioned diverse potentials holds promise to develop vaccines with prolonged immunogenicity against infectious diseases or cancer (125,126).

There is a paradigm shift brought down by the continual breakthroughs in research exploring the potential of the exosomes that have resulted in the development of novel therapeutic options that are reshaping the landscape of the global market from time to time. Despite being started as a subject of academic interest, exosomal therapy has now been transformed into a potential platform with immense promise for future therapeutics (127). This sowed the seeds for start-ups into exosome platforms with their proprietary technologies. Some of them are elaborated in [Table 1](#). These companies are using patented technologies to tap the potential of exosomes. For example, the company Capricor Therapeutics developed an exosomal therapeutic technology from cardiosphere-derived cells (CDCs) called CAP-2003 which is in the preclinical testing phase to explore the anti-inflammatory, pro-angiogenic, antiapoptotic, and antifibrotic effects associated with their parent CDCs. Additionally, the company is evaluating the role of CDC-exosomes for the treatment of trauma-related injuries and conditions (135).

Table 1
Companies targeting on exosomal research and their potential products for commercial use

Company	Exosomal source	Exosomal product	Exosomal potential
Capricor Therapeutics (128)	Cardiosphere-derived cells (CDCs)	CAP-2003 (preclinical testing)	Explore the anti-inflammatory, pro-angiogenic, antiapoptotic and antifibrotic effects associated with their parent CDCs
Kimera Labs	Placental MSC-	XoGlo	Tap into the potential for tissue repositioning.

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Review Perspective Insights of Exosomes in Neurodegenerative Diseases: A Crit [Front Aging Neurosci. 2017]

Review Stem Cell-Derived Exosomes: A Potential Alternative Therapeutic Agent in Orthopaedics. [Stem Cells Int. 2016]

Extracellular vesicle-mediated transfer of donor genomic DNA to recipient cells is a novel mechanism for gene transfer. [J Mol Cell Biol. 2013]

Review Exosomes in Cancer Liquid Biopsy: A Focus on Breast Cancer. [Mol Ther Nucleic Acids. 2018]

Review Therapeutic applications of extracellular vesicles: clinical promise and open questions. [Annu Rev Pharmacol Toxicol. 2015]

Proangiogenic compositions of microvesicles derived from human umbilical cord mesenchymal stem cells. [PLoS One. 2014]

Review Stem Cell-Derived Exosomes: A Potential Alternative Therapeutic Agent in Orthopaedics. [Stem Cells Int. 2016]

Exosomes released from human induced pluripotent stem cell-derived MSCs facilitate cutaneous wound healing. [J Transl Med. 2015]

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Review Current Knowledge and Future Perspectives on Mesenchymal Stem Cell-Derived Exosomes [Int J Mol Sci. 2020]

Macrophages mediate cardioprotective cellular preconditioning in acute myocardial infarction. [J Clin Invest. 2015]

(129)	derived exosome		preventing healing-associated scarring
ExosomeDx (130)	Plasma or serum-derived exosomes	ExoDx	CLIA certified product to conduct advanced clinical testing
NanoSomaX (131)	Brain-derived exosomes (BDEs)	ExoM and ExoC	Biomarkers for prediction of potential nervous system disorders
Evox Therapeutics (132)			For rare metabolic and lysosomal storage diseases engaging endogenous and exogenous drug loading
Codiak Biosciences (133)	Engineered therapeutic exosomes		Encompasses therapeutics for vaccines, anti-infectives, oncology, autoimmune and anti-inflammatory diseases
Aruna Biomedical (134)	Neural derived exosomes	AB126	Murine thromboembolic models of stroke and its translation to clinical therapies

MSC, mesenchymal stem cell; CLIA, Clinical Laboratory Improvement Amendments.

Conclusions

Go to:

Exosomes play a natural role by enacting as a vehicle for the transfer of biological substances between cells and thereby renders a broader prospect to serve as a channel for delivering drugs of therapeutic interest. However, the intricate composition and uncertain functioning are inquisitive facets warranting further exploration. In view of making the exosome-based therapy a reality, more accurate, faster, cheaper, standardized, specific, and easier methods of their separation and purification have to evolve along with concrete adducing on its safety, feasibility, pharmacokinetic and pharmacodynamic characteristics through large scale prospective research studies.

Acknowledgments

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Notes

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Footnotes

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/sci-2020-037>). The authors have no conflicts of interest to declare.

References

Go to:

1. Wu D, Abezguz L, Danino D, et al. Alternating polymer vesicles. *Soft Matter* 2008;4:1066-71. 10.1039/b715608a [PubMed] [CrossRef] [Google Scholar]
2. Jeyaraman M, Muthu S, Gulati A, et al. Mesenchymal Stem Cell-Derived Exosomes: A Potential Therapeutic Avenue in Knee Osteoarthritis. *Cartilage* 2020. doi: 10.1177/1947603520962567 [PubMed] [CrossRef] [Google Scholar]

3. Pata V, Dan N. The effect of chain length on protein solubilization in polymer-based vesicles (polymersomes). *Biophys J* 2003;85:2111-8. 10.1016/S0006-3495(03)74639-6 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
4. Zhang XY, Zhang PY. Polymersomes in Nanomedicine - A Review. *Current Nanoscience* 2016. doi:10.2174/1573413712666161018144519 [CrossRef] [Google Scholar]
5. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science* 2020;367:eaau6977. 10.1126/science.aau6977 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
6. Pegtel DM, Gould SJ. Exosomes. *Annu Rev Biochem* 2019;88:487-514. 10.1146/annurev-biochem-013118-111902 [PubMed] [CrossRef] [Google Scholar]
7. Becker A, Thakur BK, Weiss JM, et al. Extracellular Vesicles in Cancer: Cell-to-Cell Mediators of Metastasis. *Cancer Cell* 2016;30:836-48. 10.1016/j.ccr.2016.10.009 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
8. Kalluri R. The biology and function of exosomes in cancer. *J Clin Invest* 2016;126:1208-15. 10.1172/JCI81135 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
9. Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. *Nat Rev Immunol* 2014;14:195-208. 10.1038/nri3622 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
10. Théry C, Witwer KW, Aikawa E, et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): a position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. *J Extracell Vesicles* 2018;7:1535750. 10.1080/20013078.2018.1535750 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
11. Cocucci E, Meldolesi J. Exosomes and exosomes: shedding the confusion between extracellular vesicles. *Trends Cell Biol* 2015;25:364-72. 10.1016/j.tcb.2015.01.004 [PubMed] [CrossRef] [Google Scholar]
12. O'Brien K, Breyne K, Ughetto S, et al. RNA delivery by extracellular vesicles in mammalian cells and its applications. *Nat Rev Mol Cell Biol* 2020;21:585-606. 10.1038/s41580-020-0251-y [PMC free article] [PubMed] [CrossRef] [Google Scholar]
13. Caby MP, Lankar D, Vincendeau-Scherrer C, et al. Exosomal-like vesicles are present in human blood plasma. *Int Immunol* 2005;17:879-87. 10.1093/intimm/dxh267 [PubMed] [CrossRef] [Google Scholar]
14. Pisitkun T, Shen RF, Knepper MA. Identification and proteomic profiling of exosomes in human urine. *Proc Natl Acad Sci U S A* 2004;101:13368-73. 10.1073/pnas.0403453101 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
15. Michael A, Bajracharya SD, Yuen PS, et al. Exosomes from human saliva as a source of microRNA biomarkers. *Oral Dis* 2010;16:34-8. 10.1111/j.1601-0825.2009.01604.x [PMC free article] [PubMed] [CrossRef] [Google Scholar]
16. Admyre C, Johansson SM, Qazi KR, et al. Exosomes with immune modulatory features are present in human breast milk. *J Immunol* 2007;179:1969-78. 10.4049/jimmunol.179.3.1969 [PubMed] [CrossRef] [Google Scholar]
17. Mathivanan S, Ji H, Simpson RJ. Exosomes: extracellular organelles important in intercellular communication. *J Proteomics* 2010;73:1907-20. 10.1016/j.jprot.2010.06.006 [PubMed] [CrossRef] [Google Scholar]
18. Sokolova V, Ludwig AK, Hornung S, et al. Characterisation of exosomes derived from human cells by nanoparticle tracking analysis and scanning electron microscopy. *Colloids Surf B Biointerfaces* 2011;87:146-50. 10.1016/j.colsurfb.2011.05.013 [PubMed] [CrossRef] [Google Scholar]
19. Kaira H, Adda CG, Liem M, et al. Comparative proteomics evaluation of plasma exosome isolation techniques and assessment of the stability of exosomes in normal human blood plasma. *Proteomics* 2013;13:3354-64. 10.1002/pmic.201300282 [PubMed] [CrossRef] [Google Scholar]

20. Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. *Nat Rev Immunol* 2009;9:581-93. 10.1038/nri2567 [PubMed] [CrossRef] [Google Scholar]
21. Daaboul GG, Gagni P, Benussi L, et al. Digital Detection of Exosomes by Interferometric Imaging. *Sci Rep* 2016;6:37246. 10.1038/srep37246 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
22. Pitt JM, Kroemer G, Zitvogel L. Extracellular vesicles: masters of intercellular communication and potential clinical interventions. *J Clin Invest* 2016;126:1139-43. 10.1172/JCI87316 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
23. Mathivanan S, Fahner CJ, Reid GE, et al. ExoCarta 2012: database of exosomal proteins, RNA and lipids. *Nucleic Acids Res* 2012;40:D1241-D1244. 10.1093/nar/gkr828 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
24. Mathivanan S, Lim JW, Tauro BJ, et al. Proteomics analysis of A33 immunofinity-purified exosomes released from the human colon tumor cell line LIM1215 reveals a tissue-specific protein signature. *Mol Cell Proteomics* 2010;9:197-208. 10.1074/mcp.M900152-MCP200 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
25. Conde-Vancells J, Rodriguez-Suarez E, Embade N, et al. Characterization and comprehensive proteome profiling of exosomes secreted by hepatocytes. *J Proteome Res* 2008;7:5157-66. 10.1021/pr8004887 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
26. Poliakov A, Spilman M, Dokland T, et al. Structural heterogeneity and protein composition of exosome-like vesicles (prostasomes) in human semen. *Prostate* 2009;69:159-67. 10.1002/pros.20860 [PubMed] [CrossRef] [Google Scholar]
27. Simons M, Raposo G. Exosomes—vesicular carriers for intercellular communication. *Curr Opin Cell Biol* 2009;21:575-81. 10.1016/j.cob.2009.03.007 [PubMed] [CrossRef] [Google Scholar]
28. Subra C, Grand D, Laulagnier K, et al. Exosomes account for vesicle-mediated transcellular transport of activatable phospholipases and prostaglandins. *J Lipid Res* 2010;51:2105-20. 10.1194/jlr.M003657 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
29. Vlassov AV, Magdaleno S, Setterquist R, et al. Exosomes: current knowledge of their composition, biological functions, and diagnostic and therapeutic potentials. *Biochim Biophys Acta* 2012;1820:940-8. 10.1016/j.bbagen.2012.03.017 [PubMed] [CrossRef] [Google Scholar]
30. Xie F, Zhou X, Fang M, et al. Extracellular Vesicles in Cancer Immune Microenvironment and Cancer Immunotherapy. *Adv Sci (Weinheim)* 2019;6:1901779. 10.1002/adv.201901779 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
31. Jeppesen DK, Fenix AM, Franklin JL, et al. Reassessment of Exosome Composition. *Cell* 2019;177:428-445.e18. 10.1016/j.cell.2019.02.029 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
32. van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat Rev Mol Cell Biol* 2018;19:213-28. 10.1038/nrm.2017.125 [PubMed] [CrossRef] [Google Scholar]
33. Valadi H, Ekström K, Bossios A, et al. Exosome-mediated transfer of mRNAs and microRNAs is a novel mechanism of genetic exchange between cells. *Nat Cell Biol* 2007;9:654-9. 10.1038/ncb1596 [PubMed] [CrossRef] [Google Scholar]
34. Guescini M, Genedani S, Stocchi V, et al. Astrocytes and Glioblastoma cells release exosomes carrying mtDNA. *J Neural Transm (Vienna)* 2010;117:1-4. 10.1007/s00702-009-0288-8 [PubMed] [CrossRef] [Google Scholar]
35. Soung YH, Ford S, Zhang V, et al. Exosomes in Cancer Diagnostics. *Cancers (Basel)* 2017;9:8. 10.3390/cancers9010008 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
36. Ratajczak J, Miekus K, Kucia M, et al. Embryonic stem cell-derived microvesicles reprogram hematopoietic progenitors: evidence for horizontal transfer of mRNA and protein delivery. *Leukemia*

2006;20:847-56. 10.1038/sj.leu.2404132 [PubMed] [CrossRef] [Google Scholar]

37. Turchinovich A, Weiz L, Langhein A, et al. Characterization of extracellular circulating microRNA. *Nucleic Acids Res* 2011;39:7223-33. 10.1093/nar/gkr254 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

38. Willms E, Cabanas C, Mager I, et al. Extracellular Vesicle Heterogeneity: Subpopulations, Isolation Techniques, and Diverse Functions in Cancer Progression. *Front Immunol* 2018;9:738. 10.3389/fimmu.2018.00738 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

39. Bard MP, Hegmans JP, Hemmes A, et al. Proteomic analysis of exosomes isolated from human malignant pleural effusions. *Am J Respir Cell Mol Biol* 2004;31:114-21. 10.1165/rcmb.2003-0238OC [PubMed] [CrossRef] [Google Scholar]

40. Navabi H, Croston D, Hobot J, et al. Preparation of human ovarian cancer ascites-derived exosomes for a clinical trial. *Blood Cells Mol Dis* 2005;35:149-52. 10.1016/j.bcmd.2005.06.008 [PubMed] [CrossRef] [Google Scholar]

41. Li P, Kaslan M, Lee SH, et al. Progress in Exosome Isolation Techniques. *Theranostics* 2017;7:789-804. 10.7150/thno.18133 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

42. Momen-Heravi F, Balaj L, Alian S, et al. Current methods for the isolation of extracellular vesicles. *Biol Chem* 2013;394:1253-62. 10.1515/hsz-2013-0141 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

43. Théry C, Amigorena S, Raposo G, et al. Isolation and characterization of exosomes from cell culture supernatants and biological fluids. *Curr Protoc Cell Biol* 2006;Chapter 3:Unit 3.22. doi: 10.1002/0471143030.ch0322a30. [PubMed] [CrossRef] [Google Scholar]

44. Xu R, Greening DW, Zhu HJ, et al. Extracellular vesicle isolation and characterization: toward clinical application. *J Clin Invest* 2016;126:1152-62. 10.1172/JCI81129 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

45. Gulei D, Irimie AI, Cojocneanu-Petric R, et al. Exosomes-Small Players, Big Sound. *Bioconjug Chem* 2018;29:635-48. 10.1021/acs.bioconjchem.8b00003 [PubMed] [CrossRef] [Google Scholar]

46. Clayton A, Court J, Navabi H, et al. Analysis of antigen presenting cell derived exosomes, based on immuno-magnetic isolation and flow cytometry. *J Immunol Methods* 2001;247:163-74. 10.1016/S0022-1759(00)00321-5 [PubMed] [CrossRef] [Google Scholar]

47. Carnell-Morris P, Tannetta D, Siupa A, et al. Analysis of Extracellular Vesicles Using Fluorescence Nanoparticle Tracking Analysis. *Methods Mol Biol* 2017;1660:153-73. 10.1007/978-1-4939-7253-1_13 [PubMed] [CrossRef] [Google Scholar]

48. Anderson W, Lane R, Korbie D, et al. Observations of Tunable Resistive Pulse Sensing for Exosome Analysis: Improving System Sensitivity and Stability. *Langmuir* 2015;31:6577-87. 10.1021/acs.langmuir.5b01402 [PubMed] [CrossRef] [Google Scholar]

49. Liu JJ, Bratkovski MA, Liu X, et al. Visualization of distinct substrate-recruitment pathways in the yeast exosome by EM. *Nat Struct Mol Biol* 2014;21:95-102. 10.1038/nsmb.2736 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

50. Keller S, Sanderson MP, Stoeck A, et al. Exosomes: from biogenesis and secretion to biological function. *Immunol Lett* 2006;107:102-8. 10.1016/j.imlet.2006.09.005 [PubMed] [CrossRef] [Google Scholar]

51. Buschow SI, van Balkom BW, Aalberts M, et al. MHC class II-associated proteins in B-cell exosomes and potential functional implications for exosome biogenesis. *Immunol Cell Biol* 2010;88:851-6. 10.1038/icc.2010.64 [PubMed] [CrossRef] [Google Scholar]

52. Stoorvogel W, Kleijmeer MJ, Geuze HJ, et al. The biogenesis and functions of exosomes. *Traffic* 2002;3:321-30. 10.1034/j.1600-0854.2002.30502.x [PubMed] [CrossRef] [Google Scholar]

53. Baietti MF, Zhang Z, Mortier E, et al. Syndecan-syntenin-ALIX regulates the biogenesis of exosomes. *Nat Cell Biol* 2012;14:677-85. 10.1038/ncb2502 [PubMed] [CrossRef] [Google Scholar]
54. Kahlert C, Kalluri R. Exosomes in tumor microenvironment influence cancer progression and metastasis. *J Mol Med (Berl)* 2013;91:431-7. 10.1007/s00109-013-1020-6 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
55. Utsugi-Kobukai S, Fujimaki H, Hotta C, et al. MHC class I-mediated exogenous antigen presentation by exosomes secreted from immature and mature bone marrow-derived dendritic cells. *Immunol Lett* 2003;89:125-31. 10.1016/S0165-2478(03)00128-7 [PubMed] [CrossRef] [Google Scholar]
56. Clayton A, Turkes A, Devitt S, et al. Adhesion and signaling by B cell-derived exosomes: the role of integrins. *FASEB J* 2004;18:977-9. 10.1096/fj.03-1094fe [PubMed] [CrossRef] [Google Scholar]
57. Rieu S, Géminard C, Rabesandratana H, et al. Exosomes released during reticulocyte maturation bind to fibronectin via integrin alpha-5beta-1. *Eur J Biochem* 2000;267:583-90. 10.1046/j.1432-1327.2000.01036.x [PubMed] [CrossRef] [Google Scholar]
58. Hao S, Bai O, Li F, et al. Mature dendritic cells pulsed with exosomes stimulate efficient cytotoxic T-lymphocyte responses and antitumor immunity. *Immunology* 2007;120:90-102. 10.1111/j.1365-2567.2006.02483.x [PMC free article] [PubMed] [CrossRef] [Google Scholar]
59. Morelli AE, Larregina AT, Shufesky WJ, et al. Endocytosis, intracellular sorting, and processing of exosomes by dendritic cells. *Blood* 2004;104:3257-66. 10.1182/blood-2004-03-0824 [PubMed] [CrossRef] [Google Scholar]
60. Fitzner D, Schnaars M, van Rossum D, et al. Selective transfer of exosomes from oligodendrocytes to microglia by macropinocytosis. *J Cell Sci* 2011;124:447-58. 10.1242/jcs.074088 [PubMed] [CrossRef] [Google Scholar]
61. Feng D, Zhao WL, Ye YY, et al. Cellular internalization of exosomes occurs through phagocytosis. *Traffic* 2010;11:675-87. 10.1111/j.1600-0854.2010.01041.x [PubMed] [CrossRef] [Google Scholar]
62. Nanbo A, Kawanishi E, Yoshida R, et al. Exosomes derived from Epstein-Barr virus-infected cells are internalized via caveola-dependent endocytosis and promote phenotypic modulation in target cells. *J Virol* 2013;87:10334-47. 10.1128/JVI.01310-13 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
63. Svensson KJ, Christianson HC, Wittrup A, et al. Exosome uptake depends on ERK1/2-heat shock protein 27 signaling and lipid Raft-mediated endocytosis negatively regulated by caveolin-1. *J Biol Chem* 2013;288:17713-24. 10.1074/jbc.M112.445403 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
64. Escrevente C, Keller S, Altevogt P, et al. Interaction and uptake of exosomes by ovarian cancer cells. *BMC Cancer* 2011;11:108. 10.1186/1471-2407-11-108 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
65. Hoshino A, Costa-Silva B, Shen TL, et al. Tumor exosome integrins determine organotropic metastasis. *Nature* 2015;527:329-35. 10.1038/nature15756 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
66. Zhang Y, Hu YW, Zheng L, et al. Characteristics and Roles of Exosomes in Cardiovascular Disease. *DNA Cell Biol* 2017;36:202-11. 10.1089/dna.2016.3496 [PubMed] [CrossRef] [Google Scholar]
67. Jansen F, Li Q. Exosomes as Diagnostic Biomarkers in Cardiovascular Diseases. *Adv Exp Med Biol* 2017;998:61-70. 10.1007/978-981-10-4397-0_4 [PubMed] [CrossRef] [Google Scholar]
68. Kanninen KM, Bister N, Koistinaho J, et al. Exosomes as new diagnostic tools in CNS diseases. *Biochim Biophys Acta* 2016;1862:403-10. 10.1016/j.bbadis.2015.09.020 [PubMed] [CrossRef] [Google Scholar]
69. Fitts CA, Ji N, Li Y, et al. Exploiting Exosomes in Cancer Liquid Biopsies and Drug Delivery. *Adv Healthc Mater* 2019;8:e1801268. 10.1002/adhm.201801268 [PubMed] [CrossRef] [Google Scholar]
70. Masyuk AI, Masyuk TV, Larusso NF. Exosomes in the pathogenesis, diagnostics and therapeutics of

- liver diseases. *J Hepatol* 2013;59:621-5. 10.1016/j.jhep.2013.03.028 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
71. Zhang W, Zhou X, Zhang H, et al. Extracellular vesicles in diagnosis and therapy of kidney diseases. *Am J Physiol Renal Physiol* 2016;311:F844-F851. 10.1152/ajprenal.00429.2016 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
72. Alipoor SD, Mortaz E, Varahram M, et al. The Potential Biomarkers and Immunological Effects of Tumor-Derived Exosomes in Lung Cancer. *Front Immunol* 2018;9:819. 10.3389/fimmu.2018.00819 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
73. Zhou X, Xie F, Wang L, et al. The function and clinical application of extracellular vesicles in innate immune regulation. *Cell Mol Immunol* 2020;17:323-34. 10.1038/s41423-020-0391-1 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
74. Cai J, Han Y, Ren H, et al. Extracellular vesicle-mediated transfer of donor genomic DNA to recipient cells is a novel mechanism for genetic influence between cells. *J Mol Cell Biol* 2013;5:227-38. 10.1093/jmcb/mjt011 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
75. Kahler C, Melo SA, Protopopov A, et al. Identification of double-stranded genomic DNA spanning all chromosomes with mutated KRAS and p53 DNA in the serum exosomes of patients with pancreatic cancer. *J Biol Chem* 2014;289:3869-75. 10.1074/jbc.C113.532267 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
76. Kalluri R, LeBleu VS. Discovery of Double-Stranded Genomic DNA in Circulating Exosomes. *Cold Spring Harb Symp Quant Biol* 2016;81:275-80. 10.1101/sqb.2016.81.030932 [PubMed] [CrossRef] [Google Scholar]
77. Thakur BK, Zhang H, Becker A, et al. Double-stranded DNA in exosomes: a novel biomarker in cancer detection. *Cell Res* 2014;24:766-9. 10.1038/cr.2014.44 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
78. Salehi M, Sharifi M. Exosomal miRNAs as novel cancer biomarkers: Challenges and opportunities. *J Cell Physiol* 2018;233:6370-80. 10.1002/jcp.26481 [PubMed] [CrossRef] [Google Scholar]
79. Thind A, Wilson C. Exosomal miRNAs as cancer biomarkers and therapeutic targets. *J Extracell Vesicles* 2016;5:31292. 10.3402/jev.v5.31292 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
80. Lian J, Lin SH, Ye Y, et al. Serum microRNAs as predictors of risk for non-muscle invasive bladder cancer. *Oncotarget* 2018;9:14895-908. 10.18632/oncotarget.24473 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
81. Hallal S, Azimi A, Wei H, et al. A Comprehensive Proteomic SWATH-MS Workflow for Profiling Blood Extracellular Vesicles: A New Avenue for Glioma Tumour Surveillance. *Int J Mol Sci* 2020;21:4754. 10.3390/ijms21134754 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
82. Halvaei S, Daryani S, Eslami-S Z, et al. Exosomes in Cancer Liquid Biopsy: A Focus on Breast Cancer. *Mol Ther Nucleic Acids* 2018;10:131-41. 10.1016/j.omtn.2017.11.014 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
83. Stevic I, Muller V, Weber K, et al. Specific microRNA signatures in exosomes of triple-negative and HER2-positive breast cancer patients undergoing neoadjuvant therapy within the GeparSixto trial. *BMC Med* 2018;16:179. 10.1186/s12916-018-1163-y [PMC free article] [PubMed] [CrossRef] [Google Scholar]
84. Zhou X, Zhu W, Li H, et al. Diagnostic value of a plasma microRNA signature in gastric cancer: a microRNA expression analysis. *Sci Rep* 2015;5:11251. 10.1038/srep11251 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
85. Yosef I, Goren MG, Qimron U. Proteins and DNA elements essential for the CRISPR adaptation process in *Escherichia coli*. *Nucleic Acids Res* 2012;40:5569-76. 10.1093/nar/gks216 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
86. Guo F, Niu CH, Huo X, et al. Comparison of secreted and surface protein expression between

80. Cho E, Nam SH, Hong J, et al. Comparison of exosomes and tetraam protein nanocages for the delivery of membrane protein therapeutics. *J Control Release* 2018;279:326-35. 10.1016/j.jconrel.2018.04.037 [PubMed] [CrossRef] [Google Scholar]
87. György B, Hung ME, Breakefield XO, et al. Therapeutic applications of extracellular vesicles: clinical promise and open questions. *Annu Rev Pharmacol Toxicol* 2015;55:439-64. 10.1146/annurev-pharmtox-010814-124630 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
88. Tian T, Zhang HX, He CP, et al. Surface functionalized exosomes as targeted drug delivery vehicles for cerebral ischemia therapy. *Biomaterials* 2018;150:137-49. 10.1016/j.biomaterials.2017.10.012 [PubMed] [CrossRef] [Google Scholar]
89. Rami S, Ryan AE, Griffin MD, et al. Mesenchymal Stem Cell-derived Extracellular Vesicles: Toward Cell-free Therapeutic Applications. *Mol Ther* 2015;23:812-23. 10.1038/mt.2015.44 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
90. Zhang B, Yin Y, Lai RC, et al. Mesenchymal stem cells secrete immunologically active exosomes. *Stem Cells Dev* 2014;23:1233-44. 10.1089/scd.2013.0479 [PubMed] [CrossRef] [Google Scholar]
91. Lee C, Mitsialis SA, Aslan M, et al. Exosomes mediate the cytoprotective action of mesenchymal stromal cells on hypoxia-induced pulmonary hypertension. *Circulation* 2012;126:2601-11. 10.1161/CIRCULATIONAHA.112.114173 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
92. Kanazawa H, Fujimoto Y, Teratani T, et al. Bone Marrow-Derived Mesenchymal Stem Cells Ameliorate Hepatic Ischemia Reperfusion Injury in a Rat Model. *PLoS One* 2011;6:e19195. 10.1371/journal.pone.0019195 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
93. Lai RC, Arslan F, Lee MM, et al. Exosome secreted by MSC reduces myocardial ischemia/reperfusion injury. *Stem Cell Res* 2010;4:214-22. 10.1016/j.scr.2009.12.003 [PubMed] [CrossRef] [Google Scholar]
94. Salomon C, Ryan J, Sobrevia L, et al. Exosomal Signaling during Hypoxia Mediates Microvascular Endothelial Cell Migration and Vasculogenesis. *PLoS One* 2013;8:e68451. 10.1371/journal.pone.0068451 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
95. Chen J, Liu Z, Hong MM, et al. Proangiogenic compositions of microvesicles derived from human umbilical cord mesenchymal stem cells. *PLoS One* 2014;9:e115316. 10.1371/journal.pone.0115316 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
96. Yang Y, Hong Y, Cho E, et al. Extracellular vesicles as a platform for membrane-associated therapeutic protein delivery. *J Extracell Vesicles* 2018;7:1440131. 10.1080/20013078.2018.1440131 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
97. Bungulawa EJ, Wang W, Yin T, et al. Recent advancements in the use of exosomes as drug delivery systems. *J Nanobiotechnology* 2018;16:81. 10.1186/s12951-018-0403-9 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
98. Jan AT, Malik MA, Rahman S, et al. Perspective Insights of Exosomes in Neurodegenerative Diseases: A Critical Appraisal. *Front Aging Neurosci* 2017;9:317. 10.3389/fnagi.2017.00317 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
99. ClinicalTrials.gov [Accessed on 23.07.2020]. Available online: https://clinicaltrials.gov/ct2/results?cond=exosomes&Search=Apply&recrs=e&age_y=&pub=&type=&rlt=
100. Wang K, Jiang Z, Webster KA, et al. Enhanced Cardioprotection by Human Endometrium Mesenchymal Stem Cells Driven by Exosomal MicroRNA-21. *Stem Cells Transl Med* 2017;6:209-22. 10.5966/sctm.2015-0386 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
101. Lou G, Chen Z, Zheng M, et al. Mesenchymal stem cell-derived exosomes as a new therapeutic strategy for liver diseases. *Exp Mol Med* 2017;49:e346. 10.1038/emm.2017.63 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
102. Kim HS, Choi DY, Yun SJ, et al. Proteomic analysis of microvesicles derived from human mesenchymal stem cells. *J Proteome Res* 2012;11:839-49. 10.1021/pr200682z [PubMed] [CrossRef]

[Google Scholar]

103. Merino-González C, Zufiga FA, Escudero C, et al. Mesenchymal Stem Cell-Derived Extracellular Vesicles Promote Angiogenesis: Potential Clinical Application. *Front Physiol* 2016;7:24. 10.3389/fphys.2016.00024 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
104. Tracy SA, Ahmed A, Tigges JC, et al. A comparison of clinically relevant sources of mesenchymal stem cell-derived exosomes: Bone marrow and amniotic fluid. *J Pediatr Surg* 2019;54:86-90. 10.1016/j.jpedsurg.2018.10.020 [PubMed] [CrossRef] [Google Scholar]
105. Ha D, Yang N, Nadithe V. Exosomes as therapeutic drug carriers and delivery vehicles across biological membranes: current perspectives and future challenges. *Acta Pharm Sin B* 2016;6:287-96. 10.1016/j.apsb.2016.02.001 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
106. Di Rocco G, Baldari S, Toietta G. Towards Therapeutic Delivery of Extracellular Vesicles: Strategies for In Vivo Tracking and Biodistribution Analysis. *Stem Cells Int* 2016;2016:5029619. 10.1155/2016/5029619 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
107. Ren S, Chen J, Duscher D, et al. Microvesicles from human adipose stem cells promote wound healing by optimizing cellular functions via AKT and ERK signaling pathways. *Stem Cell Res Ther* 2019;10:47. 10.1186/s13287-019-1152-x [PMC free article] [PubMed] [CrossRef] [Google Scholar]
108. Zhang K, Yu L, Li FR, et al. Topical Application of Exosomes Derived from Human Umbilical Cord Mesenchymal Stem Cells in Combination with Sponge Spicules for Treatment of Photoaging. *Int J Nanomedicine* 2020;15:2859-72. 10.2147/IJN.S249751 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
109. Ferreira ADF, Gomes DA. Stem Cell Extracellular Vesicles in Skin Repair. *Bioengineering (Basel)* 2018;6:4. 10.3390/bioengineering6010004 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
110. Sengupta V, Sengupta S, Lazo A, et al. Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19. *Stem Cells Dev* 2020;29:747-54. 10.1089/scd.2020.0080 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
111. Ilic N, Savic S, Siegel E, et al. Examination of the regulatory frameworks applicable to biologic drugs (including stem cells and their progeny) in Europe, the U.S., and Australia. Part II—A method of software documentary analysis. *Stem Cells Transl Med* 2012;1:909-20. 10.5966/scnm.2012-0038 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
112. Ilic N, Savic S, Siegel E, et al. Examination of the regulatory frameworks applicable to biologic drugs (including stem cells and their progeny) in Europe, the U.S., and Australia: part I—a method of manual documentary analysis. *Stem Cells Transl Med* 2012;1:898-908. 10.5966/scnm.2012-0037 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
113. European Union. Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use; Annex 2, Manufacture of Biological Active Substances and Medicinal Products for Human Use.
114. GMPguidelines. [assessed on 28 July 2020]. Available online: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm
115. ClinicalTrialsGuidelines. [assessed on 28 July 2020]. Available online: http://ec.europa.eu/health/documents/eudralex/vol-10/index_en.htm
116. EMA CHMP BWP/534898/2008. Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials.
117. Lener T, Gimona M, Aigner L, et al. Applying extracellular vesicles based therapeutics in clinical trials - an ISEV position paper. *J Extracell Vesicles* 2015;4:30087. 10.3402/jev.v4.30087 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
118. EMEA-CHMP/410869/2006. Guideline on human cell-based medicinal products.

119. Ruiss R, Jochum S, Mocikat R, et al. EBV-gp350 Confers B-Cell Tropism to Tailored Exosomes and Is a Neo-Antigen in Normal and Malignant B Cells—A New Option for the Treatment of B-CLL. *PLoS One* 2011;6:e25294. 10.1371/journal.pone.0025294 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
120. REGULATION/EC/1394/2007. Regulation on advanced therapy medicinal products.
121. EMA CAT/CPWP/686637/2011. Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products.
122. Kriebardis A, Antonelou M, Stamoulis K, et al. Cell-derived microparticles in stored blood products: innocent-bystanders or effective mediators of post-transfusion reactions? *Blood Transfus* 2012;10 Suppl 2:s25-s38. [PMC free article] [PubMed] [Google Scholar]
123. Burke J, Kolhe R, Hunter M, et al. Stem Cell-Derived Exosomes: A Potential Alternative Therapeutic Agent in Orthopaedics. *Stem Cells Int* 2016;2016:5802529. 10.1155/2016/5802529 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
124. Zhang J, Guan J, Niu X, et al. Exosomes released from human induced pluripotent stem cells-derived MSCs facilitate cutaneous wound healing by promoting collagen synthesis and angiogenesis. *J Transl Med* 2015;13:49. 10.1186/s12967-015-0417-0 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
125. Devhare PB, Ray RB. A novel role of exosomes in the vaccination approach. *Ann Transl Med* 2017;5:23. 10.21037/atm.2016.12.75 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
126. Nolte-t'Hoën E, Cremer T, Gallo RC, et al. Extracellular vesicles and viruses: Are they close relatives? *Proc Natl Acad Sci U S A* 2016;113:9155-61. 10.1073/pnas.1605146113 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
127. Joo HS, Suh JH, Lee HJ, et al. Current Knowledge and Future Perspectives on Mesenchymal Stem Cell-Derived Exosomes as a New Therapeutic Agent. *Int J Mol Sci* 2020;21:727. 10.3390/ijms21030727 [PMC free article] [PubMed] [CrossRef] [Google Scholar]
128. Capricor Therapeutics. [assessed on 28 July 2020]. Available online: <http://capricor.com/>
129. Kimera Labs. [assessed on 28 July 2020]. Available online: <https://kimeralabs.com/>
130. Exosome Diagnostics. Personalized Precision Healthcare. [assessed on 28 July 2020]. Available online: <http://www.exosomedx.com/>
131. NanoSomiX Inc. [assessed on 28 July 2020]. Available online: <http://www.nanosomix.com/technology>
132. Evox Therapeutics. [assessed on 28 July 2020]. Available online: <https://www.evoxtherapeutics.com/>
133. Codiak Biosciences. Realizing the potential of exosome biology. [assessed on 28 July 2020]. Available online: <http://www.codiakbio.com/#cellular-communicators>
134. ArunA Biomedical. [assessed on 28 July 2020]. Available online: <https://www.arunabiomedical.com/>
135. de Couto G, Liu W, Tselioui E, et al. Macrophages mediate cardioprotective cellular postconditioning in acute myocardial infarction. *J Clin Invest* 2015;125:3147-62. 10.1172/JCI81321 [PMC free article] [PubMed] [CrossRef] [Google Scholar]

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- ABSTRACT
- KEYWORDS
- INTRODUCTION
- BIOGENESIS OF EXOSOMES
- MOLECULAR COMPOSITION OF EXOSOMES
- EXOSOMES AS MESSENGERS OF INTERCELLULAR COMMUNICATION
- EXOSOMES AS VECTORS OF STEM CELL THERAPY
- EXOSOMES AS BIOMARKERS AND VEHICLES OF DRUG DELIVERY
- CONCLUSIONS AND FUTURE PROSPECTS
- DISCLOSURE STATEMENT
- ACKNOWLEDGMENTS
- LITERATURE CITED

Abstract

Mesenchymal stem cells (MSCs), whose mechanism of action is predominantly paracrine, are being widely tested for the treatment of a variety of human diseases. No one factor has been proven sufficient to mediate the therapeutic effects of MSCs. However, exosomes – membrane vesicles secreted by many cells, including MSCs – are appealing candidates as vectors of their efficacy. Exosomes can transport and deliver a large cargo of proteins, lipids, and nucleic acids and can modify cell and organ function. In addition to their key role as vehicles of intercellular communication, exosomes are increasingly recognized as biomarkers and prognosticators of disease. Moreover, they have the potential to be used as vehicles of gene and drug delivery for clinical application. This article reviews the biogenesis of exosomes, their molecular composition, and their role as messengers of intercellular communication, focusing on their potential as therapeutic vectors for stem cell therapy.

Keywords

mesenchymal stem cells, microRNA, lung vascular disease, regenerative medicine, secretome

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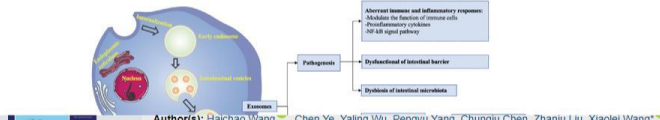


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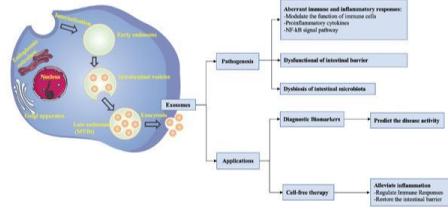
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Inflammatory bowel disease (IBD) is an immune-mediated chronic inflammatory disease. Although the etiology is uncertain, there is marked disbalance of mucosal immune responses in part shaped by genetic susceptibility and intestinal microbial dysbiosis. Suppressing inflammatory activity adequately and maintaining this suppression are the main goals of current therapies. However, corticosteroids are only suitable for therapy of active disease, and the effects of immunosuppressive agents are mainly limited to maintenance of remission. Biologics have become widely available and provide therapeutic benefits to IBD patients. However, only a part of patients benefits from them. Thus, there is an urgent need for the development of new substances in the therapy of IBD. Exosomes are nanosized lipid vesicles identified recently. They are secreted from all living cells and then distributed in various human body fluids. The components, such as microRNAs and functional proteins, secreted by exosomes in different cells have been reported to be involved in the pathogenesis of IBD. Therefore, exosomes have the potential to become appealing particles in treating IBD as a cell-free therapeutic approach as well as biomarkers for diagnosis and monitoring disease status. Further studies are needed to investigate the practicality, safety and desirable effects of exosomes in clinical applications in IBD.

Keywords: Exosomes, inflammatory bowel disease, pathogenesis, cell-free therapy, clinical application, microRNAs.

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you've probably heard about the regenerative powers of stem cell therapy but there's a "new"

Y kid on the block. Research suggests that exosome therapy may work better for tissue repair, anti-aging treatments, [immune support](#), hair loss, sexual health and fighting illnesses like lung diseases. What is an exosome and what role do exosomes play in fighting aging and disease? Read on!

What are exosomes and what is the function of exosomes?

The definition of exosome and extracellular vesicles (EVs): Exosomes are extracellular vesicles, which are tiny fluid-filled sacs or nanoparticles that originate in many different types of cells in the body, including stem cells. While stem cell therapy is generally known to provide regenerative benefits, [recent research suggests that EVs, including exosomes, play a vital role.](#)

[Exosomes have been shown to carry cell-specific cargos](#)—or exosomal cargos—of proteins, lipids and nucleic acids like RNAs, which can be selectively transferred to recipient cells in the body (located both near and far). Through a form of cell-to-cell communication—or intercellular communication—known as paracrine signaling, exosomes deliver tiny messages (biochemical signals) from cell to cell, which alter the behavior of the recipient cells.

By manufacturing and deploying exosomes, the cells are able to orchestrate the regeneration of tissue, help control inflammation, repair injuries and support regenerative therapies to treat certain diseases.



Is exosome therapy a form of stem cell therapy?

Exosomes are derived from stem cells and essentially perform the same biological functions as stem cells do. However, [evidence suggests that stems cells without extracellular vesicles](#) like exosomes don't provide any beneficial function. Exosomes may outperform stem cells due to:

- Their tiny size, which may allow for widespread distribution and absorption into spaces inaccessible by the cells themselves.
- Eliminating the downsides of direct stem cell transplantation, [including low cell survival.](#)

· Compensating for the low quality and quantity of available stem cells that is typical as we get older.

According to Guiot et al., [exosomes have also been shown to](#) have a long circulating half-life, the inherent ability to target tissues, biocompatibility (meaning they are not harmful to human tissue) and little or no inherent toxicity issues.

What is exosome therapy and how does it work?

Exosome therapy is similar to [platelet-rich plasma \(PRP\) therapy](#), another type of regenerative therapy, in that it utilizes stem cells to restore healthy function to tissues compromised by aging, injury or disease. Both forms of therapy involve the injection of a product (exosomes or PRP) into damaged tissue, which helps enable cellular regeneration.

While PRP is derived from the patient's own blood, the exosome product EVEXIAS uses contains exosomes isolated from mesenchymal stem cells (MSCs)—or stromal cells—in human donor perinatal tissue. The exosome product includes growth factors, hyaluronic acid and micro RNA, as well as cytokines and chemokines (two proteins that support cell signaling), which all work together to help heal and regenerate tissue.

Can weekend warriors benefit from exosome therapy?

If you've experienced a mild to moderate musculoskeletal injury and pain after a "harmless" tag football game with friends or want to promote tissue repair after surgery, regenerative stem cell therapy with exosomes may be a good option for you.

Regenerative therapy injections have been shown to stimulate stem cells and growth factors in the body to create healthy, new tissue and repair old, damaged tissue. Exosomes also help regulate inflammation, which may help minimize pain associated with injury or surgery.

Can exosomes be used in anti-aging treatments like facial rejuvenation?

Yes! EVEXIAS offers minimally invasive exosome facial rejuvenation that utilizes [microneedling](#) along with the exosome product—exosomes, growth factors, hyaluronic acid and micro RNA—to help stimulate healing and regenerate new skin. [Dermal fillers](#) may also be used during exosome facials and facelifts to help lift and plump sagging skin.

Following the microneedling procedure, the aesthetician injects the exosome product into the area of concern. By rejuvenating the skin, exosome anti-aging treatments have been shown to:

· Restore facial contours and shape for a more youthful look.

- Enhance skin quality, texture and tone.
- Minimize hyperpigmentation and sunspots.
- Reduce fine lines and wrinkles.
- Improve skin tightness.

What role do exosomes play in the immune system and immune responses?

According to their recent article in the journal *Annals of Translational Medicine*, authors Beverlie Baquir and Robert E. W. Hancock state "mesenchymal stromal cells (MSCs) have a profound effect on the regulation of the immune system." Baquir and Hancock note that MSCs play a key role in modulating the immune system "in a paracrine manner (intercellular communication), involving the secretion of exosomes." Exosomes also play a role in the function of cells of the immune system, such as dendritic cells (DCs) and T-lymphocytes (T-cells), which can absorb and secrete exosomes.



Numerous studies have also shown that exosomes are rich in proteins and RNA, including mRNA and microRNA. This further supports the immune boosting power of exosomes, as it is widely accepted that microRNA helps regulate immune responses. Baquir and Hancock also note that several studies show that microRNAs help regulate the function of recipient cells related to cancer, heart disease and sepsis.

What is the role of exosomes in fighting lung diseases?

Numerous studies support using exosomes derived from MSCs to treat lung diseases such as asthma and ARDS (acute respiratory distress syndrome). The ability of exosomes to promote tissue repair and wound healing, combined with their anti-inflammatory and immune boosting qualities, all point to the use of exosomes to treat lung disease.

A recent study by Sengupta et al. also revealed that exosomes could be beneficial to patients suffering from ARDS associated with COVID-19. That study concluded that exosomes were a promising therapeutic candidate for severe cases of COVID-19 due to the therapy's safety profile and its ability to restore oxygenation and boost immunity.

Is stem cell therapy for hair loss effective?

While practitioners have only recently started offering exosome therapy for hair loss, other forms of cellular therapy to regrow natural hair have been available for many years. In a study from 2017, Gentile et al. were able to increase hair density after treating the scalps of men with stem cells isolated from human hair follicles.

Platelet-rich plasma (PRP) therapy has also been used for many years as a form of stem cell therapy for hair loss. At EVEXIAS, we're excited to offer exosome therapy for hair loss because the quantity and quality of stem cells available in the exosome product are typically higher than PRP.

Can exosome therapy help support sexual health?

Since exosome therapy helps heal damaged tissue and regenerate new tissue, we're also delighted to offer this exciting new therapy to treat men and women who want to feel like their younger, sexier selves. The exosome product for intimate wellness includes many growth and healing factors, which provide regenerative abilities to help stimulate healing and rejuvenation.

For women, injecting exosomes into the pelvic floor and around the sexual organs may help enhance sensitivity, rejuvenate the female orgasm system and mitigate the symptoms of incontinence.

Exosome intimate wellness therapy for men helps increase the growth of new blood vessels and improve circulation in the penis, providing many benefits, including increased sexual stamina and satisfaction.

Have additional questions about exosomes and regenerative therapies?

If you'd like to learn more about exosomes, contact the EVEXIAS location nearest you. Your practitioner can explain the pros, cons and risks of exosomes and help you determine whether exosome therapy or another [regenerative therapy](#) or [aesthetic treatment](#) may be a good fit for you.

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Speaker, Author, and Board-Certified Nurse Practitioner, Dr. Terri DeNeui, DNP, ACNP, APRN-BC, has extensive training in her field. She earned her B.A in Nursing from Texas Women's University and her Master's and Doctoral degrees at UT Arlington. In addition to her training in acute and emergency medicine, she has extended her education to include certifications in Preventative Wellness Medicine, Functional Medicine and Hormone Replacement Therapy.

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- 2. A cellular protein complex containing enzymes that degrade nuclear and cytoplasmic RNA.

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Translation

Goods/Services

- IC 005. US 005 006 018 044 046 051 052.G & S: Pharmaceutical agents affecting sensory organs; Pharmaceutical agents for epidermis; Pharmaceutical agents for treating physically caused lesions; Pharmaceutical anti-allergic preparations and substances; Pharmaceutical for the **treatment** of erectile dysfunction; Pharmaceutical preparation for skin care; Pharmaceutical preparations and substances for the **treatment** of damaged skin and tissue; Pharmaceutical preparations and substances for the **treatment** of infectious diseases, blood disorders, pain, inflammation, sepsis, alopecia, obesity and cognitive disorders; Pharmaceutical preparations for animal skincare; Pharmaceutical preparations for ocular or intraocular surgery; Pharmaceutical preparations for skin care; Pharmaceutical preparations for the prevention and **treatment** of ocular disorders or diseases, bacteria-based diseases or disorders, autoimmune diseases or disorders, kidney diseases or disorders, and diabetes; Pharmaceutical preparations for the **treatment** and prevention of infectious diseases; Pharmaceutical preparations for the **treatment** of eye diseases and conditions; Pharmaceutical preparations for the **treatment** of immune system related diseases and disorders; Pharmaceutical preparations for the **treatment** of infectious diseases; Pharmaceutical preparations for treating allergic rhinitis and asthma; Pharmaceutical preparations for treating allergies; Pharmaceutical preparations for treating dandruff; Pharmaceutical preparations for treating skin disorders; Pharmaceutical preparations for treating sunburn; Pharmaceutical preparations for use in chemotherapy; Pharmaceutical preparations for use in dermatology; Pharmaceutical preparations for wounds; Pharmaceutical preparations, namely, a topical preparation for the **treatment** of ocular disorders prescribed by ophthalmologists, eye surgeons, and optometrists; Pharmaceutical preparations, namely, antivirals; Pharmaceutical products and preparations against dry skin caused by pregnancy; Pharmaceutical products and preparations for hydrating the skin during pregnancy; Pharmaceutical products and preparations for pregnancy blemishes; Pharmaceutical products and preparations for preventing skin blemishes during pregnancy; Pharmaceutical products and preparations to prevent stretch marks; Pharmaceutical products for ophthalmological use; Pharmaceutical products for skin care for animals; Pharmaceutical products for the prevention and **treatment** of cancer; Pharmaceutical products for the **treatment** of viral and infectious diseases, for the **treatment** of cancer; Pharmaceutical skin lotions; Analgesic and muscle relaxant pharmaceutical preparations; Antibacterial pharmaceuticals; Balms for pharmaceutical purposes; Chemical preparations for pharmaceutical or medical purposes, namely, for infectious diseases; Dermatological pharmaceutical products; **Drug delivery agents** consisting of compounds that facilitate delivery of a wide range of pharmaceuticals; Ocular pharmaceuticals; Plant extracts for pharmaceutical purposes. FIRST USE: 20190731. FIRST USE IN COMMERCE: 20190731
- IC 042. US 100 101.G & S: Development of pharmaceutical preparations and medicines; Research and development in the pharmaceutical and biotechnology fields; Research on the subject of pharmaceuticals; Testing of pharmaceuticals. FIRST USE: 20181130. FIRST USE IN COMMERCE: 20181130

Mark Drawing Code

(4) STANDARD CHARACTER MARK

Design Code

Serial Number

88044977

Filing Date

20180719

Current Filing Basis

1A

Original Filing Basis

1B

Publication for Opposition Date

20181113

Registration Number

6283602

Date Registered

20210302

Owner

(REGISTRANT) GLOBAL HEALTH SOLUTIONS, INC. CORPORATION DELAWARE 23632 Calabasas Rd, Suite 100 Calabasas CALIFORNIA 91302

Priority Date

Disclaimer Statement

NO CLAIM IS MADE TO THE EXCLUSIVE RIGHT TO USE "THERAPEUTICS" APART FROM THE MARK AS SHOWN

Description of Mark

Type of Mark

TRADEMARK. SERVICE MARK

Register

PRINCIPAL

Live Dead Indicator

LIVE

Attorney of Record

Todd M. Malynn

(4) STANDARD CHARACTER MARK

TABMELT

Mark Punctuated
TABMELT

Translation

Goods/Services

- IC 005. US 006 018 044 046 051 052.G & S: Drug delivery agents consisting of compounds that facilitate delivery of a wide range of pharmaceuticals; Drug delivery agents in the form of capsules that provide controlled release of the active ingredients for a wide variety of pharmaceuticals; Drug delivery agents in the form of powders that provide controlled release of the active ingredients for a wide variety of pharmaceuticals; Drug delivery agents in the form of tablets that provide controlled release of the active ingredients for a wide variety of pharmaceuticals; Drug delivery agents in the form of dissolvable tablets that facilitate the delivery of pharmaceutical preparations; Nutraceuticals for use as a dietary supplement; Pharmaceutical agents affecting digestive organs; Pharmaceutical agents affecting metabolism; Pharmaceutical agents affecting peripheral nervous system; Pharmaceutical agents affecting sensory organs; Pharmaceutical for the treatment of erectile dysfunction; Pharmaceutical preparation for skin care; Pharmaceutical preparations acting on the central nervous system; Pharmaceutical preparations and substances for the treatment of damaged skin and tissue; Pharmaceutical preparations and substances for the treatment of gastro-intestinal diseases; Pharmaceutical preparations and substances for the treatment of infectious diseases, blood disorders, pain, inflammation, sepsis, alopecia, obesity and cognitive disorders; Pharmaceutical preparations and substances for the treatment of psychiatric diseases and disorders; Pharmaceutical preparations and substances for the treatment of viral, metabolic, endocrine, musculoskeletal, cardiovascular, cardiopulmonary, genitourinary, sexual dysfunction, oncological, hepatological, ophthalmic, respiratory, neurological, gastrointestinal, hormonal, dermatological, psychiatric and immune system related diseases and disorders; Pharmaceutical preparations for inhalation for the treatment of pulmonary hypertension; Pharmaceutical preparations for peripheral nervous system; Pharmaceutical preparations for skin care; Pharmaceutical preparations for the treatment of heart rhythm disorders; Pharmaceutical preparations for the treatment of hormonal disorders and the prevention of osteoporosis; Pharmaceutical preparations for the treatment of hypercholesteremia; Pharmaceutical preparations for the treatment of hyperlipidemia; Pharmaceutical preparations for the treatment of immune system related diseases and disorders; Pharmaceutical preparations for the treatment of infectious diseases; Pharmaceutical preparations for the treatment of kidney diseases; Pharmaceutical preparations for the treatment of the cardiovascular system, the circulatory system, the endocrine system, the digestive system, the excretory system, the lymphatic system, the immune system, the muscular system, the nervous system, the renal system, the urinary system, the reproductive system, the respiratory system, and/or the skeletal system; Pharmaceutical preparations for treating allergic rhinitis and asthma; Pharmaceutical preparations for treating allergies; Pharmaceutical preparations for treating and preventing tendon and muscle injuries and disorders, sports related injuries, and for knee cartilage regeneration; Pharmaceutical preparations for treating chemical imbalances; Pharmaceutical preparations for treating diabetes; Pharmaceutical preparations for treating hypertension; Pharmaceutical preparations for treating skin disorders; Pharmaceutical preparations for use in dermatology; Pharmaceutical

preparations for use in urology; Pharmaceutical preparations, namely, a blood clotting aid and delivery system for use in human and veterinary medicine; Pharmaceutical preparations, namely, an analgesic for human consumption taken orally; Pharmaceutical preparations, namely, anticoagulants; Pharmaceutical products for the prevention and treatment of cancer; Pharmaceutical products for the treatment of bone diseases; Pharmaceutical products for the treatment of joint disease; Pharmaceutical products for the treatment of viral and infectious diseases, for the treatment of cancer; Pharmaceutical products for treating respiratory diseases; Pharmaceutical products for treating respiratory diseases and asthma; Pharmaceutical solutions used in dialysis; Pharmaceuticals for the treatment of erectile dysfunction; Pharmaceuticals, namely, lipid lowering agents; Pharmaceuticals, namely, psychotropics; Vaccine preparations; Cardiovascular pharmaceuticals; Chemical preparations for pharmaceutical or medical purposes, namely, for the endocannabinoid; Human vaccine preparations; Oral vaccine preparations; Pharmaceutical preparations, namely, a drug delivery system comprising polymer-based oral tablets for the continuous release of a wide variety of therapeutic agents. FIRST USE: 20180103. FIRST USE IN COMMERCE: 20180505

Mark Drawing Code

(4) STANDARD CHARACTER MARK

Design Code

Serial Number

87718255

Filing Date

20171212

Current Filing Basis

1A

Original Filing Basis

1B

Publication for Opposition Date

Registration Number

5771628

Date Registered

20190604

Owner

(REGISTRANT) Sentar Pharmaceuticals CORPORATION NEVADA 17809 Gillette Avenue Irvine CALIFORNIA 92614

Priority Date

Disclaimer Statement

Description of Mark

Type of Mark

TRADEMARK

Register

SUPPLEMENTAL

Live Dead Indicator

LIVE

Attorney of Record
Samuel Fifer

(4) STANDARD CHARACTER MARK

PHOREUS

Mark Punctuated
PHOREUS

Translation

Goods/Services

- IC 001. US 001 005 006 010 026 046.G & S: Biological preparations for in vitro use in laboratories; chemical, biological, and diagnostic reagents and preparations for scientific, medical and veterinary research use; biological preparations, other than for medical use, namely, for use in biotechnological product development, manufacture of vaccines, drugs and medicines; biochemical reagents in the form of peptide capsules, microspheres, or nanospheres used for non-medical purposes; transfection reagents in the form of peptide capsules, microspheres, or nanospheres for transfecting cells for scientific and research use; peptide-based fertilizers as vehicles to deliver active substances in the nature of horticultural preparations, plant nutrients, and soil amendments. FIRST USE: 20171024. FIRST USE IN COMMERCE: 20180927
- IC 005. US 006 018 044 046 051 052.G & S: Pharmaceutical and veterinary preparations for the **treatment** of infectious diseases and/or **treatment** or prevention of cancer; diagnostic preparations for medical or veterinary purposes; peptide-based preparations and substances for drug delivery, namely, **drug delivery agents** for active ingredients in the nature of nucleic acids, proteins, enzymes, small molecules, therapeutic drugs, organic compounds, plasmids, dyes, nutrients, minerals, colloidal metal, pesticides, insecticides, parasiticides, and fungicides; peptides for drug delivery, namely, **drug delivery agents** consisting of peptide capsules, microspheres, or nanospheres containing or attached to active substances that facilitate delivery of a wide variety of pharmaceutical or veterinary preparations; peptide-based preparations for destroying vermin; fungicides; herbicides; imaging agents in the form of peptide capsules, microspheres, or nanospheres for medical and veterinary diagnostic purposes, namely, contrasting agents for ultrasound or near-infrared diagnostic imaging, diagnostic radiopharmaceutical agent for use in pet imaging, imaging agents for magnetic resonance imaging (MRI), radiopharmaceutical imaging agents for diagnosing and monitoring cancer. FIRST USE: 20171024. FIRST USE IN COMMERCE: 20180927
- IC 042. US 100 101.G & S: Research and development for others in the field of pharmaceutical and veterinary preparations and diagnostic agents; design and custom development for others of peptide-based preparations and substances as vehicles for delivery of active ingredients, namely, nucleic acids, proteins, enzymes, small molecules, therapeutic drugs, organic compounds, plasmids dyes, nutrients, minerals, colloidal metal, pesticides, insecticides, parasiticides, fungicides, and fertilizers; design and custom development for others of transfection reagents in the form of peptide capsules, microspheres, or nanospheres for transfecting cells. FIRST USE: 20171024. FIRST USE IN COMMERCE: 20180927

Mark Drawing Code

(4) STANDARD CHARACTER MARK

Design Code

Serial Number

88157215

Filing Date
20181016

Current Filing Basis
1A

Original Filing Basis
1B

Publication for Opposition Date
20190903

Registration Number
6257608

Date Registered
20210126

Owner
(REGISTRANT) PHOREUS BIOTECHNOLOGY, INC. CORPORATION KANSAS 22201 W. Innovation
Drive Olathe KANSAS 66061

Priority Date

Disclaimer Statement

Description of Mark

Type of Mark
TRADEMARK. SERVICE MARK

Register
PRINCIPAL

Live Dead Indicator
LIVE

Attorney of Record
Crissa A. Cook

(4) STANDARD CHARACTER MARK

SLTX

Mark Punctuated
SLTX

Translation

Goods/Services

- IC 001. US 001 005 006 010 026 046.G & S: Chemical agents for coating of medical devices and medical materials; reagents for research purposes; reagents for scientific or medical research use. FIRST USE: 20200917. FIRST USE IN COMMERCE: 20200917
- IC 005. US 006 018 044 046 051 052.G & S: Chemical, pharmaceutical, biopharmaceutical and biomedical agents for medical use, namely, pharmaceutical agents for modulating immune response; chemical agents for pharmaceutical or medical purposes, namely, pharmaceutical agents for modulating immune response; pharmaceutical agents for encapsulating transplanted cells to prevent the risk of rejection from immune attack, for medical purposes; pharmaceutical preparations for the prevention and **treatment** of fibrosis, inflammation, cancer or infection; **drug delivery agents** in the form of coatings for capsules that facilitate the tolerance and delivery of pharmaceutical preparations; chemical agents, namely, **drug delivery agents** in the form of coatings that facilitate the delivery of pharmaceutical agents and cells. FIRST USE: 20200728. FIRST USE IN COMMERCE: 20200728

Mark Drawing Code

(4) STANDARD CHARACTER MARK

Design Code

Serial Number

88197578

Filing Date

20181116

Current Filing Basis

1A

Original Filing Basis

1B

Publication for Opposition Date

20190409

Registration Number

6201037

Date Registered

20201117

Owner

(REGISTRANT) Sigilon Therapeutics, Inc. CORPORATION DELAWARE 100 Binney Street, Suite 600

Cambridge MASSACHUSETTS 02142

Priority Date

Disclaimer Statement

Description of Mark

Type of Mark

TRADEMARK

Register

PRINCIPAL

Live Dead Indicator

LIVE

Attorney of Record

Ann Lamport Hammitte

(4) STANDARD CHARACTER MARK

Cetosomes

Mark Punctuated
CETOSOMES

Translation

Goods/Services

- IC 005. US 006 018 044 046 051 052.G & S: Drug delivery agents consisting of compounds that facilitate delivery of a wide range of pharmaceuticals; Drug delivery agents in the form of a coating for biological actives that facilitate the delivery of a wide range of pharmaceuticals; Drug delivery agents in the form of nanoparticles that facilitate the delivery of pharmaceutical preparations; Pharmaceutical preparations and substances for the treatment of damaged skin and tissue; Pharmaceutical preparations and substances for the treatment of infectious diseases, blood disorders, pain, inflammation, sepsis, alopecia, obesity and cognitive disorders; Pharmaceutical preparations and substances for the treatment of viral, metabolic, endocrine, musculoskeletal, cardiovascular, cardiopulmonary, genitourinary, sexual dysfunction, oncological, hepatological, ophthalmic, respiratory, neurological, gastrointestinal, hormonal, dermatological, psychiatric and immune system related diseases and disorders. FIRST USE: 20150721. FIRST USE IN COMMERCE: 20181101

Mark Drawing Code

(4) STANDARD CHARACTER MARK

Design Code

Serial Number
88388677

Filing Date
20190416

Current Filing Basis
1A

Original Filing Basis
1A

Publication for Opposition Date
20200303

Registration Number
6056485

Date Registered
20200519

Owner

(REGISTRANT) Cymbiotics, Inc. CORPORATION NEVADA 135 St. James Drive Sonoma CALIFORNIA 95476

Priority Date

Disclaimer Statement

Description of Mark

Type of Mark

TRADEMARK

Register

PRINCIPAL

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LIVE

Attorney of Record

CHRIS POPOV

(4) STANDARD CHARACTER MARK

MiDROPS

Mark Punctuated
MIDROPS

Translation

Goods/Services

- IC 005. US 006 018 044 046 051 052.G & S: Eye drops; Ophthalmic preparations; Pharmaceutical agents affecting sensory organs; Pharmaceutical anti-allergic preparations and substances; Pharmaceutical preparations and substances for the **treatment** of infectious diseases, blood disorders, pain, inflammation, sepsis, alopecia, obesity and cognitive disorders; Pharmaceutical preparations for ocular or intraocular surgery; Pharmaceutical preparations for skin wounds; Pharmaceutical preparations for the prevention and **treatment** of ocular disorders or diseases, bacteria-based diseases or disorders, autoimmune diseases or disorders, kidney diseases or disorders, and diabetes; Pharmaceutical preparations for the prevention and **treatment** of ocular disorders or diseases, for the **treatment** of bacteria-based diseases, and for the **treatment** of diabetes, and anti - infective preparations, antiviral preparations, antibiotics, antifungal preparations and vaccines; Pharmaceutical preparations for the **treatment** of eye diseases and conditions; Pharmaceutical preparations for the **treatment** of infectious diseases; Pharmaceutical preparations for treating allergies; Pharmaceutical preparations, namely, a topical preparation for the **treatment** of ocular disorders prescribed by ophthalmologists, eye surgeons, and optometrists; Pharmaceutical preparations, namely, antivirals; Pharmaceutical products for ophthalmological use; Antibiotic preparations; **Drug delivery agents** consisting of compounds that facilitate delivery of a wide range of pharmaceuticals; **Drug delivery agents** in the form of emulsions that facilitate the delivery of pharmaceutical preparations; **Drug delivery agents** in the form of micelle that facilitate the delivery of pharmaceutical preparations; Ocular pharmaceuticals; Ophthalmologic preparations; Ophthalmological preparations; Optic preparations; Pharmaceutical preparations and substances for the **treatment** of viral, metabolic, endocrine, musculoskeletal, cardiovascular, cardiopulmonary, genitourinary, sexual dysfunction, oncological, hepatological, ophthalmic, respiratory, neurological, gastrointestinal, hormonal, dermatological, psychiatric and immune system related diseases and disorders. FIRST USE: 20150503. FIRST USE IN COMMERCE: 20150503

Mark Drawing Code

(4) STANDARD CHARACTER MARK

Design Code

Serial Number

88199169

Filing Date

20181119

Current Filing Basis

1A

Original Filing Basis

1A

Publication for Opposition Date
20190604

Registration Number
6170100

Date Registered
20201006

Owner
(REGISTRANT) EyeCRO LLC LIMITED LIABILITY COMPANY OKLAHOMA 5301 N. Beverly Drive
Oklahoma City OKLAHOMA 73105

Priority Date

Disclaimer Statement

Description of Mark

Type of Mark
TRADEMARK

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LIVE

Attorney of Record
Gordon R. Moriarty

(4) STANDARD CHARACTER MARK

CORMUNE

Mark Punctuated
CORMUNE

Translation

Goods/Services

- IC 005. US 005 006 018 044 046 051 052.G & S: Anti-cancer preparations; Anti-diabetic pharmaceuticals; Anti-diabetic preparations; Anti-inflammatories; Anti-inflammatory preparations; Antidiabetic preparations; Antihistamines; Antivirals; Dietary supplements; Dietary supplements for pets; **Drug delivery agents** consisting of compounds that facilitate delivery of a wide range of pharmaceuticals; **Drug delivery agents** in the form of capsules that provide controlled release of the active ingredients for a wide variety of pharmaceuticals; **Drug delivery agents** in the form of edible wafers for wrapping powdered pharmaceuticals; **Drug delivery agents** in the form of powders that provide controlled release of the active ingredients for a wide variety of pharmaceuticals; **Drug delivery agents** in the form of tablets that provide controlled release of the active ingredients for a wide variety of pharmaceuticals; Food for babies; Food for infants; Food supplements; Medical dressings; Medical plasters; Medicated dentifrices; Medicated shampoo; Medicated shampoos; Medicated soap; Medicated soaps; Medicated sweets; Nutritional and dietary supplements formed and packaged as bars; Nutritional supplement energy bars; Nutritional supplement for eliminating toxins from the body; Nutritional supplement meal replacement bars for boosting energy; Nutritional supplement shakes; Nutritional supplements; Nutritional supplements in capsule form for dogs; Nutritional supplements in lotion form sold as a component of nutritional skin care products; Nutritional supplements in the nature of nutritionally fortified soft chews; Nutritionally fortified beverages for medical purposes; Nutritive substances for micro-organisms for medical use; Nutritive substances for microorganism cultures; Pharmaceutical preparations for animal skincare; Pharmaceutical preparations for treating allergies; Pharmaceutical preparations for treating diabetes; Pharmaceutical preparations for use in dermatology; Pharmaceutical preparations for use in urology; Pharmaceutical preparations, namely, antidepressants; Prebiotic supplements; Probiotic animal feed; Probiotic preparations for medical use; Probiotic supplements; Vaccine adjuvants; Vaccine preparations; Vaccine stabilizers; Vaccines; Vaccines against flu; Vaccines against pneumococcal infections; Vaccines for cattle; Vaccines for horses; Adjuvants for use with vaccines; Amino acids for nutritional purposes; Animal feed additive for use as a nutritional supplement for medical purposes; Animal feed additives for use as nutritional supplements; Baby food; Candy, medicated; Central nervous system stimulants; Cultures of microorganisms for medical or veterinary use; Dietary and nutritional supplements; Dietary and nutritional supplements for endurance sports; Dietary supplement for eliminating toxins from the intestinal tract; Fungal extracts sold as a component ingredient of nutritional supplements and vitamins; Gastro-intestinal **treatment** preparations; Hair growth stimulants; Human vaccine preparations; Ketogenic dietary and nutritional supplements; Ketogenic dietary and nutritional supplements used for weight loss; Liquid nutritional supplement; Medicated mouth care and **treatment** preparations; Medicated mouth washes; Medicated anti-cavity mouth rinses; Medicines for intestinal disorders; Mineral nutritional supplements; Natural remedy preparations for the **treatment** of gastro-intestinal conditions, hormonal and chemical imbalances, and sleep disorders; Non-medicated additives

for animal feed for use as nutritional supplements; Nutritional supplement for eliminating toxins from the intestinal tract; Nutritional supplements, namely, probiotic compositions; Nutritive substances for microorganisms for medical purposes; Oral vaccine preparations; Pharmaceutical preparations and substances for the **treatment** of gastro-intestinal diseases; Pharmaceutical preparations and substances for the **treatment** of viral, metabolic, endocrine, musculoskeletal, cardiovascular, cardiopulmonary, genitourinary, sexual dysfunction, oncological, hepatological, ophthalmic, respiratory, neurological, gastrointestinal, hormonal, dermatological, psychiatric and immune system related diseases and disorders; Pharmaceutical preparations for the **treatment** of hormonal disorders; Pharmaceutical preparations for the **treatment** of hormonal disorders and the prevention of osteoporosis; Pharmaceutical preparations for the **treatment** of immune system related diseases and disorders; Pharmaceutical preparations, namely, antivirals; Pharmaceutical preparations, namely, a drug delivery system comprising polymer-based oral tablets for the continuous release of a wide variety of therapeutic agents; Powdered nutritional supplement concentrate; Powdered nutritional supplement drink mix; Respiratory stimulants; Therapeutic vaccines; Vegan protein for use as a nutritional supplement in ready-to-drink beverages; Veterinary vaccine for horses; Veterinary vaccines; Veterinary preparations for **treatment** of intestinal bacteria.
FIRST USE: 20200101. FIRST USE IN COMMERCE: 20200626

Mark Drawing Code

(4) STANDARD CHARACTER MARK

Design Code

Serial Number

88867322

Filing Date

20200410

Current Filing Basis

1A

Original Filing Basis

1B

Publication for Opposition Date

20200811

Registration Number

6296869

Date Registered

20210316

Owner

(REGISTRANT) CHANDLER BIOPHARMACEUTICAL INC. DBA CHANDLER
BIOPHARMACEUTICAL CORPORATION INDIANA 2206 TOLEDO ROAD ELKHART INDIANA 46516

Priority Date

Disclaimer Statement

Description of Mark

Type of Mark

TRADEMARK

Register

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Attorney of Record



HARVARD CATALYST

Harvard Catalyst Profiles

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Pharmaceutical Preparations

"Pharmaceutical Preparations" is a descriptor in the National Library of Medicine's controlled vocabulary thesaurus, MeSH (Medical Subject Headings). Descriptors are arranged in a hierarchical structure, which enables searching at various levels of specificity.

MeSH information

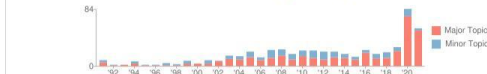
Definition | Details | More General Concepts | Related Concepts | More Specific Concepts

Drugs intended for human or veterinary use, presented in their finished dosage form. Included here are materials used in the preparation and/or formulation of the finished dosage form.

publications

Timeline | Most Recent

This graph shows the total number of publications written about "Pharmaceutical Preparations" by people in Harvard Catalyst Profiles by year, and whether "Pharmaceutical Preparations" was a major or minor topic of these publication.



To see the data from this visualization as text, [click here](#).

Related Networks

People

- Bates, David
- Kesselheim, Aaron
- Langer, Robert
- Darrow, Jonathan
- Sarpawatari, Armeet

Explore

Similar Concepts

- Drug Industry
- Legislation, Drug
- Medication Errors
- Patents as Topic
- Polymers
- United States Food and Drug Administration
- Drug Costs
- Drugs, Generic
- Drug Approval
- Prescription Drugs

Top Journals

- N Engl J Med
- JAMA
- J Pharm Sci
- J Control Release
- PLoS One
- Nat Rev Drug Discov
- BMJ
- Clin Pharmacol Ther
- Adv Drug Deliv Rev
- Annu Rev Pharmacol Toxicol

United States Patent and Trademark Office (USPTO)

USPTO OFFICIAL NOTICE

Office Action (Official Letter) has issued
on December 08, 2021 for
U.S. Trademark Application Serial No. 79209128

A USPTO examining attorney has reviewed your trademark application and issued an Office action. You must respond to this Office action in order to avoid your application abandoning. Follow the steps below.

- (1) **Read the Office action [HERE](#).** This email is NOT the Office action.
- (2) **Respond to the Office action by the deadline** using the Trademark Electronic Application System (TEAS). Your response must be received by the USPTO on or before 11:59 p.m. **Eastern Time** of the last day of the response period. Otherwise, your application will be [abandoned](#). See the Office action itself regarding how to respond.
- (3) **Direct general questions** about using USPTO electronic forms, the USPTO [website](#), the application process, the status of your application, and whether there are outstanding deadlines to the [Trademark Assistance Center \(TAC\)](#).

After reading the Office action, address any question(s) regarding the specific content to the USPTO examining attorney identified in the Office action.

GENERAL GUIDANCE

- **[Check the status of your application periodically](#)** in the [Trademark Status & Document Retrieval \(TSDR\)](#) database to avoid missing critical deadlines.
- **[Update your correspondence email address](#)** to ensure you receive important USPTO notices about your application.
- **[Beware of misleading notices sent by private companies about your application.](#)** Private companies not associated with the USPTO may mail or email you trademark-related offers and notices - most of which require fees. The USPTO will only email **official USPTO correspondence from the domain "@uspto.gov"**.
- **[Hiring a U.S.-licensed attorney.](#)** If you do not have an attorney and are not required to have one under the trademark rules, we encourage you to hire a U.S.-licensed attorney specializing in trademark law to help guide you through the registration process. The

USPTO examining attorney identified above is not your attorney and cannot give you legal advice, but rather works for and represents the USPTO in trademark matters.