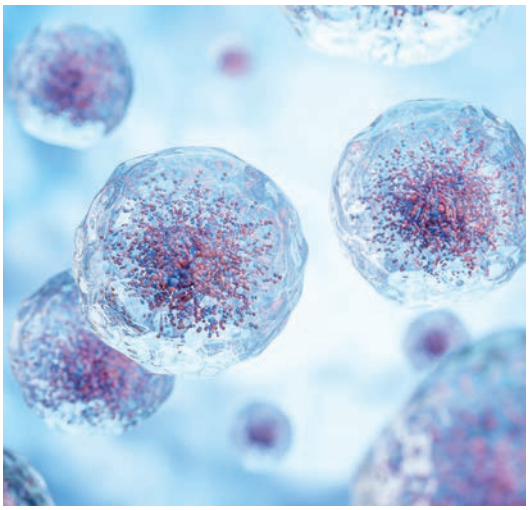
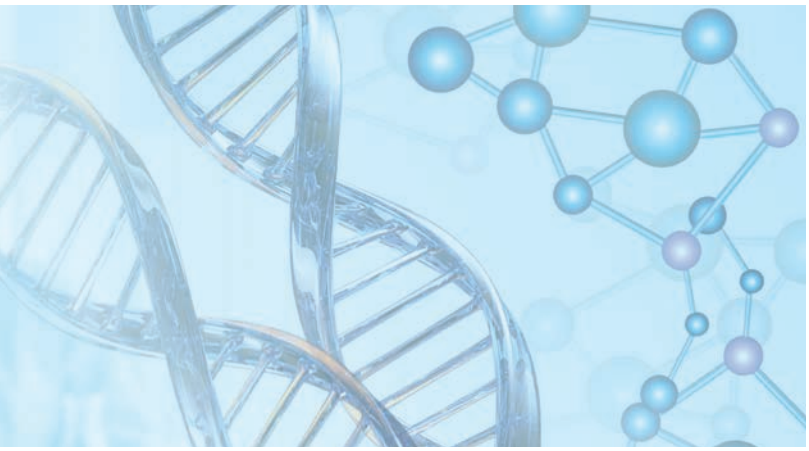




ZEOSCIENTIFIX™

The Nation's Leading Therapeutics Research Company
Pioneering Innovative Technologies in Regenerative Medicine

Founded in 2008, ZEO Scientifix is a publicly traded biotech company (OTCMKTS: ZEOX) committed to the research, development, and manufacturing of new biologic medicine. Our focus is on current and potential tissue-derived regenerative therapeutics. ZEO is a leading, fully integrated Biologic Medicine Company. **Our mission is to transform regenerative medicine through development of novel nanotechnologies and to become the health care incubator for the next generation of biologic medicines.**

ZEO Science Team

Mike Bellio, Ph.D

Vice President, Manufacturing & Processing

As the Vice President of Research and Manufacturing at ZEO ScientifiX, Dr. Bellio leads the research, development, and manufacturing of novel biologics. Dr. Bellio earned a PhD in Molecular and Cellular Pharmacology at the University of Miami's Interdisciplinary Stem Cell Institute (ISCI), where he received comprehensive training in cGMP manufacturing of primary stem cells and extracellular vesicles for pre-clinical and clinical trial applications.

George Shapiro MD, FACP

Chief Medical Officer

Dr. Shapiro has been a practicing physician for 30 years, specializing in Internal Medicine, Cardiovascular Disease and Age Management Medicine. His career in medicine began in 1988 when he graduated from New York Medical College. An internship and residency then followed at Albert Einstein College of Medicine, after which he completed a fellowship at Columbia University College of Physicians and Surgeons in 1994, focusing on Cardiovascular Disease Management, including Congestive Heart Failure and Heart Transplantation.

Ivan Santos
Biologics Manufacturing Manager

Cassie Bennett, Ph.D.
Senior Quality Assurance Scientist

Lillian Davis, RN/ACRP-CP
Associate Director of Clinical Development

Julian Milberg, M.S.
Senior Process Engineer

Zanub Abdullah
Clinical Processing Specialist

Mohamed-Tamar Toussaint, M.S.
Laboratory Technician

Maria Saavedra
Quality Assurance Associate

Quintin Spey, M.S.
Quality Assurance Associate

ZEO Research Center

ZEO ScientifiX operates an analytical research laboratory and a cGMP manufacturing facility within Nova Southeastern University's Center for Collaborative Research Center located in Davie, Florida. ZEO ScientifiX's manufacturing facility is registered with the US FDA as a Human Cell and Tissue Establishment. Product manufacturing is performed in a designated clean room space qualified to maintain air quality of ISO-Class 7 (ISO 14644, previously Class 10,000) standards. All tissue handling and final product filling is completed within a certified Class II A2 Biological Safety Cabinet in the clean room space. Environmental monitoring controls are standardized to monitor air and surface quality in both ambient conditions and during active procedures. ZEO ScientifiX's analytical research lab contains essential equipment for extracellular vesicle product development and testing. Critical equipment includes fluorescent nanoparticle analyzers, absorbent and florescent plate readers, flow cytometers, fluorescent microscopes, endotoxin testing system, microbiology culture systems, quantitative PCR machines, high to ultra-speed centrifuges, and various cold storage.

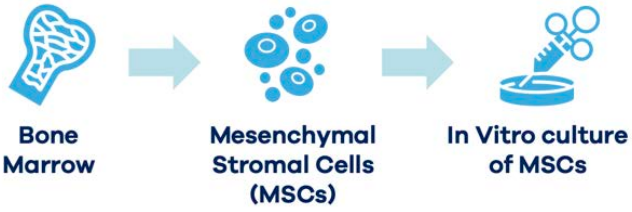
cGMP COMPLIANT

FDA REGISTERED FACILITY

ZEO's proprietary patented products are derived from allogenic and autologous sources and are manufactured in an FDA registered, cGMP compliant laboratory.

NOT ALL EXOSOMES ARE CREATED EQUAL

Culture Expanded Cells



- Requires weeks of in vitro expansion
- Exosome cargo dependent on lab conditions
- Sourced from a single cell type

Biological Fluids

- Saliva
- Urine
- Breast milk
- Semen
- Plasma / Serum
- Amniotic fluid
- Cerebrospinal Fluid
- Ascites fluid

- Minimal Manipulation
- Extraction of naturally occurring Exosomes
- Heterogeneous exosome mixture of multiple cell sources

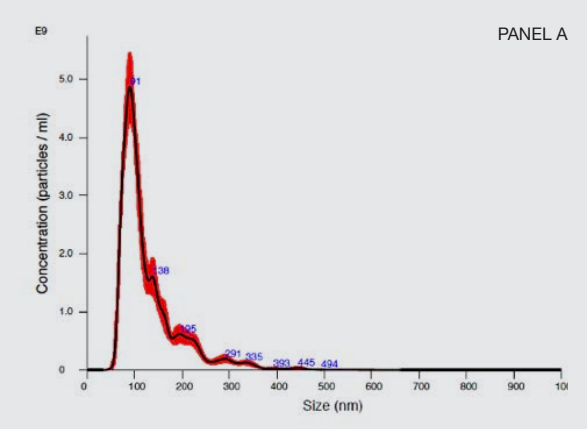
The ZEO ScientifiX Difference

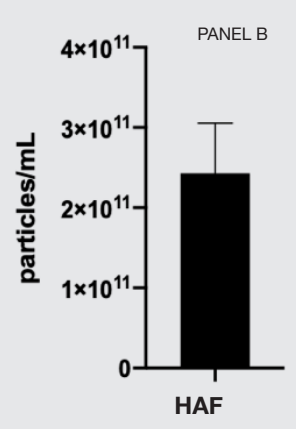
ZEO exosomes are derived from biological fluids, specifically amniotic fluid or whole blood, in a proprierty manner and are considered one the purest forms of extracellular vesicles. Amniotic fluid is immunologically “neutral”, offering the highest concentrations of exosomes (EVs).

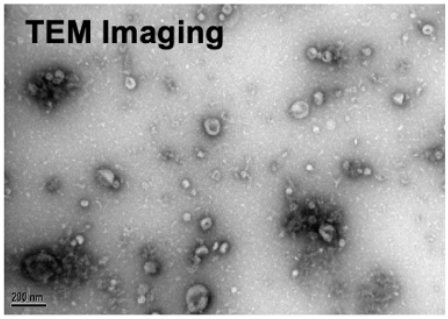
ZEO’s patent pending process of autologous exosomes is the first of its kind. The proprietary method of isolation and analysis from a simple blood draw concentrates up to 600 billion exosomes per milliliter.

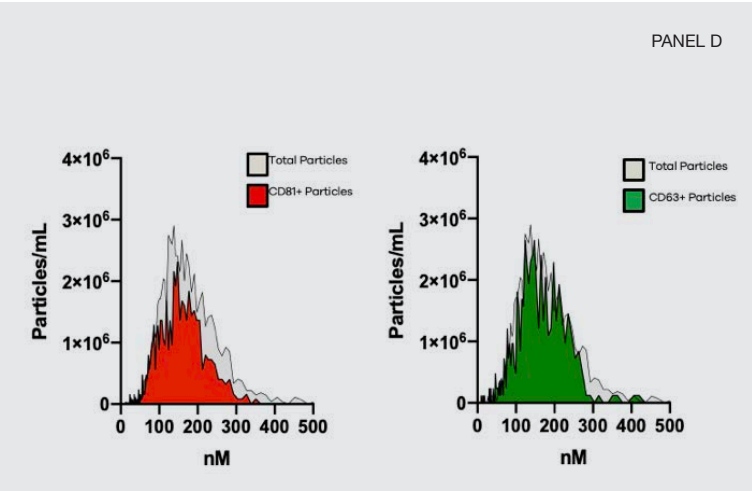
Our ground-breaking research and multiple peer reviewed papers demonstrate the therapeutic potential of nanotechnology. Each biologic contains ultra-high concentrations of billions of nanoparticles per mL with cargo including miRNA, RNA, bioactive proteins, lipids, and enzymes that reduce inflammation and promote tissue regeneration.

ZEO ScientifiX's technology is designed to convert natural biofluids containing rich exosomes into concentrated exosome therapeutics. Using various forms of fluorescent nanoparticle tracking analysis and imaging, we can confirm the isolation and manufacturing of these products.









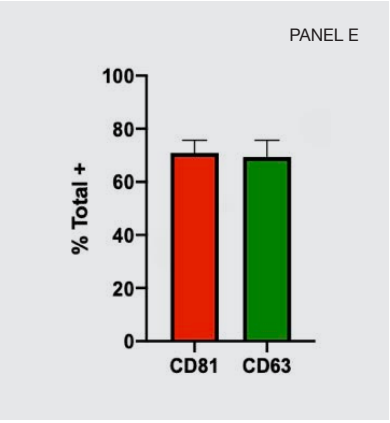


Figure 1: Representative Analysis of Exosome Products: A) Nanoparticle tracking analysis and size distribution analysis of processed AF-derived product. B) The average particles per mL concentration of processed AF-derived. C) Representative TEM image of nanoparticles isolated from product. D) fluorescent nanoparticle tracking analysis of CD81+ and CD63+ particles compared to the total unstained particles. E) The average percentage of CD81+ and CD63+ particles. Error bars represent standard error of the mean.

ZEO ScientifiX tests their products in various pre-clinical models to determine therapeutic potential. In one model, amniotic fluid-derived exosomes were tested in a lung injury model to demonstrate immunomodulatory, anti-inflammatory, and tissue reparative effects. In this model, administration of amniotic fluid-derived exosomes protected the lung tissue, reduced inflammatory cell invasion, and blocked the expression of multiple pro-inflammatory cytokines.

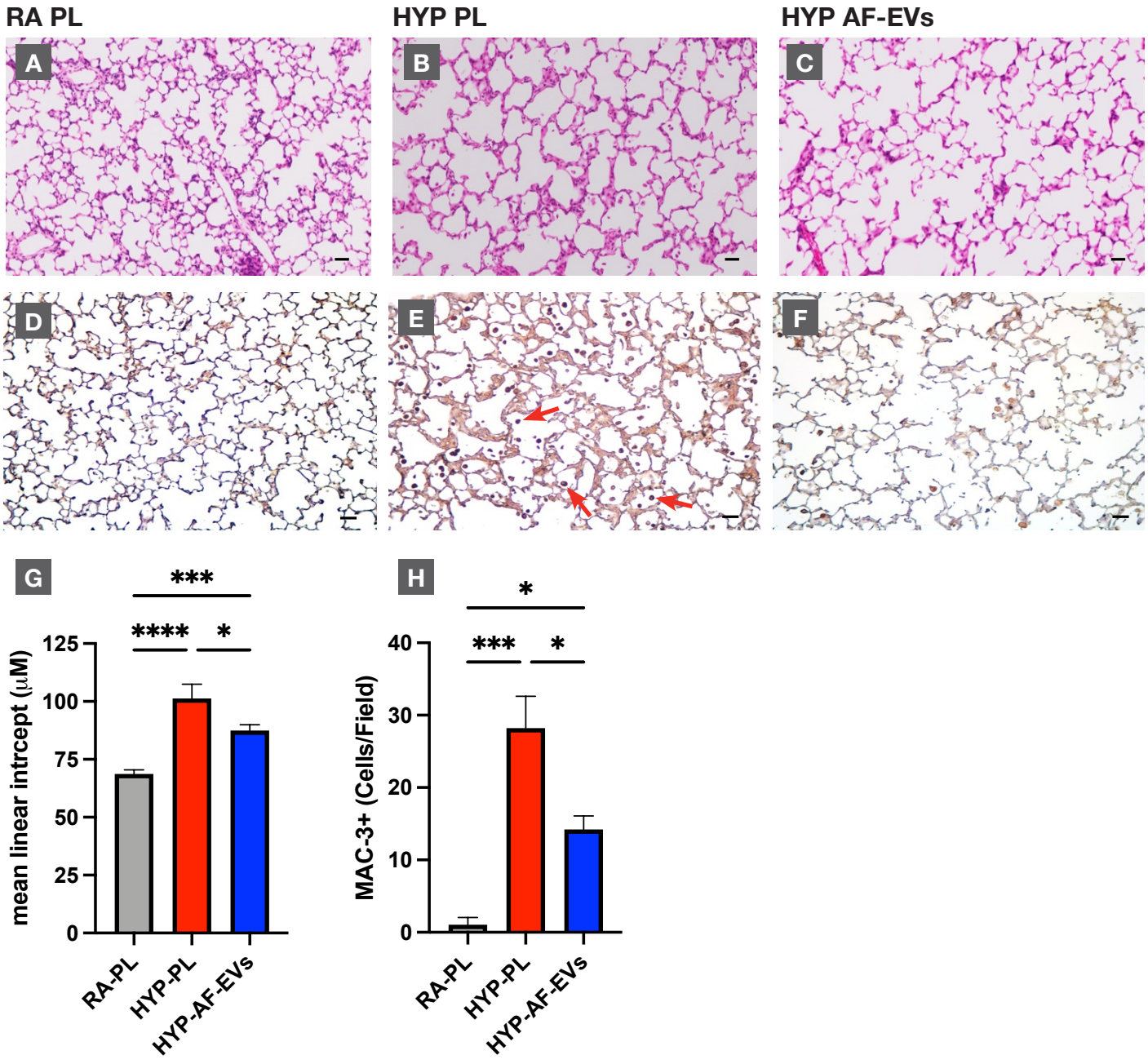


Figure: AF-EVs Prevent Damage to Alveolar Structure and Reduce Macrophage Invasion. A-C) Histology staining of lung alveolar structure. Hyperoxia placebo (HYP PL) showed damaged alveolar structure compared to the room air placebo (RA PL) control. Treatment with amniotic fluid-derived exosomes in hyperoxia (HYP AF-Evs) improved lung structure compared to HYP PL. D-F) Histology staining of MAC3+ macrophages in the lung tissue. Hyperoxia placebo (HYP PL) showed increased macrophage invasion compared to the room air placebo (RA PL) control. Treatment with amniotic fluid-derived exosomes in hyperoxia (HYP AF-Evs) reduced macrophage invasion compared to HYP PL. G) Quantification of the alveolar mean linear intercept in each of the three groups. Arrows indicate an example of macrophage staining. H) Quantification of MAC-3+ macrophages in the lung tissue in each of the three groups. Imaged magnification is 20X. Black or white magnification scale bars, bottom right of image, represent 50μM. Error bars represent standard error of the mean. * p-value <0.05, *** p-value <0.001, **** p-value <0.0001.

Figure Referenced From Bellio et al. Cytotherapy 23:12, Dec 21; 1097-1107

Read Published Study at: ZeoScientifiX.com

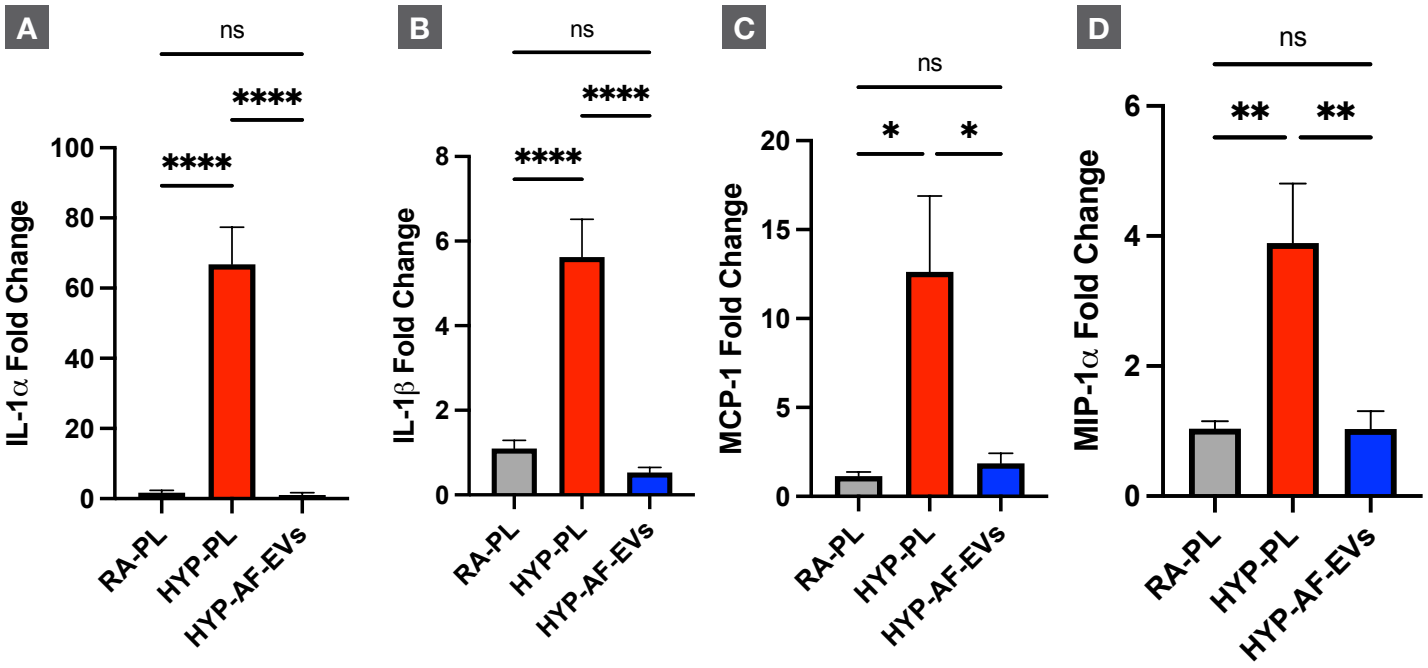


Figure: The Effect of Amniotic Fluid-derived Exosome Administration on Inflammatory Cytokine Expression in the Lungs. Decreased mRNA gene expression was found in injured and exosome treated animals (HYP-AF-EVs) compared to the lung injury group (HYP-PL). A) Fold change of IL-1α RNA expression in each group relative to RA-PL. B) Fold change of IL-1β RNA expression in each group relative to RA-PL. C) Fold change of MCP-1, RNA expression in each group relative to RA-PL. D) Fold change of MIP-1α RNA expression in each group relative to RA-PL. n=6/group. Error bars represent standard error of the mean. * p-value <0.05, **p-value <0.01, **** p-value <0.0001.

Figure Referenced From Bellio et al. Cytotherapy 23:12, Dec 21; 1097-1107

Read Published Study at: ZeoScientifiX.com

PPX™

By ZEOSCIENTIFIX™

PPX™ is a first-of-its-kind concentrated autologous exosome product that contains nanoparticles and proteins extracted from the patient's blood that can decrease elements of cellular inflammation and promote tissue healing.

PPX™ goes beyond PRP as an autologous blood-derived biologic that concentrates only the regenerative fraction of the patients' blood, specifically the exosomes and other bioactive proteins. The proprietary high-speed centrifugation process isolates approximately 400 billion exosomes. Once placed in the body, these powerful exosome messengers immediately begin the cascade of cellular reprogramming and tissue repair.

The specific exosomes isolated in PPX™ contain many bioactive proteins and miRNA markers which are considered the mechanism of action that reduces inflammation and induces regeneration at the cellular level.

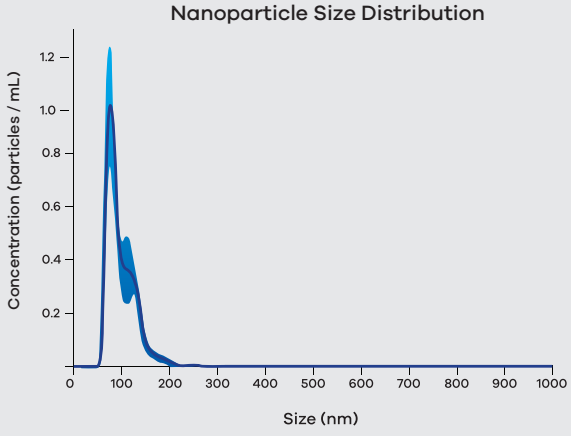
FEATURES	PPX™	PRP
Concentrated plasma fraction rich in nanoparticles	✓	✗
Cell reprogramming for long term physiological changes	✓	✗
Cell-free, Non-HCT/P product*	✓	✗
FDA-compliant laboratory facility	✓	✗
Tested free of microbial contamination and endotoxins	✓	✗

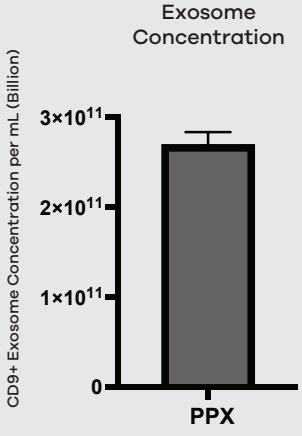
*Non-human cells, tissues and cellular and tissue-based products

PPX™ — The Next Generation Biologic – Autologous Exosomes

Nanoparticle Quantification

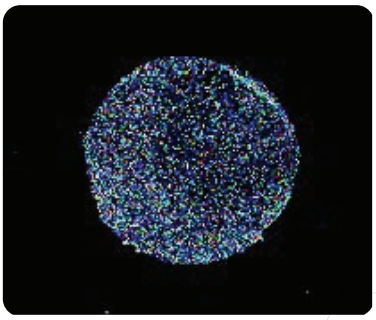
Targeted nanoparticle tracking analysis to quantify the specific exosome fraction.





Extracellular Vesicle Identification

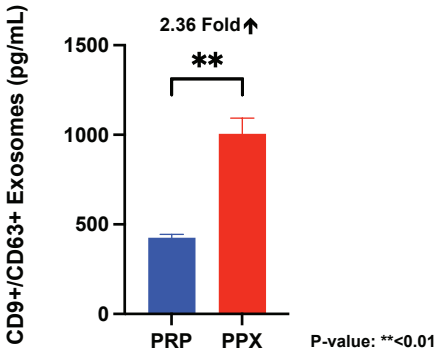
Exo Dot immunofluorescent analysis reveals the presence of Extracellular Vesicles (CD9+) in PPX™.



PPX™ vs PRP — Exosome Concentration & Nanoparticle Purity

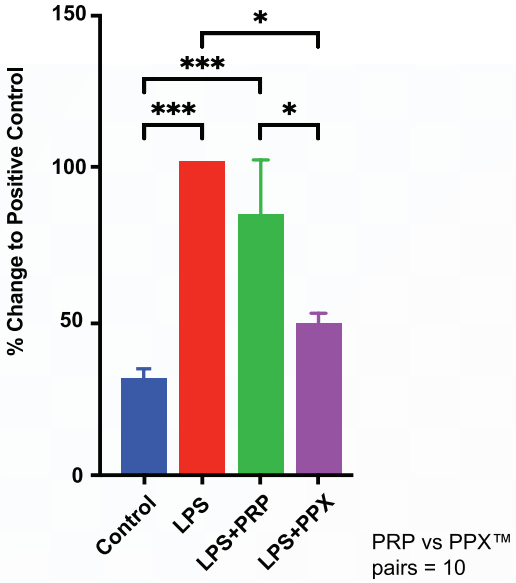
Exosome Concentration

CD9-CD63 ELISA Analysis quantifies the concentration of exosomes in PRP vs PPX™



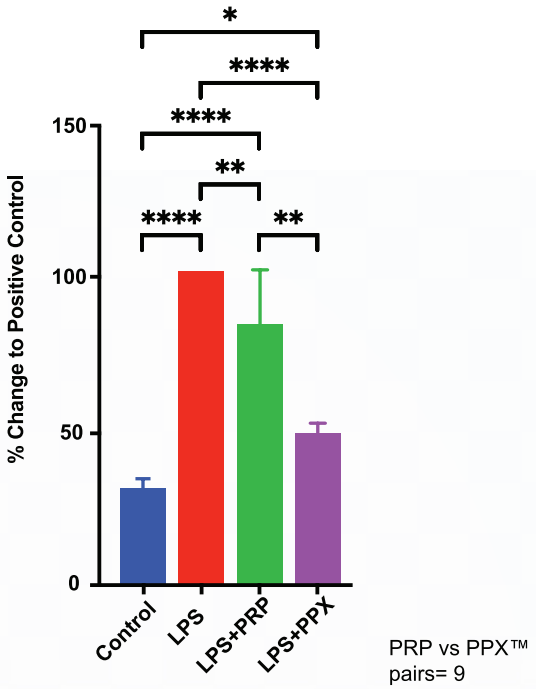
PPX™ vs. PRP — Impact on Inflammatory Markers (IL-6 and IL-1β)

Measurement of IL-6 mRNA Expression



PRP vs PPX™ pairs = 10

Measurement of IL-1β Protein Secretion



PRP vs PPX™ pairs= 9

P-values: * <0.5, **<0.01, ***<0.001, ****<0.0001

- Monocytes are converted to M1-type Macrophages (pro-inflammatory) with the addition of LPS (lipopolysaccharide,) resulting in expression of Il-6 and IL-1β cytokines.
- IL-6 and IL-1β are well known markers of inflammation.
- PPX™ has a significantly more potent effect than PRP at reducing these inflammatory markers – and this effect is more consistent with PPX™ than PRP.

PPX™ Compared to PRP

- Using an ELISA technology, PPX™ was shown to have TWICE (2.4) the concentration of exosomes than PRP in multiple subjects.
- Using a highly specific CD9+ assay, in multiple test subjects, the purity of exosomes (that have the CD9+ surface marker) in PPX™ was 3X that of PRP.
- PPX™ has a more potent anti-inflammatory effect than PRP - as demonstrated by the reduction of IL-6 and IL-1β secreted from M1 (pro-inflammatory) macrophages.
- This research is helpful in understanding why, in clinical practice, PPX™ typically generates a very rapid anti-inflammatory response (and reduction in pain,) which does not generally occur with PRP.

Additional Supportive RESEARCH

To date, studies have shown the great potential of PRP derived-EVs in the field of tissue repair and regeneration and, to some extent, revealed their related mechanisms. Recent findings suggest that PRP-exosomes may be a superior alternative in regenerative medicine, compared to the well-studied PRP. [1-4,7]

Although it remains to be further demonstrated, PRP-exosomes may have more significant advantages over PRP in regenerative medicine for the following reasons:

- some studies have confirmed the higher concentration of growth factors in PRP-exosomes as compared to PRP1-3;
- the smaller size of PRP-exosomes is beneficial for their transfer across biological barriers and helps to retain stability in the extracellular environment;
- they represent a subcellular therapeutic strategy with lower immunogenicity;
- they provide more sufficient protection for loaded cargoes from the phospholipid bilayer structures;
- abundant information molecules such as proteins, lipids and RNAs in PRP-exosomes contribute to their participation in intercellular communication.5,6;
- some studies have demonstrated that PRP-exosomes have effective and potentially greater therapeutic effects than PRP preparations 7,8.

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2. Tao SC, Yuan T, Rui BY, Zhu ZZ, Guo SC, Zhang CQ. Exosomes derived from human platelet-rich plasma prevent apoptosis induced by glucocorticoid-associated endoplasmic reticulum stress in rat osteonecrosis of the femoral head via the Akt/Bad/Bcl-2 signal pathway. Theranostics. 2017;7(3):733-750.
3. Guo SC, Tao SC, Yin WJ, Qi X, Yuan T, Zhang CQ. Exosomes derived from platelet-rich plasma promote the re-epithelization of chronic cutaneous wounds via activation of YAP in a diabetic rat model. Theranostics. 2017;7(1):81-96.
4. Johnson J, Wu YW, Blyth C, Lichtfuss G, Goubran H, Burnouf T. Prospective therapeutic applications of platelet extracellular vesicles. Trends Biotechnol. 2020;39(6):598–612
5. Aatonen M, Grönholm M, Siljander PR. Platelet-derived microvesicles: multitalented participants in intercellular communication. Semin Thromb Hemost. 2012;38(1):102-113.
6. Preußer C, Hung LH, Schneider T, et al. Selective release of circRNAs in platelet-derived extracellular vesicles. J Extracell Vesicles. 2018;7(1):1424473.
7. Zhao H, Zhao Z, Li D, Wang X, Dai D, Fu H. Effect study of exosomes derived from platelet-rich plasma in the treatment of knee cartilage defects in rats. J Orthop Surg Res. 2023 Mar 2;18(1):160. doi: 10.1186/s13018-023-03576-0.

CLINICAL RESEARCH & DEVELOPMENT

Biological Pipeline

Product Program	Therapeutic Target	Research & Pilot Studies	Phase I	Phase 2	Phase 3
ZOFIN	Acute Respiratory Distress-COVID-19	Complete	Complete		
	COVID-19 Long Hauler Syndrome	Complete	Complete		
	COPD	Complete	IND Approved		
	Osteoarthritis	Complete	IND Approved		
	Traumatic Brain Injury	Complete	IND Pending		

Clinical Research to Obtain FDA Approval for Specific Conditions

5 IND's – Investigative New Drug Filing – Approved

4 Phase 1 – Clinical Trials Completed:

I. Knee Osteoarthritis
II. Long-COVID
III. Moderate-Severe ARDS from COVID
IV. Mild-Moderate ARDS from COVID

Principal Investigator

George Shapiro, MD, FACP
Chief Medical Officer,
ZEO ScientifiX Inc.


Organicell
Clinical Research Protocol Synopsis
CONFIDENTIAL


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Clinical Research Protocol Synopsis
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Clinical Research Protocol Synopsis
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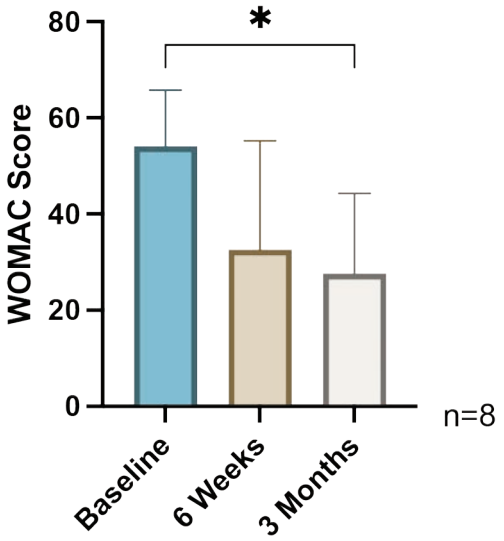
ZEO ScientifiX has led several pre-clinical and clinical research studies to investigate the therapeutic potential of exosome-based biologics. Our research has focused on extracellular vesicle and exosome products derived from natural biofluid including human amniotic fluid and whole blood. Using academic research and innovative biotechnology platforms, ZEO ScientifiX is advancing these new therapeutics on the world stage.

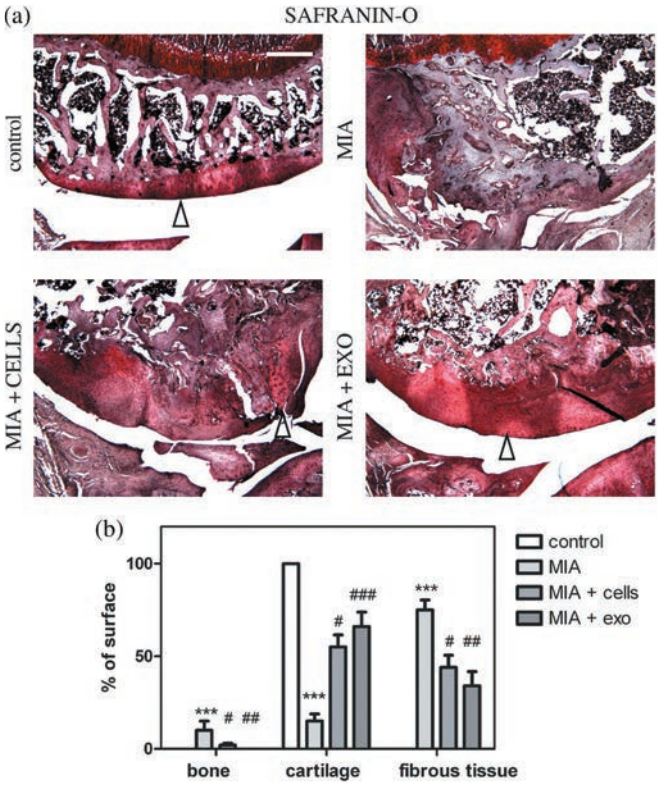
Clinical Studies

ZEO ScientifiX has completed to an IRB-approved pilot study to evaluate the safety of intravenous infusion (IV) and intra-articular injection (IA) with autologous exosomes to treat pain associated with Osteoarthritis. In this study, eight subjects were treated with autologous exosomes at baseline and 6 weeks. WOMAC (Western Ontario and McMaster Universities Index) score was reported to assess joint pain, stiffness, and function at baseline, 6 week, and 3 months. Analyzed results showed a significant decrease in WOMAC score after 3 months compared to baseline reporting.

PPX Treatment and WOMAC Score



*Unpublished stat, * P Value <0.05, repeated measure one-way Anova, Tukey comparison

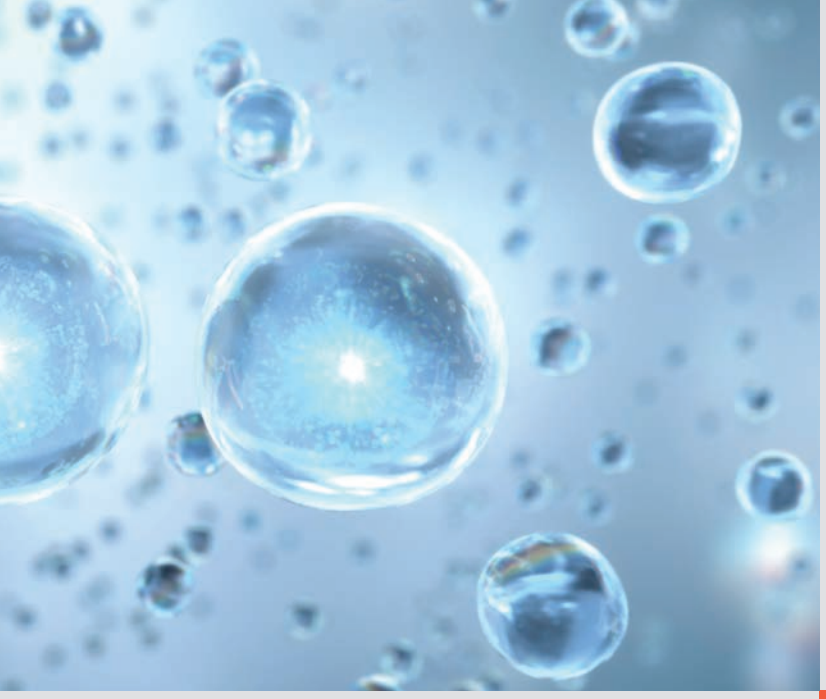


Additional Supportive RESEARCH

The effect of human stem cells and exosomes on the repair of cartilage in models of knee Osteoarthritis has been presented in the literature. In one model, intra-articular injection with monoiodoacetate (MIA) induced an OA-like degredation of cartilage tissue, as shown by a disruption in Safranin-O staining around the bone tissue. Zavatti et al, published results using this model to demonstrate a significant repair of cartilage tissue in both stem cell and exosome treated animals. In particular, the most promising results were found in the exosome treatment group where significantly more cartilage tissue covered almost all fibrous tissue.

Staining of joint tissue composition.(a) Representative images of safranin-O staining (in red indicated by arrow heads) of negative control, MIA alone or treated for 3 weeks with amniotic stem cells (MIA + CELLS) or amniotic stem cell-derived exosomes (MIA + EXO). Scalebar = 500μM. (b) Graph of quantitative tissue analysis measuring the percentage of tissues, such as bone, cartilage, fibrous tissue, covering the joint surface. One-way ANOVA with Bonferroni post-test.***p< .0001 = versus control group,###p< .0001;##p< .01;#p< .05 = versus. MIA group.

Study referenced from: Zavatti, M., et. al., Comparison of the therapeutic effect of amniotic fluid stem cells and their exosomes on monoiodoacetate-induced animal model of osteoarthritis. BioFactors 46, 106–117 (2019).



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Biomaterials and Biosystems 4 (2021) 100031

Contents lists available at ScienceDirect

Biomaterials and Biosystems

journal homepage: www.elsevier.com/locate/bbiosy

Proof-of-concept trial of an amniotic fluid-derived extracellular vesicle biologic for treating high risk patients with mild-to-moderate acute COVID-19 infection.

Michael A. Bellio, Cassie Bennett, Alissa Arango, Aisha Khan, Xiumin Xu, Cesar Barrera, Vincent Friedewald, Maria Ines Mitrani.

ABSTRACT

A pandemic brought on by COVID-19 has created a scalable health crisis. The search to help alleviate COVID-19-related complications through therapeutics has become a necessity. Zofin is an investigational, acellular biologic derived from full-term perinatal amniotic fluid that contains extracellular vesicles. Extracellular nanoparticles as such have been studied for their immunomodulatory benefits via cellular therapeutics and, if applied to COVID-19-related inflammation, could benefit patient outcome. Subjects (n = 8) experiencing mild-to-moderate COVID-19 symptoms were treated with the experimental intervention. Complete blood count, complete metabolic panel, inflammatory biomarkers, and absolute lymphocyte counts were recorded prior to and on days 4, 8, 14, 21, and 30 as markers of disease progression. Additionally, chest x-rays were taken of the patients prior to and on days 8 and 30. Patients experienced no serious adverse events. All COVID-19-associated symptoms resolved or became stable with no indication of disease worsening as found by patient and chest x-ray reports. Inflammatory biomarkers (CRP, IL-6, TNF-) and absolute lymphocyte counts improved throughout the study period. Findings from a proof-of-concept, expanded access trial for COVID-19 patients prove the acellular biologic is safe and potentially effective to prevent disease progression in a high-risk COVID-19 population with mild-to-moderate symptoms.

Read complete study at zeoscientifix.com

Cytotherapy 23 (2021) 1097–1107

Contents lists available at ScienceDirect

CYTOTHERAPY

journal homepage: www.isct-cytotherapy.org

Amniotic fluid-derived extracellular vesicles: characterization and therapeutic efficacy in an experimental model of bronchopulmonary dysplasia.

Michael A Bellio, Karen C Young, Julian Milberg, Ivan Santos, Zanub Abdullah, Danique Stewart, Alissa Arango, Pingping Chen, Jian Huang, Kevin Williams, Kaitlyn Kelly, Shanique Sterling, Aisha Khan, Xiumin Xu, George C Shapiro, Maria Ines Mitrani

ABSTRACT

Background aims: Extracellular vesicles (EVs) are being tested for their use as novel therapeutics. However, the optimal source of EVs is currently under investigation. Amniotic fluid (AF) is a natural source of EVs that can be easily obtained for use in regenerative medicine, yet AF-EV characterization has not been fully explored.

Methods: Here the authors demonstrate AF as a rich source of EVs and identify the microRNA and proteomic cargo. Bioinformatics analysis of this cargo revealed multiple pathway targets, including immunomodulatory, anti-inflammatory and free radical scavenging networks. The authors further demonstrated the therapeutic potential of this EV product as a novel preventative agent for bronchopulmonary dysplasia (BPD).

Results: Intra-tracheal administration of AF-EVs preserved alveolar development, attenuated vascular remodeling and pulmonary hypertension, decreased lung pro-inflammatory cytokine expression and reduced macrophage infiltration in an experimental BPD model.

Conclusions: The authors' results suggest that AF is a viable biological fluid for EV harvest and that AF-EVs have strong therapeutic potential for pulmonary diseases, such as BPD, warranting further development to transition this novel EV product into the clinic.

Read complete study at zeoscienfix.com

frontiers in Medicine

CASE REPORT
published: 17 March 2021
doi: 10.3389/fmed.2021.583842

Case Report: Administration of Amniotic Fluid-Derived Nanoparticles in Three Severely Ill COVID-19 Patients.

Maria Ines Mitrani, Michael A. Bellio, Anthony Sagel, Marie Saylor, William Kapp, Kathryn VanOsdol, Gwendolyn Haskell, Danique Stewart, Zanub Abdullah, Ivan Santos, Julian Milberg, Alissa Arango, Albert Mitrani, George C. Shapiro

ABSTRACT

Rationale/Objectives: A human coronavirus (HCoV-19) has caused the novel coronavirus disease (COVID-19) outbreak worldwide. There is an urgent need to develop new interventions to suppress the excessive immune response, protect alveolar function, and repair lung and systemic organ damage. Zofin (previously known as Organicell Flow) is a novel therapeutic that is derived from the soluble and nanoparticle fraction (extracellular vesicles and exosomes) of human amniotic fluid. Here within, we present the clinical outcomes after Zofin treatment in three critically ill patients suffering from severe, multi-organ complications induced by COVID-19 infection. All patients were diagnosed with COVID-19, developed respiratory failure, and were hospitalized for more than 40 days.

Methods: Zofin was administered to patients concurrently with ongoing medical care who were monitored for 28-days post-therapy. SOFA score assessment, chest X-rays, and inflammatory biomarker testing was performed.

Main Results: There were no adverse events associated with the therapy. The patients showed improvements in ICU clinical status and experienced respiratory improvements. Acute delirium experienced by patients completely resolved and inflammatory biomarkers improved.

Conclusions: Primary outcomes demonstrate the therapy was safe, accessible, and feasible. This is the first demonstration of human amniotic fluid-derived nanoparticles as a safe and potentially efficacious therapeutic treatment for respiratory failure induced by COVID-19 infection.

Read complete study at zeoscientifix.com

Respiratory Medicine Case Reports 34 (2021) 101502

Contents lists available at ScienceDirect

Respiratory Medicine Case Reports

journal homepage: www.elsevier.com/locate/rmcr

Treatment of a COVID-19 long hauler with an amniotic fluid-derived extracellular vesicle biologic.

Maria Ines Mitrani, Michael A. Bellio, Allen Meglin, Aisha Khan, Xiumin Xu, Gwendolyn Haskell, Alissa Arango, George C. Shapiro

ABSTRACT

Post-COVID-19 infection symptoms such as mental fog, tachycardia, and extreme fatigue are just a few of the symptoms wreaking havoc on patients' lives. Patients with long-term symptoms following COVID-19 are being called long haulers. To date, long haulers are receiving little to no guidance from physicians on their lingering COVID-19 symptoms with limited treatment options available. Zofin is an acellular biologic that contains the extracellular vesicle (EV) fraction of human amniotic fluid and is under investigation for use as a COVID-19 therapeutic. We obtained FDA and IRB approval to investigate the therapeutic use of Zofin in a single long hauler patient case experiencing prolonged shortness of breath and respiratory impairment. Administration of the EV product was shown to be safe. Furthermore, demonstrated respiratory improvements through chest X ray images and oxygen saturation measurement. The single patient IND studies were completed without any reported adverse events or safety concerns. Furthermore, these completed studies demonstrate the feasibility and a therapeutic potential of amniotic fluid-derived EVs for COVID-19 long hauler intervention.

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Human amniotic fluid derived extracellular vesicles attenuate T Cell immune response.

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ABSTRACT

Introduction: Extracellular vesicles isolated from human amniotic fluid (AF-EVs) have previously been found to modulate inflammation and macrophage infiltration in a mouse model. However, the effects of acellular amniotic fluid (acAF) or AF-EVs on the T-Cell immune response have not been explored.

Methods: In this study, we investigated the effects of acAF and AF-EVs on the T cell immune response in an in vitro cell culture model. Peripheral Blood Mononuclear Cells (PBMCs) were stimulated with Phytohemagglutinin (PHA) to induce the immune response and were subsequently treated with either serum-free media (vehicle), acAF, or concentrated AF-EVs.

Results: Both acAF and AF-EV treatment suppressed PHA-induced T cell proliferation and PHA-induced T cell activation; however, treatment with concentrated AF-EVs had a greater effect. Additionally, both acAF and AF-EVs reduced PBMC pro-inflammatory cytokine release. AF-EVs were found to be taken up by both CD4+ and CD8+ effector T cell subsets.

Conclusion: Overall, this data demonstrates that AF-EVs have a robust immunomodulatory effect on T cells and suggests AF-EVs could be used as an immunotherapeutic tool.

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Molecular Therapy
Commentary
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Extracellular Vesicles: A promising therapy against SARS-CoV-2 infection.

Yan Leyfam, Greta Gohring, Muskan Joshi, Gayathri Pramil Menon, Alexandra Van de Kieft, Tania del Rivero, Michael A. Bellio, Maria Ines Mitrani

Summary: In recent years, researchers have focused on intracellular secreted factors, such as extracellular vesicles (EVs), to improve and build upon the knowledge gained from cell-based research and spearhead the use as potential therapeutic agents for various diseases, including SARS-CoV-2. EVs are small membranous structures secreted by the cell membrane or the cell's internal recycling pathways and have emerged as a promising therapeutic strategy due to their involvement in a range of biological processes, including cell signaling, immune response, and disease progression. The objective of this analysis is to examine the potential efficacy of EV-based therapies in the treatment of SARS-CoV-2 severity, with a particular emphasis on their common mechanisms and suitability for future therapeutic use in human patients.

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viruses

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Acellular human amniotic fluid-derived extracellular vesicles as a novel anti-inflammatory therapeutic against SARS-COV-2 Infection.

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Viruses, 2024, 16(2), 273.

ABSTRACT

The ongoing COVID-19 pandemic caused by SARS-CoV-2 is associated with acute respiratory distress syndrome (ARDS) and fatal pneumonia. Excessive inflammation caused by SARS-CoV-2 is the key driver of ARDS and lethal disease. Several FDA-approved drugs that suppress virus replication are in clinical use. However, despite strong evidence for the role of virus-induced inflammation in severe COVID-19, no effective anti-inflammatory drug is available to control fatal inflammation as well as efficiently clear the virus. Therefore, there is an urgent need to identify biologically derived immunomodulators that suppress inflammation and promote antiviral immunity. In this study, we evaluated acellular human amniotic fluid (acAF) containing extracellular vesicles (hAF-EVs) as a potential non-toxic and safe biologic for immunomodulation during COVID-19. Our in vitro results showed that acAF significantly reduced inflammatory cytokine production in TLR2/4/7 and SARS-CoV-2 structural protein-stimulated mouse macrophages. Importantly, an intraperitoneal administration of acAF reduced morbidity and mortality in SARS-CoV-2-infected mice. A detailed examination of SARS-CoV-2-infected lungs revealed that the increased protection in acAF-treated mice was associated with reduced viral titers and levels of inflammatory myeloid cell infiltration. Collectively, our results identify a novel biologic that has potential to suppress excessive inflammation and enhance survival following SARS-CoV-2 infection, highlighting the translational potential of acAF against COVID-19.

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