



Large Scale Manufacturing, Characterization, and Functionality of Extracellular Vesicles

Heather Branscome, PhD Supervisor, Laboratory Operations, ATCC

Credible Leads to Incredible™



About ATCC

Founded in 1925, ATCC is a non-profit organization with HQ in Manassas, VA, and an R&D and Services center in Gaithersburg, MD

- World's largest, most diverse biological materials and information resource for microbes – the "gold standard"
- Innovative R&D company featuring gene editing, microbiome, NGS, advanced models
- cGMP biorepository

- Partner with government, industry, and academia
- Leading global supplier of authenticated cell lines, viral and microbial standards
- Sales and distribution in 150 countries, 18 international distributors
- Talented team of 450+ employees, over one-third with advanced degrees



Agenda

- I. Large scale extracellular vesicle (EV) manufacturing
- II. ATCC EV characterization and application data
- III. EV functionality in 2D and 3D models
- IV. Future directions







Large Scale EV Manufacturing and Characterization



Outstanding Need for EV Reference Standards

- Reference standards reduce time and costs associated with developmental work
- Reference standards increase assay reproducibility
- Reference standards add value to research work and/or product development
- Reference standards regulate the quality of one's own research



Global Market for Exosome Diagnostics, 2017-2023 (\$ Millions)



EVs as Biomarkers/Reference Standards

International Journal of Nanomedicine

8 Open Access Full Text Article

REVIEW

Dovepress

Cancer-Derived Exosomes: Their Role in Cancer **Biology and Biomarker Development**

Role of Exosomal miRNA in Bladder Cancer: A Promising

Xuan-Mei Piao ¹, Eun-Jong Cha ^{2,3}, Seok Joong Yun ^{1,4} and Wun-Jae Kim ^{1,3,*}

SCIENTIFIC **REPCRTS**

OPEN Exosomal miR-126 as a circulating

biomarker in non-small-cell

Franca Saccucci¹, Jiri Neuzil^{4,5}, Marco Tomasetti² & Lory Santarelli²

progression

lung cancer regulating cancer

Franco Grimolizzi¹, Federica Monaco², Francesca Leoni¹, Massimo Bracci⁰, Sara Staffolani², Cristiana Bersaglieri², Simona Gaetani², Matteo Valentino², Monica Amati², Corrado Rubini³,

Victor C Kok 017 Cheng-Chia Yu 024
Division of Medical Oracitogy, Kang Ther General Hasp of Change Comp Indiang, January, Department of
And Lincontry, Turking, Tarwor, Trackase of Oral Sciences, Chang Sh Hiddai University, Takwang, Talwang, School of Density, Chang Rawing
University, Tableng, Talwar

nternational Journal of Molecular Sciences

Liquid Biopsy Biomarker

MDPI

for breast cancer



REVIEW

Doireann P. Joyce, Michael J. Kerin and Róisín M. Dwyer

Exosome-based liquid biopsies in cancer: opportunities and challenges

IJC

International Journal of Cance

W. Yu¹, J. Hurley¹, D. Roberts¹, S. K. Chakrabortty¹, D. Enderle², M. Noerholm², X. O. Breakefield^{3,4} & J. K. Skog^{1*}

¹Exosome Diagnostics, Inc., a Bio-Techne brand, Waltham, USA; ²Exosome Diagnostics GmbH, a Bio-Techne brand, Martinsried, Germany; ³Department of Neurology, Massachusetts General Hospital, Boston; ⁴Neuroscience Program, Harvard Medical School, Boston, USA

Cancer Medicine WILEY

REVIEW

Exosomal miRNAs as biomarkers for diagnostic and prognostic

Exosome-encapsulated microRNAs as circulating biomarkers

Discipline of Surgery, School of Medicine, Lambe Institute for Translational Research, National University of Ireland Galway, Galway, Ireland

in lung cancer

Jing Wu¹ . Zuojun Shen^{1,2}

OPEN CACCESS Freely available online

PLOS ONE

Circulating Exosomal microRNAs as Biomarkers of Colon Cancer

Hiroko Ogata-Kawata¹, Masashi Izumiya³, Daisuke Kurioka^{1,4}, Yoshitaka Honma⁵, Yasuhide Yamada⁵, Koh Furuta⁶, Toshiaki Gunji⁷, Hideki Ohta⁸, Hiroyuki Okamoto⁸, Hikaru Sonoda⁸, Masatoshi Watanabe⁴, Hitoshi Nakagama², Jun Yokota^{1,9}, Takashi Kohno¹, Naoto Tsuchiya¹*

RESEARCH ARTICLE

WILEY

Tumor-derived exosomal miRNA-320d as a biomarker for metastatic colorectal cancer

Youyong Tang^{1,2} | Yajing Zhao^{1,2} | Xingguo Song³ | Xianrang Song² | Limin Niu² Li Xie² 💿



SCIENTIFIC REPORTS natureresearch

Check for updates

OPEN The proteomic analysis of breast cell line exosomes reveals disease patterns and potential biomarkers

Yousef Risha¹, Zoran Minic², Shahrokh M. Ghobadloo³ & Maxim V. Berezovski^(01,2,3)

Review Article

Exosomes in Cancer: Circulating Immune-Related Biomarkers

Alicja Głuszko (0,1 Mirosław J. Szczepański (0,1 Nils Ludwig,^{2,3} Shafaq M. Mirza,¹ and Wioletta Olejarz 04,5

¹Chair and Department of Biochemistry, Medical University of Warsaw, Poland ²Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213, USA ³University of Pittsburgh Cancer Institute, Hillman Cancer Center, Pittsburgh, PA 15213, USA ⁴Department of Biochemistry and Pharmacogenomics, Faculty of Pharmacy, Medical University of Warsaw, Poland ⁵Laboratory of Biochemistry and Clinical Chemistry at the Centre for Preclinical Research, Medical University of Warsaw, Poland

frontiers in Immunology

The Potential Biomarkers and Immunological Effects of Tumor-**Derived Exosomes in Lung Cancer**



Shamila D. Alipoor¹, Esmaeil Mortaz^{2,3*}, Mohammad Varahram⁴, Mehrnaz Movassaghi³ Aletta D. Kraneveld^{5,6}, Johan Garssen^{5,7} and Ian M. Adcock^{8,5}



REVIEW

Received: 20 October 201

Accented: 27 October 2017

Published online: 10 November 2017



Exosomes as a new frontier of cancer liquid biopsy

Dan Yu¹, Yixin Li¹, Maoye Wang¹, Jianmei Gu², Wenrong Xu¹, Hui Cai³, Xinjian Fang^{4*} and Xu Zhang^{1,3,4*}

Open Access

ATCC EV Manufacturing



ATCC EV Portfolio

ATCC [®] No.		Parental Cell Designation		Cancer Model		
SCRC-4000-EXM™	hTERT-imr	nortalized adipose-derived mesenchymal stem	N/A			
CCL-185-EXM™	A549			Carcinoma, lung		
CRL-1435-EXM™	PC-3			Adenocarcinoma, prostate		
CCL-247-EXM [™]	HCT 116	Carcinoma, colorectal				
CRL-1740-EXM [™]	LNCaP		Carcinoma, prostate			
Attributes		Test	Specification			
Protein concentration/v	ial	BCA	Report results			
Particle number/vial		NTA	≥ 10 ⁹ particles			
Size distribution (% particles wit nm)	hin 50-200	NTA	Cell type dependent			
Protein marker expressi	ion	Western Blot	Positive expression of 1 transmembrane prot and 1 cytosolic protein			
Sterility		iAST bottle (aerobic) at 32.5°C iNST bottle (anaerobic) at 32.5°C	No growth detected			
Mycoplasma		PCR based assay		Negative		



EV Manufacturing & Reproducibility



Batch	% between 50-200 nm	Percent variance
Lot 1	82.1%	3.0%
Lot 2	79.7	



Batch	% between 50-200 nm	Percent variance
Lot 1	89.9%	2.1%
Lot 2	91.8%	



Batch	% between 50-200 nm	Percent variance
Lot 1	84.4%	1.9%
Lot 2	82.9%	

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Batch	% between 50-200 nm	Percent variance
Lot 1	92.4%	1.4%
Lot 2	91.1%	







EV Application Data



EV Application Data



ATCC

Long-term (3 Year) EV Storage







Functionality of ATCC EVs



Stem Cell EVs

- Contain various biological cargo (miRNAs, IncRNAs, proteins, cytokines) that can be transferred to recipient cells
- Proposed to play a role in homeostasis through tissue repair, regeneration, and immunomodulation
- Potential alternative to stem cell therapy due to higher potency, increased stability/shelf life, and lower immunogenicity
- Widely studied for reparative functions (eg, skin/wound healing, cardiac repair, CNS-related pathologies)



Stem Cell EVs and CNS Repair

SCIENTIFIC REPORTS

Autorial 21 Septemb 2017 National 21 Septemb 2017 National and Septemb

Journal of Neurotrauma, Vol. 36, No. 1 | Original Articles

Mesenchymal Stem Cell-Derived Exosomes Provide Neuroprotection and Improve Long-Term Neurologic Outcomes in a Swine Model of Traumatic Brain Injury and Hemorrhagic Shock

Aaron M. Williams, Isabel S. Dennahy, Umar F. Bhatti, Ihab Halaweish, Ye Xiong, Panpan Chang, Vahagn C. Nikolian, Kiril Chtrakii Jordana Brown, Vanlu Zhang, Zheng Gang Zhang, Michael Chopp, Benjamin Buller, and Hasan B. Alam 😒

Cellular Physiology	Cell Physiol Biochem 2018;50:1535-1559		Open access
and Biochemistry	DDI: 10.1159;000494652 Published online: 26 October 2018 Accepted: 18 October 2018	© 2018 The Author(s) Published by S. Karger AG, Basel www.karger.com/cpb	1535
	This article is licensed under the Creative Commons Attribution tional License (CC IV-NC-ND) (http://www.karper.com/Servicey for commercial purposes as well as any distribution of modified -	NonCommercial NoDerivatives 4.0 Interna- OpenAccessitionnel, Usage and distribution naterial requires written permission.	
Original Paper			

Mesenchymal Stem Cell-Derived Exosomes Reduce A1 Astrocytes via Downregulation of Phosphorylated NFkB P65 Subunit in Spinal Cord Injury

Lin Wang^a Shuang Pei^a Linlin Han^a Bin Guo^a Yanfei Li^a Ranran Duan^a Yaobing Yao^a Bohan Xue^b Xuemei Chen^b Yanjie Jia^a

"The First Affiliated Hospital of Zhengzhou University, Zhengzhou, "School of Basic Medical Sciences, Zhengzhou University, Zhengzhou, China



Published in final edited form as: Neurochem Int. 2017 December ; 111: 69–81. doi:10.1016/j.neuint.2016.08.003.

Systemic administration of cell-free exosomes generated by human bone marrow derived mesenchymal stem cells cultured under 2D and 3D conditions improves functional recovery in rats after traumatic brain injury

Yaniu Zhang, MS, MD¹, Michael Chopp, PhD^{2,3}, Zheng Gang Zhang, MD, PhD², Mark Katakowski, PhD², Hongqi Xin, PhD², Changsheng Qu, MD¹, Meser Ali, PhD⁴, Asim Mahmood, MD¹, and Ye Xiong, MD, PhD¹

ience

🐉 frontiers

Exosomes Derived From Bone Mesenchymal Stem Cells Ameliorate Early Inflammatory Responses Following Traumatic Brain Injury

ORIGINAL RESEARCH published: 24 January 2019

Haoqi Ni^{1,2}, Su Yang^{1,2}, Felix Siaw-Debrah^{1,2}, Jiangnan Hu², Ke Wu^{1,2}, Zibin He^{1,2}, Jianjing Yang^{1,2}, Sishi Pan^{1,2}, Xiao Lin^{1,2}, Haotuo Ye^{1,2}, Zhu Xu^{1,2}, Fan Wang^{1,2}, Kunlin Jin^{1,3}, Qichuan Zhuge^{1,2} and Lije Huang^{1,2}*

HHS Public Access

Neurorehabil Neural Repair. Author manuscript; available in PMC 2020 July 02.

Published in final edited form as:
Neurorehabil Neural Repair. 2020 July ; 34(7): 616–626. doi:10.1177/1545968320926164.

Mesenchymal stem cell-derived exosomes improve functional recovery in rats after traumatic brain injury: a dose response and therapeutic window study

Yanlu Zhang, MS, MD¹, Yi Zhang, PhD², Michael Chopp, PhD^{2,3}, Zheng Gang Zhang, MD, PhD², Asim Mahmood, MD¹, Ye Xiong, MD, PhD¹ ¹Department of Neurosurgery, Henry Ford Hospital, Detroit, MI 48202, USA

²Department of Neurology, Henry Ford Hospital, Detroit, MI 48202, USA ³Department of Physics, Oakland University, Rochester, MI 48309, USA

cells

Intracerebral Injection of Extracellular Vesicles from Mesenchymal Stem Cells Exerts Reduced Aβ Plaque Burden in Early Stages of a Preclinical Model of Alzheimer's Disease

Chiara A. Elia ^{1,2}, Matteo Tamborini ¹, Marco Rasile ^{1,3}, Genni Desiato ^{1,4}, Sara Marchetti ^{1,5,4}, Paolo Swuec ^{6,7}, Sonia Mazzitelli ^{1,4}, Francesca Clemente ^{5,8,6}, Achille Anselmo ⁸, Michela Matteoli ^{1,3}, Maria Luisa Malosio ^{1,2,4}, and Silvia Coco ^{5,4}

Journal of Neurotrauma, Vol. 34, No. 24 | Original Articles

Systemic Administration of Exosomes Released from Mesenchymal Stromal Cells Attenuates Apoptosis, Inflammation, and Promotes Angiogenesis after Spinal Cord Injury in Rats

Jiang-Hu Huang, Xiao-Ming Yin, Yang Xu, Chun-Cai Xu, Xi Lin, Fu-Biao Ye, Yong Cao 🕐 and Fei-Yue Lin 🕾

Chen et al. Cell Death and Disease (2020)11:288 https://doi.org/10.1038/s41419-020-2473-5

ARTICLE

Exosomes derived from mesenchymal stem cells repair a Parkinson's disease model by inducing autophagy

Hong-Xu Chen¹², Fu-Chao Liang²³, Ping Gu¹, Bian-Ling Xu²⁴, Hong-Jun Xu²³, Wen-Ting Wang¹, Jia-Yang Hou²³, Dong-Xiao Xie², Xi-Qing Chai¹ and Sheng-Jun An²³ > Neurochem Res. 2018 Nov;43(11):2165-2177. doi: 10.1007/s11064-018-2641-5. Epub 2018 Sep 26.

Exosomes Isolated From Human Umbilical Cord Mesenchymal Stem Cells Alleviate Neuroinflammation and Reduce Amyloid-Beta Deposition by Modulating Microglial Activation in Alzheimer's Disease

Mao Ding 3 , Yang Shen 3 , Ping Wang 2 , Zhaohong Xie 2 , Shunliang Xu 2 , ZhengYu Zhu 2 , Yun Wang 2 , Yongtao Lyu 3 , Dewei Wang 2 , Linlin Xu 2 , JianZhong Bi 4 , Hui Yang 5



Neural Regen Res. 2019 Sep; 14(9): 1626–1634. dol: 10.4103/1673-5374.255978 PMCID: PMC6557105 PMID: <u>31089063</u>

Mesenchymal stem cell-derived exosomes promote neurogenesis and cognitive function recovery in a mouse model of Alzheimer's disease

Edwin E. Reza-Zatelivar,¹ Mercedes A. Hernandez-Sapilens,¹ Yanet K. Gutlernz-Afercado,¹ Bergio Sandoval-Avia,¹ Ulises.Gomez-Pinedo,² Ana L. Marquez-Aguire,¹ Estefania Vázquez-Méndez,¹ Eduardo, Padilla-Camberos,¹ and Alojandro, A. Canales-Aguire¹

Immunity & Ageing



RVG-modified exosomes derived from mesenchymal stem cells rescue memory deficits by regulating inflammatory responses in a mouse model of Alzheimer's disease

Guo-hong Cui¹¹, Hai-dong Guo²¹, Han Li²¹, Yu Zhai¹, Zhang-bin Gong³, Jing Wu¹, Jian-sheng Liu¹ You-rong Dong¹, Shuang-xing Hou^{4*} and Jian-ren Liu^{1*}

frontiers

Cui et al. Immunity & Ageing (2019) 16:10

RESEARCH

Stem Cell-Derived Exosomes Protect Astrocyte Cultures From *in vitro* Ischemia and Decrease Injury as Post-stroke Intravenous Therapy

Xiaoyun Sun¹, Ji-Hye Jung^{2,3}, Oiva Arvola¹, Michelle R. Santoso², Rona G. Giffard¹, Phillip C. Yang^{2,3*} and Creed M. Stary^{1*}



Extracellular Vesicles Improve Post-Stroke Neuroregeneration and Prevent Postischemic Immunosuppression

THORSTEN R. DOEPPNER,^{a,b,*} JOSEPHINE HERZ,^{a,c,*} ANDRÉ GÖRGENS,^b JANA SCHLECHTER, Anna-Kristin Ludwig,^b Stefan Radike,^b Kyra de Miroscheda,^b Peter A. Horn,^b Bernd Giebel,^b Dirk M. Hernann^a



Stroke. 2018 May; 49(5): 1248–1256. Published online 2018 Apr 12. doi: 10.1161/STROKEAHA.117.020353 PMCID: PMC5916046 NIHMSID: <u>NIHMS952221</u> PMID: <u>29650593</u>

Human Neural Stem Cell Extracellular Vesicles Improve Recovery in a Porcine Model of Ischemic Stroke

Robin L. Webb, PhD,^{*1,2} Erin E. Kaiser, BSA,^{*2,3} Brian J. Jurgielewicz, MS,² Samantha Snellicy, BS,² Shelley, L. Scoville, BS,¹ Tyler A. Thomoson, MS,¹ Raymond L. Swetenburg, PhD,¹ David C. Hess, MD,⁴ Franklin D. West, PhD,^{2,3} and Steven L. Stice, PhD³²

Akbari and Rezale Stem Cell Research & Therapy (2020) 11:356 https://doi.org/10.1186/s13287-020-01866-6

Lippincott Williams & Wilkins

Stem Cell Research & Therapy

en Access

REVIEW

Potential therapeutic application of mesenchymal stem cell-derived exosomes in SARS-CoV-2 pneumonia

Stem Cells and Development, Vol. 29, No. 12 | Clinical Trial

Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe COVID-19

Vikram Sengupta 🖂 Sascha Sengupta, Angel Lazo, Peter Woods, Anna Nolan, and Nicholas Bremer

ORIGINAL ARTICLE			
			Check
Stem Cell Extr	acellular Vesicles and	their Potential to Contribute	updat
to the Repair	of Damaged CNS Cell	s	

P	frontiers		
	in Cell and	Developmental	Biolog

Use of Stem Cell Extracellular Vesicles as a "Holistic" Approach to CNS Repair

Heather Branscome^{1,2}, Siddhartha Paul³, Dezhong Yin³, Nazira El-Hage⁴, Emmanuel T. Agbottah¹, Mohammad Asad Zadeh¹, Lance A. Liotta⁵ and Fatah Kashanchi^{1,*}



RVG-mod mesench

MDPI

Cell Death & Disease

Open Access

EVs and Donor Cells

Mesenchymal Stem Cells (MSCs; ATCC[®] PCS-500-012[™])

- Human, normal
- Bone-marrow derived
- Authenticated for characteristic surface marker expression (CD90, CD73, CD105 positive; CD14, CD34, CD45 negative)
- Multi-lineage differentiation potential (adipocyte, chondrocyte, osteocyte)

Induced Pluripotent Stem Cells (iPSCs; ATCC[®] ACS-1019[™])

- Human, normal
- Foreskin fibroblast-derived
- Sendai virus reprogrammed
- Authenticated for expression of stem cell markers (TRA-1-60, SSEA-4 positive; SSEA-1 negative)
- Evaluated for pluripotency
- A549 Lung Carcinoma (ATCC[®] CCL-185[™])
 - Control used for large-scale manufacturing and isolation
 - Equivalent to CCL-185-EXM[™] exosomes



EV uptake in A549 cells



EV Isolation and Characterization





A549 EVs





A549 EVs

100

0

200

Size (nm)

300



a)	iPSC EVs	b)	MSC EVs		C)	<u>A549 EVs</u>	
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EV Functionality



b) <u>MSC EVs</u>





Branscome et al. 2021 ATCC°

EV Functionality



Angio-*Ready*[™] Angiogenesis Assay System (ATCC[®] ACS-2001-2[™])



EV Functionality



ATCC

Branscome et al. 2021

Generation of Neurospheres





Infection of Neurospheres



C)





EV Uptake



ATCC[®]

EV Function

a)



b)





Summary

- High yields of EVs were isolated from well characterized and authenticated ATCC cell lines using TFF
- ATCC EV isolation protocols are robust, reproducible, and demonstrate low lotto-lot variability
- ATCC EVs meet high quality standards and may serve as reliable reference material to the research community
- EVs can be stored for up to 3 years without a significant reduction in NTA profile
- Phenotypic and biochemical properties of EVs are cell-type specific
- Stem cell EVs are functional in multiple different in vitro and in vivo assays and this highlights their reparative properties





Future Work

Further study of cell-specific EV repair in 3D cultures



Branscome et al. 2021 ATCC°

Future Work

Better definitions of death and EV-mediated mechanisms of repair





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- Gwen Cox

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- Dr. Elzafir Elsheikh
- Dr. Wyatt Vreeland
- Dr. Thomas Cleveland

ATCC

<u>MSD</u>

 Dr. David Routenberg













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