
Future Science
OA
ISSN: 2056-5623
OPEN ACCESS
Future
Science
an imprint of
fsg

VOLUME 7, ISSUE 10 / DECEMBER 2021

Commentary Open Access OCTOBER 2021

The critical role of mobile phase pH in the performance of oligonucleotide ion-pair liquid chromatography–mass spectrometry methods

Guilherme J Guimaraes & Michael G Bartlett

Published Online: 23 October 2021

First Page | Full text | PDF/EPUB

Case Report Open Access OCTOBER 2021

Metastatic myxoid liposarcoma of the brain: a case report and review of the literature

Baha'eddin A Muhsen, Ansam Ghzawi, Ahmad Salah Fares, Maysa Al-Hussaini & Samer Salah

Published Online: 23 October 2021

Abstract | Full text | PDF/EPUB

Preview Abstract

Research Article Open Access NOVEMBER 2021

Oral vinorelbine and capecitabine as first-line therapy in metastatic breast cancer: a retrospective analysis

Maria Rosaria Valerio, Pietro Spadaro, Concetta Arcanà, Nicolò Borsellino, Calogero Cipolla, Paolo Vigneri, Dario Piazza & Vittorio Gebbia

Published Online: 12 November 2021

Abstract | Full text | PDF/EPUB

Preview Abstract

Research Article Open Access OCTOBER 2021

Do medical student mental stress and burnout vary with virtual versus in-person residency interviews

Dani Zoorob, Kara Richardson, Korina Gaishauser, Benjamin Hinkel, Hind N Moussa, James Van Hook & Rose A Maxwell

Published Online: 23 October 2021

Abstract | Full text | PDF/EPUB

Preview Abstract

Research Article Open Access OCTOBER 2021

Public attitudes in Japan toward the reproductive use of gametes derived from human-induced pluripotent stem cells

Kyoko Akatsuka, Taichi Hatta, Tsutomu Sawai & Misao Fujita

Published Online: 23 October 2021

Abstract | Full text | PDF/EPUB

Preview Abstract

Research Article Open Access OCTOBER 2021

Public attitudes in Japan toward the creation and use of gametes derived from human-induced pluripotent stem cells

Tsutomu Sawai, Taichi Hatta, Kyoko Akatsuka & Misao Fujita

Published Online: 23 October 2021

Abstract | Full text | PDF/EPUB

Preview Abstract

Research Article Open Access NOVEMBER 2021

Concordance of acquired mutations between metastatic lesions and liquid biopsy in metastatic colorectal cancer

Fumitaka Taniguchi, Akihiro Nyuya, Toshiaki Toshima, Kazuya Yasui, Yoshiko Mori, Makoto Okawaki, Hiroyuki Kishimoto, Yuzo Umeda, Toshiyoshi Fujiwara, Hiroaki Tanioka, Yoshiyuki Yamaguchi, Ajay Goel & Takeshi Nagasaka

Published Online: 7 November 2021

Abstract | Full text | PDF/EPUB

Preview Abstract

Review Open Access OCTOBER 2021

Challenges and strategy in treatment with exosomes for cell-free-based tissue engineering in dentistry

Ika Dewi Ana, Anggraini Barlian, Atik Choirul Hidajah, Christofora Hanny Wijaya, Hari Basuki Notobroto & Triati Dewi Kencana Wungu

Published Online: 29 October 2021

Abstract | Full text | PDF/EPUB

Preview Abstract

Future Science OA - Editorial Advisory Board

Senior Editors

Ian A Blair, University of Pennsylvania, USA

Dr. Blair received his Ph.D. in Organic Chemistry in 1971 from Imperial College of Science and Technology, London, under the mentorship of the 1969 Nobel Laureate, Sir Derek H.R. Barton. He was appointed as the A.N. Richards Professor of Pharmacology at University of Pennsylvania in 1997 and Director of a new Center for Cancer Pharmacology. In 2002, Dr. Blair was appointed as Vice-Chair of the Department of Systems Pharmacology and Translational Therapeutics. In 2014, he became Director of the NIEHS-funded Penn Superfund Research and Training Program Center. Dr. Blair is an expert in the use of mass spectrometric methods for the structural elucidation and quantification of endogenous biomolecules. His current research is involved with the development of biomarkers in order to establish genetic/phenotype correlations and to assess the interaction between genes and exposure to environmental chemicals. He is particularly interested in the regulation of cellular oxidative stress and how this underpins mechanisms involved in carcinogenesis, cardiovascular disease, and neurodegeneration. Dr. Blair discovered electron capture atmospheric pressure chemical ionization, a technique that makes it possible to conduct high sensitivity quantitative analyses of chiral biomolecules. He is a Fellow of the American Association for the Advancement of Science and the American Association of Pharmaceutical Scientists. He received the 2011 Eastern Analytical Award for Outstanding Achievements in Mass Spectrometry. Dr. Blair is on the editorial boards of the Molecular and Cellular Proteomics, Journal of Lipid Research, and Chemical Research in Toxicology. He has published 329-refereed manuscripts, they have been cited 13,970 times, and he has an h-index of 59. Read more about his work here.

Editorial Board

Cardiology

Vasilios Athyros, Aristotle University of Thessaloniki, Greece

Dr. V.G. Athyros studied medicine and was trained in Internal Medicine in the Aristotle University of Thessaloniki, Greece. He founded the Atherosclerosis and Metabolic Syndrome Outpatient Clinics in 1990 and he remains the Head of these clinics. He has performed more than 426 studies, and has 282 entries in PubMed, 342 in Scopus, 340 in Google Scholar, and 330 in ResearchGate covering lipoprotein metabolism, atherogenisity and clinical properties of plasma lipids and lipoproteins, in therapeutic interventions in all kinds of high-risk patients including those with dyslipidemia, obesity, diabetes, arterial hypertension, chronic kidney disease, non-alcoholic fatty liver disease and the metabolic syndrome, both in primary and secondary cardiovascular disease prevention. Dr. Athyros is a Faculty member at the School of Medicine, Aristotle University of Thessaloniki, Greece with a joint position in the Clinic of Internal Medicine at the University (HippoKration) Hospital. Furthermore, Dr. Athyros has been a member of the Advisory Board of the Hellenic Society of Lipidology since 1995 and of the Hellenic (Greek) Atherosclerosis Society (HAS) since 2002. He has been elected as Vice-President (2008-2010) and as a President (2010-2012) of HAS, while he continues to be a member of the Advisory Board of HAS today. For 12 years he was responsible for Scientific Programming and Research Planning of HAS. Since 2013 he has been the Vice-President in the Hellenic (Greek) Society for Medical Education.

Catherine Martel, Université de Montréal, Canada - section social media editor

Catherine obtained her PhD from the Université de Montréal, and pursued a postdoctoral fellowship first at Mount Sinai School of Medicine in New York, then at Washington University School of Medicine in St. Louis, Missouri, and obtained the Junior Investigator Award for Women from the Arteriosclerosis, Thrombosisand Vascular Biology (ATVB) council of the American Heart Association. Her postdoctoral work is certainly groundbreaking and brings forward new considerations in the field: she discovered that the lymphatic vessel route, the network that runs in parallel with the blood vessels, is critical for removing cholesterol from multiple tissues, including the aortic wall. In 2013, Dr. Martel joined the ATVB's Early Career Committee in 2013, eager to bring a Canadian perspective to the group and get involved in council activities. Since 2014, Dr. Catherine Martel has been an Assistant professor at the Department of Medicine at the Université de Montréal, and a research scientist at the Montreal Heart Institute. Her research program now focuses on characterizing the physiopathologic role of the lymphatics in the initiation, progression and regression of atherosclerosis. Basic and translational research will allow her team to identify the causes of lymphatic dysfunction, and eventually target potential therapeutic strategies aiming at improving lymphatic function at the different levels of the atherothrombotic disease. You can follow Catherine's lab at @LaboMartel_ICM. Catherine joined the Future Science OAboard via our Young Ambassador panel. We interviewed Cath about her time as an early career researcher, and what advice she has for others. You can read the full interview here.

Italo Porto, University of Genova, Italy

Dr. Porto graduated in medicine in 1998 from at the Catholic University of the Sacred Heart, Gemelli Hospital in Rome, Italy, where he also finished his General Medicine and Cardiology residency in 2002. He was then Clinical and Interventional Fellow at the John Radcliffe Hospital Oxford (UK), where his research resulted in several high-level scientific publications. His PhD was awarded by Catholic University of the Sacred Heart, Rome in 2006. Following this, he held positions at the Gemelli Hospital, San Donato Hospital and the Catholic University. He moved back to his mother hospital (Gemelli Hospital Catholic University of the Sacred Heart) in November 2014 as Senior Interventional Cardiologist. The focus of his research is mainly integrative, at the edge between basic and clinical science in the cath lab.His current H-index is 36, with more than 4400 citations received.

Kjell Sakariassen, KellSa s.a.s, Italy

Kjell gained his Ph.D. in Medical Physiology from the University Hospital of Utrecht in 1984. He underwent post-doctoral studies in arterial thrombosis and vascular inflammation/arteriosclerosis at Roche, Basel and University of Washington, Seattle from 1984—1987. Between 1987 and 2004 he held, sequentially, the positions of Research Scientist at Roche; Group Leader at the Biotechnology Center of Oslo, University of Oslo; Head of Discovery at Nycomed, Oslo; Professor of Physiology at University of Oslo; Head of Pharmacology, Pharmacia and Biovitrum, Stockholm and Uppsala; and World-Wide Head of Pharmacology and Early Safety Evaluation at Serono Int., Ivrea, Geneva and Boston. He is currently CEO and Managing Director of KellSa s.a.s., Biella (2004—present), and KellSa Diagnostics GmbH, Basel, (2012—present). He was a member of Scientific and Cardiovascular Boards of Evolva SA, Basel (2007—2013), and is currently a member of the National Swedish Board of the SciLifeLab Drug Discovery and Development Platform, Stockholm and Uppsala (2014—present). His professional expertise particularly lies in research and development of cardiovascular, bleeding and inflammatory disorders, including diagnostics. You can follow Kjell on Twitter at @SakariassenS.

Jaap Jan Zwaginga, Leiden University Medical Center, The Netherlands

After his PhD on uremic bleeding at the medical school at University Utrecht in 1989, Jaap Jan became an MD in 1991. Following subsequent positions at the University Hospital Utrecht; and the Academic Medical Centre in Amsterdam in combination with Sanquin Amsterdam, he is currently a haematologist, transfusion specialist and professor in Transfusion Medicine at the Leiden University Medical Center in the Netherlands. He is, moreover, head of the Centre for Stem cell Therapy at the LUMC and a clinical JACIE inspector. Finally, he is Clinical and Laboratory manager of the Sanquin-LUMC Jon J van Rood Research Center for Clinical transfusion medicine. With over 125 publications, he has been principle or co-investigator for several project grants and clinical studies. His current research interests surround evidence-based transfusion medicine, and regenerative and immunomodulatory cell therapies.

Dermatology

Kavita Beri, Young Ambassador panel, Jersey Shore University Medical Center, USA -section social media editor

Michael H Gold, Tennessee Clinical Research Center, Gold Skin Care Center, Nashville, TN, USA

Dr. Michael H. Gold is the founder & medical director of Gold Skin Care Center, Advanced Aesthetics Medical Spa, The Laser & Rejuvenation Center, and Tennessee Clinical Research Center in Nashville, TN. He is a board-certified dermatologist and dermatologic surgeon and oversees the various facets of the center's operations. Dr. Gold has earned worldwide recognition for providing patients with leading-edge technological advances in dermatology and aesthetic skin care. He plays an integral role in the development of new pharmaceutical products and medical devices through his clinical research and has authored over 300 published scientific articles, 28 textbook chapters. In addition, Dr. Gold helped establish the Tennessee Society for Laser Medicine and Surgery (TSLMS). He also helped start two international groups: the Dermatologic Aesthetic Surgery International League (DASIL) and 5-Continent-Congress (5CC), one of the world's leading conferences on Dermatologic and Aesthetic Surgery.

Adam J Friedman, George Washington School of Medicine and Health Sciences, Washington, DC, USA

Having undergone undergraduate training at the University of Pennsylvania, Adam Friedman graduated with Distinction in Dermatologic Research from the Albert Einstein College of Medicine (NY, USA). He then went on to complete his internship at New York Hospital Queens, before returning to Einstein for his dermatology residency, where he was appointed Chief Resident. He served as the Director of Dermatologic Research at Einstein for five years, and is currently the Residency Program Director and Director of Translational Research in the Department of Dermatology at The George Washington University School of Medicine & Health Sciences. His broad interests cover medical and pediatric dermatology, and research utilizing nanotechnology for dermatological treatment. He has published numerous articles and textbooks, and received multiple awards. He also serves on various committees and advisory boards, and regularly appears in the media discussing his field. Adam led a special focus issue on nitric oxide in medical applications, which you can read here.

Microbiology & Infectious Disease

Dayle Daines, Old Dominion University, USA

Dr. Daines obtained a B.Sc. at the University of Calgary and her Master's and Ph.D. degrees at the University of Rochester School of Medicine and Dentistry in the Department of Microbiology & Immunology (USA). She has worked in research institutes, government laboratories, and academic institutions and is currently an Assistant Professor in the Department of Biological Sciences at Old Dominion University. Her research focuses on bacterial pathogenesis and molecular mechanisms of host-pathogen interactions, particularly those that involve persistence and growth arrest. Another related area of interest is the characterization of novel drug targets and the discovery of new therapeutic compounds.

Medicinal Chemistry, Pharmacology & Drug Discovery

George Baillie, University of Glasgow, UK

George Baillie is a Professor and PI within the Institute of Cardiovascular and Medical Sciences at the University of Glasgow (UK). His research over the last 15 years has examined many aspects of the cAMP signaling pathway in disease and he has published over 140 papers on the subject. His major discovery was that phosphodiesterases are "compartmentalized", and it is their location within cells that direct their function. The Baillie/Houslay lab was the first to discover a specific function for a single isoform of PDE4 (namely PDE4D5 with beta-arrestin desensitizes the beta2-adrenergic receptor). His lab has since gone on to ascribe functions to several other PDE4 isoforms and these discoveries have been published in Science, Nature, PNAS, EMBO, Molecular Cell and Current Biology. Professor Baillie is founder and director of Sannox Therapeutics, a spin-out venture within University of Glasgow. You can follow George on Twitter at @qbma25. Read more about his work here.

Jürgen Bajorath,University of Bonn, Germany

Jürgen Bajorath received his diploma and PhD degrees (1988) in biochemistry from the Free University in West-Berlin, Germany. He was a postdoc with Arnie Hagler at Biosym Technologies in San Diego. From 1990-2004, Jürgen held various positions in academia and the pharmaceutical industry in Seattle including 7 years at the Bristol-Myers Squibb Pharmaceutical Research Institute. In 1995, he became an Affiliate Professor at the University of Washington. In 2004, Jürgen was appointed Professor and Chair of the newly formed Department of Life Science Informatics at the University of Bonn. He also continues to be an Affiliate Professor at the University of Washington. Jürgen is a member of a number of editorial and scientific advisory boards and an editor of the Journal of Medicinal Chemistry. His research focuses on chemoinformatics, the development and application of computational methods for pharmaceutical research, and drug discovery. Jürgen has more than 550 publications and 25 patents.

Hugo Cerecetto, Universidad de la República, Uruguay

Hugo Cerecetto is Professor of Chemistry in the Nuclear Research Centre at School of Sciences, University of the Republic (Uruguay) working on the research and development of new therapeutic agents. Dr. Cerecetto's research interests are tropical diseases and cancer. He has been a researcher in the different stages of Drug Discovery and Development Platform involving design and synthesis of new bio-active agents, in vitro and in vivo biological studies, QSAR, and pre-clinical assays (studies of mutagenicity, stability, metabolism, and formulation). The developed hits, leads and drugs belong mainly to anti-T. cruzi agents, selective hypoxic cytotoxins and theragnostic agents for tumoral hypoxia.

X Margeret Liu, The University of Alabama, USA

Dr. X. Margaret Liu obtained her Ph.D. degree in 2005 in the Department of Chemical and Biomolecular Engineering at The Ohio State University. She had worked as Sr. scientist and team leader in biopharmaceutical and biotechnology industries for six and a half years. In January, 2012, she joined academic research as an assistant professor in the Department of Chemical and Biological Engineering at The University of Alabama. Dr. Liu's research focuses on the improvement of biopharmaceuticals production by host cell engineering and integrated process development, and the development of next-generation bioenergy and biochemical using rational metabolic cell-process engineering facilitated with systems biology.

Bioengineering, Drug Delivery & Nanotechnology

Raj Bawa,Bawa Biotech LLC, PRI at Albany College of Pharmacy; Guanine, Inc., USA

Raj Bawa, MS, PhD, MD ('22) is president of Bawa Biotech LLC (founded 2002), a biotech/pharma consultancy and patent law firm based in Ashburn, Virginia, USA. Trained as a microbiologist and biochemist, he is an inventor, entrepreneur, professor, and registered patent agent licensed to practice before the US Patent & Trademark Office. He is currently a scientific advisor to Teva Pharmaceutical Industries, Ltd. (Israel), a visiting research scholar at the Pharmaceutical Research Institute of Albany College of Pharmacy (Albany, NY), and vice president/chief IP officer at Guanine, Inc. (Rensselaer, NY). Currently, he is also a medical student and will receive the MD degree in 2022. He has served as a principal investigator in the past, most recently as a principal investigator of a CDC grant to develop an assay for carbapenemase-resistant bacteria. He was an adjunct professor at Rensselaer Polytechnic Institute in Troy, NY from 1998-2018, where he received his doctoral degree in three years (biophysics/biochemistry). In the 1990s, Dr. Bawa held various positions at the US Patent & Trademark Office, including primary examiner from 1996-2002. Presently, he is a life member of Sigma Xi, co-chair of the nanotech and precision medicine committees of the American Bar Association and founding director of the American Society for Nanomedicine (founded 2008). He has authored over 100 publications, co-edited 7 texts, and serves on the editorial boards of numerous peer-reviewed journals, including serving as an associate editor of Nanomedicine (Elsevier). Some of Dr. Bawa's awards include the Innovations Prize from the Institution of Mechanical Engineers, London, UK; Appreciation Award from the Undersecretary of Commerce, Washington, DC; Key Award from Rensselaer's Office of Alumni Relations; and Lifetime Achievement Award from the American Society for Nanomedicine.

Marianna Foldvari, University of Waterloo, Canada

Dr. Marianna Foldvari is a Professor of Pharmaceutical Sciences at the University of Waterloo's School of Pharmacy in Canada. She is an internationally recognized expert in nanomedicine. Her interests include pharmaceutical nanotechnology and drug delivery system design for dermatology, neurodegenerative disorders such as glaucoma, and autoimmune diseases. Current investigations include novel materials, mechanisms and pathways that enable the discovery and invention of needle-free administration methods of medicines (dermal, transdermal, transmucosal, ocular, oral and intranasal), especially proteins and nucleic acids.

John G Hardy, Lancaster University, UK

Dr. Hardy received his Ph.D. in Chemistry from the University of York in 2007. He enjoyed postdoctoral fellowships in France, Germany, Northern Ireland and the USA, working with the Nobel Laureate Jean-Marie Lehn (Strasbourg), Thomas Scheibel (Bayreuth), Colin McCoy (Belfast), David Kaplan (Tufts) and Christine Schmidt (Austin, Texas and Gainesville, Florida). He is currently a Lecturer (Assistant Professor) in the Department of Chemistry and Materials Science Institute at Lancaster University. His current research focus is the development of materials that respond to electricity, light and magnetism and their application for biomedical applications (such as drug delivery, or tissue engineering and regenerative medicine). You can follow his lab at @JGHardyLab.

Ali Khademhosseini, Terasaki Institute, USA

Ali Khademhosseini is Professor of Medicine at Harvard Medical School and Director of the Biomaterials Innovation Research Center at Brigham and Women's Hospital. He is also a faculty at the Harvard-MIT Division of Health Sciences and Technology as well as an Associate Faculty at the Wyss Institute for Biologically Inspired Engineering and a Junior PI at Japan's World Premier International-Advanced Institute for Materials Research at Tohoku University where he directs a satellite laboratory. He is recognized as a leader in combining micro- and nano-engineering approaches with advanced biomaterials for regenerative medicine applications. In particular, his laboratory has pioneered numerous technologies and materials for controlling the architecture and function of engineered vascularized tissues. He has authored over 450 journal papers (H-index = 80, >23,000 citations) and 50 books/chapters. In addition, he has delivered 250+ invited/keynote lectures. Dr. Khademhosseini's interdisciplinary research has been recognized by over 30 major national and international awards. He is a recipient of the Presidential Early Career Award for Scientists and Engineers, the highest honor given by the US government for early career investigators. He is also a fellow of the American Institute of Medical and Biological Engineering (AIMBE), the Royal Society of Chemistry (RSC), Fellow of the Biomaterials Sciences and Engineering (FBSE) and the American Association for the Advancement of Science (AAAS). Currently he serves on the editorial board of numerous leading journals. He received his Ph.D. in bioengineering from MIT (2005), and MASc (2001) and BASc (1999) degrees from University of Toronto both in chemical engineering. Read more here.

Jae-Young Lee, Gwangju Institute of Science and Technology, Republic of Korea

Dr. Jae-Young Lee is an assistant professor of School of Materials Science and Engineering, Gwangju Institute of Science and Technology (GIST), Republic of Korea. Dr. Lee received B.S. and M.S. degrees in Chemical Technology from Seoul National University in 1997 and 1999, respectively. He worked as a research manager in LG Life Science Ltd from 1999 to 2005. He received his Ph.D. from The University of Texas at Austin in 2010. He studied his postdoctoral research at University of California Berkeley with an American Heart Association (AHA) postdoctoral fellowship. He joined GIST in 2012. His current research focuses on the development of functional biomaterials that can improve biomaterial-cell interactions for various uses. His research interests include designs of surface modification of implantable bio-electrodes, tissue engineering scaffolds, and nano-biomaterials for therapeutic applications.

Didier Letourneur, CNRS, France

Didier is Research Director at CNRS. In 2002, he founded a research structure focused on the use of biomedical polymers for 3D structures and contrast agents for vascular imaging. Since 2005, he has led the team of Cardiovascular Bioengineering at Inserm-X Bichat hospital - University Paris Nord and Paris Diderot (France). He is now the Director of the Laboratory for Vascular Translational Science (LVTS–Inserm U1148) with about 160 persons. He is actively involved in several regional, national and European projects. Since 2013, he has been the European coordinator of "NanoAthero", a large scale NMP FP7 program on imaging and treatment of cardiovascular diseases with nanotechnologies. The author of 118 international publications and inventor of 15 patents, he has won several prizes: "Coup d'Elan for Research" Foundation Bettencourt 2001, Diderot Innovation Award 2009 CNRS-University Paris 7, Cardiovascular Innovation Award 2011 from the Medical Research Foundation, and OSEO/BPI emergence 2012 & Creation-Dev 2013 for start-up creation "IMMATIS". He has more than 90 invited lectures and seminars and is the co-organizer of several national and international conferences and two Inserm training workshops for regenerative medicine. He is the vice-chairman for Regenerative Medicine at the European Technology Platform for Nanomedicine and President of BIOMAT, French Society for Biomaterials.

Niren Murthy, University of California at Berkeley, USA

XiuJun (James) Li, University of Texas at El Paso (UTEP), USA

XiuJun (James) Li received his Ph.D. in bioanalytical chemistry in 2008 from Simon Fraser University, Canada, and then moved to University of California Berkeley and Harvard University for his postdoctoral research from 2009 to 2011, as a NSERC Postdoctoral Fellow. Currently, he is a tenure-track Assistant Professor in the Department of Chemistry at University of Texas at El Paso (UTEP), USA. His current research interest is centered on bioanalysis and bioengineering using microfluidic lab-on-a-chip and nanosensing. Dr. Li is the recipient of UT STARS Award in 2012, UTEP Outstanding Performance Award in 2014, and the 2014 Bioanalysis Young Investigator Award.

Oncology

Lev Berstein, Petrov Research Institute of Oncology, St. Petersburg, Russia

Lev is Chief of Laboratory of Oncoendocrinology at Petrov Research Institute of Oncology, St. Petersburg, Russia. His main scientific interests include mechanisms of hormonal carcinogenesis, studying of risk factors of hormone-associated tumors and new approaches to prevention and treatment of the latter. He received several international distinctions (including UICC Translational Cancer Research Fellowship), serves as a Member of Council of Russian Endocrine Association, at editorial boards of two national journals and as a reviewer for Future Oncology, J. Cancer Res. Clin. Oncol., Mol. Cell. Endocrinology, Cancer Epidemiology, Biomarkers & Prevention and others. In his bibliography are 7 monographs, 16 chapters and more than a hundred papers in peer-reviewed journals. He graduated as MD at Tartu University in Estonia and received his PhD and DMS degrees from Cancer Endocrinology at Petrov Institute in St.Petersburg.

Carlo Buonerba, Cancer Center of Excellence of Basilicata (CROB), Italy

Dr Carlo Buonerba studied electronic engineering before earning his medical degree, summa cum laude, at University Federico II of Naples in 2009. He is an active clinical researcher and medical writer. He has served as co-investigator in 7 prospective trials and has authored more than 60 papers, with an h index of 13. He is also an entrepreneur having founded and become the CEO of two companies that provide scientific editorial assistance and develop medical software. Genitourinary cancer and thymic epithelial tumors comprise his main fields of research.

Liang Cheng, Indiana University School of Medicine, USA

Dr. Liang Cheng is Professor of Pathology and Urology at Indiana University School of Medicine, Indianapolis, Indiana, USA. Currently, he is Chief of the Genitourinary Pathology Service, Director of the Urologic Pathology Fellowship, and Director of Molecular Diagnostics and Molecular Pathology Laboratories. Dr. Cheng has published over 600 peer-reviewed articles in high-impact scientific journals. His published work has been cited more than 21,000 times (h-index: 75). He is also the author and editor of several textbooks, including Bladder Pathology, Urologic Surgical Pathology, Essentials of Anatomic Pathology, Molecular Genetic Pathology , Atlas of Genitourinary Pathology, Molecular Surgical Pathology , Renal Tumors, and Atlas of Anatomic Pathology.

John Greenman, University of Hull, UK

John is a tumour immunologist with extensive experience of developing lab on a chip technology for analysing tumour biopsies. He has published over 150 peer-reviewed publications and his immunobiology group works closely with clinicians, chemists and engineers. The majority of this research work has focused on tumours of the Head & Neck region, identifying novel markers of progression or treatment response. He gained his PhD at the Tenovus Cancer Research Institute (Southampton University), and worked as a postdoc at the Dunn School of Pathology in Oxford before moving to Hull in 1995; he was awarded his Professorship in 2009. He was made Heart Research UK's researcher of the year in 2012 for his work on heart on a chip. He is currently Head of the School of Life Sciences.

Simon Lo, University of Washington School of Medicine - Radiation Oncology, Seattle, WA, USA

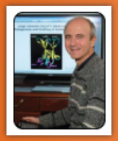
Dr. Lo is Professor of Radiation Oncology and Vice Chair for Strategic Planning of Department of Radiation Oncology. Previously, he was a Professor of Radiation Oncology and Director of Neurologic Radiation Oncology and Gamma Knife Radiosurgery at University Hospitals Seidman Cancer Center, Case Western Reserve University. He has served previously on the faculty at the Indiana University Cancer Center and Arthur G. James Cancer Hospital, Ohio State University. Dr. Lo's research interest is in delivering stereotactic radiation to all body sites as well as neurologic radiation oncology. He is the Chair of the American College of Radiology Appropriateness Criteria Bone Metastasis Expert Panel and Member of the American Society for Radiation Oncology Bone and Brain Metastasis Taskforce. His collaborative work on radiobiologic modeling for ablative radiation dose range with his colleagues at Ohio State University has been recognized internationally. He has published 170 peer-reviewed publications and over 50 book chapters and has edited or co-edited 4 textbooks, including a comprehensive textbook in stereotactic body radiation therapy, which has had 36,000 chapter downloads and is available in most medical libraries worldwide. Dr. Lo has lectured in national and international meetings and at a number of prestigious medical schools as a visiting professor. He is the Radiation Oncology Track Chair for the Radiological Society of North America refresher courses and the President-Elect of the Council of Affiliated Regional Radiation Oncology Societies (CARROS) of American College of Radiology. He is a member of the CNS/Pediatric Committee of the American Board of Radiology. He is currently a Fellow of American College of Radiology.

Srdjan Saso, Imperial College London, UK

Dr Saso qualified in 2007 from Imperial College, School of Medicine. He went on to complete basic training in Northwick Park and St. Mary's Hospitals before being appointed, in 2009, to the North West Thames Deanery Obstetrics and Gynecology program. In 2011 he became a member of the Royal College of Surgeons. He completed his PhD at Imperial College London in 2014, which focused on aspects of fertility preservation and uterine transplantation. In addition to his clinical appointments, he worked on the application of statistical methodology to review various aspects of surgical practice, holding an Honorary Clinical Research Fellowship in the Department of Biosurgery and Surgical Technology at Imperial College under the supervision of Professor Thanos Athanasiou and Lord Ara Darzi.

J Richard Smith, West London Gynaecological Cancer Centre, UK

J Richard Smith trained as a doctor at the University of Glasgow and in London, obtaining his MRCOG in 1988 and graduating with an MD in 1992, covering cervical cancer, immunity and infection. Subsequently lecturing at Charing Cross and Westminster Medical School, he went on to become Director of Gynaecology at Chelsea and Westminster Hospital and visiting associate professor at NYU Medical Centre in New York. He has been based at the West London Gynaecological Cancer Centre, Queen Charlotte's & Chelsea Hospital, Imperial College London for the last 6 years. He is also an adjunct associate professor at NYU Medical Centre. With an interest in doctor/patient communication, he is the series editor for the Patient Pictures book series. He is also editor of the Atlas of Gynaecological Oncological surgery (4th edition; 2016). He has written over 20 books and also has over 130 peer review publications, plus 50 others. Mr Smith has, for the past 15 years, been involved with the UK Uterine Transplantation research team, and is currently its leader. He is also interested in fertility-sparing surgery for women with cancer.



Dimiter Dimitrov, University of Pittsburgh, USA

Dr. Dimitrov joined the National Cancer Institute of the National Institutes of Health, USA, in 1990 where he is senior investigator and appointed at the senior biomedical research service. His research group includes molecular biologists who are experts in display/screening/libraries methodologies, antibody engineering, protein biochemistry, structural and computational biology. His major long-term goal is the development of clinically useful therapeutics and vaccines based on human monoclonal antibodies including engineered antibody domains. He has authored and coauthored more than 360 articles cited about 15,000 times, and is inventor or coinventor of more than 50 inventions, patent applications or patents.

Ajay Goel, City of Hope, CA, USA

Ajay earned his PhD degree from Panjab University, Chandigarh, India in 1996. After a brief tenure at University of Virginia, Charlottesville, Dr. Goel joined University of California San Diego in 1998 for a post-doctoral training fellowship in a gastrointestinal cancer research lab. In 2001, he became Assistant Professor at the School of Medicine, UCSD, La Jolla. He moved to Baylor in 2003 and is now at the City of Hope in Duarte. Dr. Goel's primary research is focused on gastrointestinal cancer pathogenesis and its prevention. A significant focus of his research lab is Cancer Epigenetics, and he is very interested in developing disease biomarkers for the early detection of various gastrointestinal malignancies. He has published almost 180 scientific articles in peer reviewed international journals and several book chapters. He is also a primary inventor on more than 11 patents aimed at developing various biomarkers for the diagnosis, prognosis and prediction of gastrointestinal cancers. Dr. Goel is a member of the American Association for Cancer Research (AACR) and the American Gastroenterology Association (AGA) and is on the international editorial boards of several journals.

Neurology

Breno Satler Diniz, CAMH and University of Toronto, Canada

Dr. Diniz graduated in Medicine at the Federal University of Minas Gerais (2003). He completed a Medical Residency in Psychiatry and Geriatric Psychiatry at the Institute of Psychiatry, Hospital das Clinicas, Faculty of Medicine, USP (2007) and earned his PhD from the Department of Psychiatry, Faculty of Medicine, USP (2011). He completed a Postdoctoral Fellow in Geriatric Psychiatry and Neurosciences at the Department of Psychiatry, University of Pittsburgh, USA (2012). His areas of research interest are: depression in the elderly neurobiology of neuropsychiatric disorders, biomarkers in geriatric depression and cognitive impairment, translational research in psychiatry and neurosciences. You can follow Breno on Twitter at @BrenoSatler.

Immunology

Vito Sabato, University of Antwerp and Antwerp University Hospital, Belgium

Vito was educated at Università Cattolica del Sacro Cuore (Rome, Italy) were he obtained his MD degree and subsequently his certificate as Specialis in Allergology and Clinical Immunology. He is currently Senior Staff Member at the Department of Immunology, Allergology and Rheumatology of Antwerp University Hospital. His activity is mainly focused on flow-assisted analysis of basophils, role of inhibitory receptors in tempering IgE-mediated disease and clonal mast cell-mediated diseases.

Frank Staal, Leiden University Medical Center, The Netherlands

Frank was educated at Utrecht University Medical School, The Netherlands were he obtained his B.Sc. and M.Sc. degrees, both cum laude. He moved to the USA to obtain a Ph.D. degree in Genetics from Stanford University under the guidance of the late Leonard Herzenberg. He moved back to Holland to work with Hergen Spits in Amsterdam and Hans Clevers in Utrecht, after which he started his own lab at Erasmus MC, Rotterdam. Currently he is full professor of Molecular Stem Cell Biology at Leiden University Medical Center. His research focuses on molecular regulation of immature T lymphocyte development and hematopoietic stem cell biology. Besides basic aspects of transcriptional regulation and cell signaling in mouse and human, this knowledge is applied to diagnosis and gene therapy applications of primary human immunodeficiencies as well as to abnormal lymphoid development in acute lymphoblastic leukemias. Translational research leading to novel diagnostic and therapeutic tools is an integral part of his research activities.

Regenerative Medicine

Chris Mason, University College London, UK

Dr. Chris Mason is Professor of Regenerative Medicine Bioprocessing in the Advanced Centre for Biochemical Engineering, University College London working on the clinical translation and commercialization of cell and gene therapies, and tissue-engineered products. He has a multidisciplinary track record, spanning therapeutics, medical devices and information technology, in discovery, clinical medicine, bioprocessing, regulation, healthcare economics, reimbursement and business. His current responsibilities include: Senior Editor of "Regenerative Medicine" journal, Chair of the BioIndustry Association (BIA) Regenerative Medicine and Cell Therapy Industry Group, Founder and Chief Executive Officer of the London Regenerative Medicine Network, and Trustee of the UK Stem Cell Foundation. Dr. Mason is on a number of national and international committees, working groups and initiatives related to the academic, clinical translation and commercialization of advanced therapies including the UK-Israel Science Council, UK Regenerative Medicine Expert Group, the Scientific Advisory Panel of the UK Cell Therapy Catapult, and the Strategic Advisory Board of the Canadian Centre for the Commercialization of Regenerative Medicine. Dr. Mason is a general spokesperson for the regenerative medicine sector including frequent newspaper, radio and TV interviews, plus on social media via Twitter at @Prof_ChrisMason.

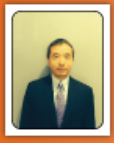
Biochemistry & Biomarkers

Pablo Moscato, University of Newcastle, Australia

Australian Research Council Future Fellow Prof. Pablo Moscato was born in 1964 in La Plata, Argentina. He obtained his BSc. of Physics at University of La Plata, and he defended his PhD at UNICAMP, Brazil. While at the California Institute of Technology Concurrent Computation Program (1988-89) he developed in collaboration with Michael Norman a methodology called "memetic algorithms" which is now widely used around the world. He is the founding co-director of the Priority Research Centre for Bioinformatics, Biomarker Discovery and Information-based Medicine (2006-) and the founding director of the Newcastle Bioinformatics Initiative (2002-2006) of The University of Newcastle. He is also Chief Investigator of the Australian Research Council Centre in Bioinformatics. He has been working in Evolutionary Computation for 25 years, and in heuristic methods for Operations Research problems since 1985. His work and ideas have been highly influential in a large number of scientific and technological fields and his manuscripts have been highly cited. He is one of Australia's most cited computer scientists. In the past seven years he has introduced a unifying hallmark of cancer progression based on the changes of information theory quantifiers, developed a novel mathematical model and an associated solution procedure based on combinatorial optimization techniques to identify drug combinations for cancer therapeutics. He has also identified proteomic signatures to predict years in advance the clinical symptoms of Alzheimer's Disease among other `firsts'. You can follow Pablo on Facebook and read more about his work here.

Nate Snyder,Drexel University, USA

Dr. Snyder is an Assistant Professor at Drexel University in Philadelphia, PA. Nathaniel studied Biochemistry at the University of Maryland and trained at the National Institutes of Health. His Ph.D. thesis in Pharmacology at the University of Pennsylvania concerned analytical measurements of low abundance biological molecules using liquid chromatography-mass spectrometry (LC-MS). Also completed at the University of Pennsylvania, Dr. Snyder's MPH work investigated non-invasive biomarkers of asbestos exposure. Nathaniel has published over 60 peer-reviewed articles and presented academic works on analytical chemistry, metabolism, inflammation, and environmental exposure assessment.



Naidong Weng, Janssen Research & Development, USA

Dr. Weng is Scientific Director, Janssen Fellow, and Head of Bioanalytical Chemistry and Pharmacokinetics, Janssen Research & Development, Johnson and Johnson. He has 97 peer-reviewed journal publications, 10 book chapters, over 100 posters and over 25 podium presentations. He also co-edited one book on bioanalysis (Eliminating bottlenecks for efficient bioanalysis: practices and applications in drug discovery and development, 2014) and one Special Focus Issue of Bioanalysis on Bioanalytical Laboratory Structure and Management (2014). He has been teaching short courses on DMPK at ASMS since 2011. He serves on the editorial advisory boards for three international scientific journals as well as on various scientific/organizational committees, most recently as the chairman for CPSA Shanghai 2013 and CPSA USA 2015. He also serves as a reviewer for (bio)analytical journals and has reviewed over 100 submitted manuscripts.

Ian Wilson, Imperial College London, UK

Ian studied biochemistry at the University of Manchester Institute of Science and Technology (UK), obtained a PhD at Keele University (UK) and then worked in Pharma finally as a Senior Principal Scientist in DMPK for AstraZeneca. Now at Imperial College (London, UK) he is author, or co-author, of some 490 publications, and has received awards in separation and analytical science from the Royal Society of Chemistry, the Chromatographic Society and the Belgian Society of Pharmaceutical Sciences. His research is directed towards the development of hyphenated techniques in chromatography and their application to problems in drug metabolism, toxicology and metabonomics.

UNIVERSITAS AIRLANGGA

FAKULTAS KESEHATAN MASYARAKAT

Kampus C Mulyorejo Surabaya 601115 Telp.031-5920948, 5920949 Fax 031-5924618

Laman : http://www.fkm.unair.ac.id: E-mail: info@fkm.unair.ac.id

SURAT KETERANGAN

Nomor : 3148/UN3.1.10/KP/2023

Yang bertandatangan di bawah ini :

Nama : Dr. Santi Martini, dr. M.Kes

NIP : 196609271997022001

Pangkat/Golongan : Pembina / Gol. (IV/a)

Jabatan : Dekan

Dengan ini menerangkan bahwa :

Nama : Dr. Hari Basuki Notobroto, dr., M.Kes

NIP : 196506251992031002

Pangkat/Golongan : Pembina (Gol. IV/a)

Jabatan : Lektor Kepala

Telah melaksanakan penelitian dengan judul sebagai berikut :

No.	Judul Karya Ilmiah	Tahun Pelaksanaan
1	Acute Respiratory Infections Associated with Exposure to Biomass Cooking Fuels and Cigarette Smoke among Children Under Five Years of Age in Developing Countries (C6)	2022
2	Challenges and strategy in treatment with exosomes for cell-free-based tissue engineering in dentistry (C7)	2021
3	Extracellular vesicles: a promising cell-free therapy for cartilage repair (C8)	2019
4	Plant-derived exosome-like nanoparticles: A concise review on its extraction methods, content, bioactivities, and potential as functional food ingredient (C10)	2021
5	Prospect of Stem Cells as Promising Therapy for Brachial Plexus Injury: A Systematic Review (C12)	2022
6	The potential of mesenchymal stem-cell secretome for regeneration of intervertebral disc: A review article (C34)	2021
7	Towards Prevention and Eradication of Leprosy : Current Status and Research Needed in Community Health & Immune Dysregulation (C75)	2020
8	Health risks associated with high waist circumference: A systematic review (C82)	2020
9	Associated Risk of Death From Covid-19 Infection in Patients with Hypertension Co-Morbidities (C120)	2021

Adapun penelitian tersebut layak dilakukan dan menghasilkan output yang sangat baik, meskipun belum ada ***Uji Ethical Clearance*** karena merupakan penelitian menggunakan metode **Systematic Review**.

Demikian surat keterangan ini kami buat untuk dapat dipergunakan sebagai persyaratan pengusulan Jabatan Fungsional Guru Besar.

Surabaya, 24 April 2023
Dekan,

Dr. Sargi Martini, dr. M.Kes
NIP.196809271997022001

Review

For reprint orders, please contact: reprints@future-science.com

Future Science OA

Challenges and strategy in treatment with exosomes for cell-free-based tissue engineering in dentistry

Ika Dewi Ana*[,1], Anggraini Barlian[2], Atik Choirul Hidajah[3], Christofora Hanny Wijaya[4], Hari Basuki Notobroto[3] & Triati Dewi Kencana Wungu[5]

[1]Department of Dental Biomedical Sciences, Faculty of Dentistry, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia

[2]School of Life Sciences & Technology, Institut Teknologi Bandung, Bandung, 40132, Indonesia

[3]Department of Epidemiology, Biostatistics, Population Studies, & Health Promotion, Faculty of Public Health, Universitas Airlangga, Surabaya, 60115, Indonesia

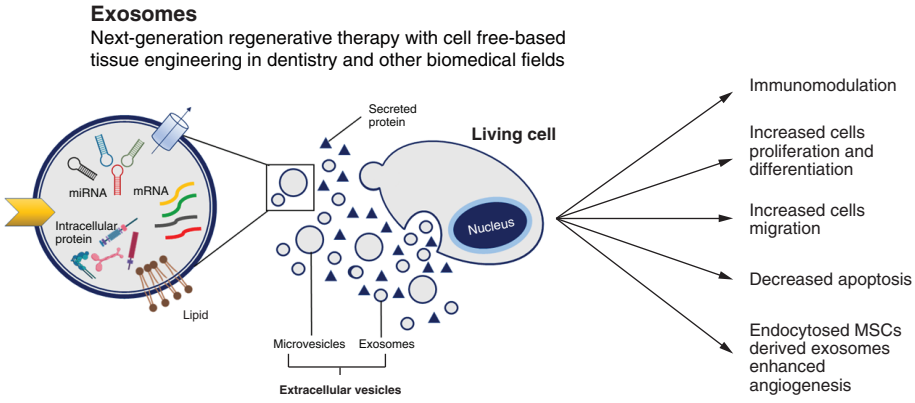
[4]Department of Food Science & Technology, Faculty of Agricultural Engineering & Technology, IPB University, Bogor, 16002, Indonesia

[5]Department of Physics, Faculty of Mathematics & Natural Sciences, Institut Teknologi Bandung, Bandung, 40132, Indonesia

*Author for correspondence: ikadewiana@ugm.ac.id

In dentistry, problems of craniofacial, osteochondral, periodontal tissue, nerve, pulp or endodontics injuries, and osteoarthritis need regenerative therapy. The use of stem cells in dental tissue engineering pays a lot of increased attention, but there are challenges for its clinical applications. Therefore, cell-free-based tissue engineering using exosomes isolated from stem cells is regarded an alternative approach in regenerative dentistry. However, practical use of exosome is restricted by limited secretion capability of cells. For future regenerative treatment with exosomes, efficient strategies for large-scale clinical applications are being studied, including the use of ceramics-based scaffold to enhance exosome production and secretion which can resolve limited exosome secretory from the cells when compared with the existing methods available. Indeed, more research needs to be done on these strategies going forward.

Graphical abstract:



Lay abstract: Application of stem cells in dental tissue engineering such as in osteochondral, periodontal, pulp, salivary gland or nerve regeneration as well as in osteoarthritis, mucosal, skin and oral wound healing, is still problematic, especially for its large clinical scales. Therefore, cell-free-based tissue engineering using exosomes isolated from stem cells is regarded next-generation treatment in dentistry. In this study, basic understanding on the exosomes, status, the potential for regenerative therapy including challenges and strategies for the clinical applications are reviewed. Future approaches to increase production and secretion from the cells are also proposed to resolve limitation in exosomes availability.

FUTURE SCIENCE

First draft submitted: 19 April 2021; Accepted for publication: 21 September 2021; Published online: 29 October 2021

Keywords: cell-free-based therapy • ceramics-based scaffold • exosome • MSC • regenerative dentistry • tissue engineering

There is a limitation of the regenerative potential in human tissue. Therefore, regenerative medicine exists to stimulate and induce healing and regeneration of human tissue or organ. In regenerative medicine, tissue engineering is considered an extremely important area involving the use of materials, cells and to a large extent, signaling molecules. Tissue engineering approach has the goal to understand tissue function and enable tissue or organ on the body to be made *de novo*. To achieve very important long-range objective of tissue engineering, research in many areas with collective interdisciplinary views are required.

Based on tissue engineering paradigm, materials are necessary to design then provide proper scaffold to support the constructive remodeling of injured, damaged or missing tissues or organ. Scaffold can be engineered to have specific structural, mechanical, physical and chemical properties that closely approximate those of extracellular matrix of the tissue replaced. The scaffold should facilitate the attachment, migration, proliferation, differentiation and three-dimensional spatial organization of the cell population required for structural and functional replacement of the targeted tissue or organ [1–3]. Any scaffold materials will be subjected to *in vivo* remodeling which covers the process of host response to the scaffold materials, the degradation and replacement of scaffold by new host tissue, and the organization and differentiation of the new host tissue in relationship to surrounding structures to fully incorporate into the host toward tissue regeneration (Figure 1). The *in vivo* remodeling is influenced by several factors such as blood supply, pH, concentration of oxygen and carbon dioxide, mechanical stressors and host–scaffold interface [4,5].

The use of cells in tissue engineering attracted scientists to pay a lot of attention to stem cells, especially mesenchymal stem cells (MSCs), because their defining properties make them an ideal candidate to cure diseases. In fact, embryonic and fetal stem cells have the greatest potential to differentiate into different cell types, but their application is limited due to ethical issues and the danger of unlimited and uncontrolled cells division. The use of stem or progenitor cells have been expanded widely for treating many types of diseases in the framework of tissue engineering. It was known from previous studies that MSCs can stimulate regeneration of several tissues or organs after injury both preclinically and in clinical trials [6–15]. Mesenchymal stem cell (MSC) is a cell that has not been differentiated and able to regenerate itself through cell division, with the ability to differentiate into other cells [16]. These cells are widely used in the field of tissue engineering to regenerate bone tissue because they can differentiate into osteogenic cells [17,18].

Despite the observed beneficial effects, there is no consistent evidence that the cells employed generate organ-specific cell population, able to replace the cell loss after injury [6]. A major MSC limit for its clinical applications is the inherent heterogenicity and variation associated with cell expansion [19,20]. Changes that may increase the risk of MSC therapeutic application could also be induced during *in vitro* cell processing and expansion. The risk of unwanted differentiation *in vivo* is also a problem due to its clinical applications. Therefore, nowadays cell-free-based therapy is considered an alternative treatment in tissue engineering, which also includes extensive research on the identification of the molecules involved in paracrine action of stem cells to open new therapeutics options.

Due to the theory of paracrine stimulation, upon the application, transplanted cells will affect residing cells by secretion of bioactive molecules into the extracellular space [20]. A lot of studies have been conducted to purify growth factors (GF) and apply the GF to stimulate regeneration, including the use of platelet-rich plasma and platelet-rich fibrin [21,22]. However, the role of purified GFs in stimulating regeneration is not as effective as expected due to their short half-life in the extracellular space [23]. Therefore, there is a need to develop a strategy to overcome the disadvantages of a cell-based approach in tissue engineering and regenerative medicine. The MSCs extracellular vesicles (EVs) which contain biologically active molecules, such as GFs, cytokines and functional RNAs known as exosomes have become a particular interest for cell-free regenerative therapy due to their epigenetic capacity and cargos.

To some extent, in tissue-engineering-based regenerative therapy, there is a 'construct' to promote the repair and/or regeneration of tissues. As explained previously, the 'construct' which is provided as a scaffold and cells/biomolecules delivery system, plays an important role as a conductive strategy to interfere regenerative process

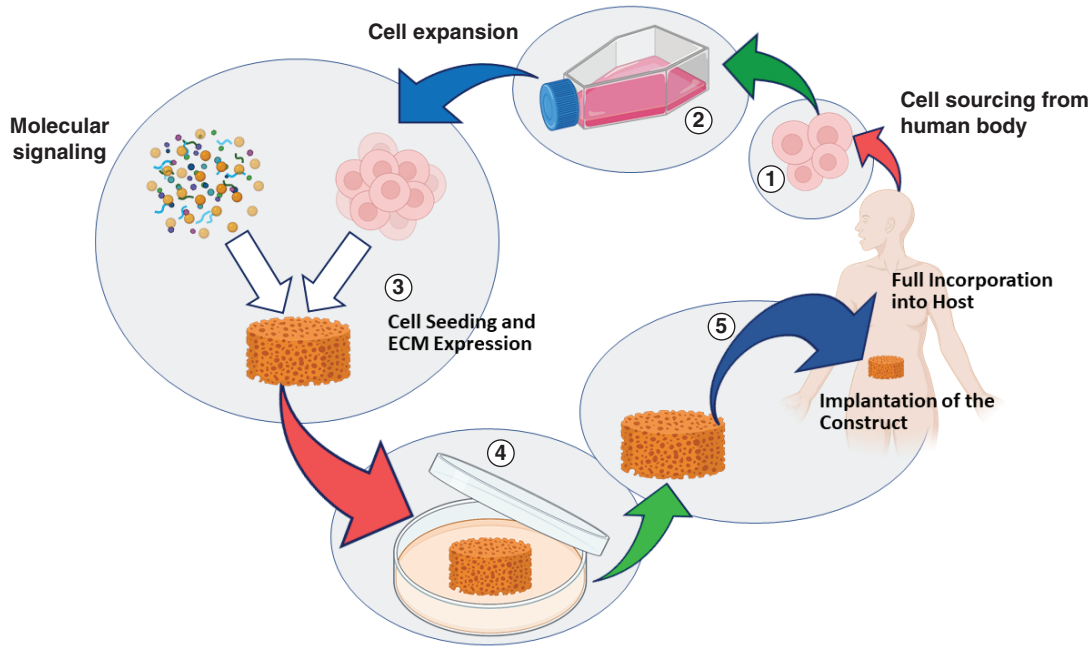


Figure 1. Tissue engineering paradigm with the scaffold as the central construct to provide 3D spatial for cells to attach, growth as well as organize structural and functional replacement of the tissue or organ.

Table 1. Types, size and origin of extracellular vesicles according to the MISEV 2018.

Types	Size (nm)	Origin
Exosome	50–100	Endosome
Micro vesicles	100–1000	Plasma membrane
Apoptotic bodies	1000–5000	Plasma membrane

Data taken from [26].

by enabling the desired host cells to populate the regeneration site [3,24]. This is because scaffold is intended to support cell migration, growth, differentiation and guide tissue development and organization into a mature and healthy state [24]. Meanwhile, it is also recognized that ceramics containing construct functions as instructive extracellular microenvironment for morphogenesis [3].

In view of the current advancement and challenges, in this study, a comprehensive, hence, concise review on the role of MSCs derived exosomes in regenerative therapy applied in dentistry is elaborated. To understand the role of exosomes in regenerative therapy, overview on the origin, functions and potentials of exosomes are described. The important aspect on the osteoconductive strategy by scaffold containing ceramics is also discussed in this study.

What is MSC-derived exosomes & why?

The cells (including MSC) produce a set of factors or molecules secreted to the extracellular space. The secreted factors include, among others, soluble proteins, free nucleic acids, lipids and EVs. The latter, EVs, can be subdivided into apoptotic bodies, microparticles or microvesicles and exosomes [25], which are differentiated based upon their biogenesis, release pathways, size, content and function. Table 1 shows type, size and origin of EVs [26]. Figure 2 describes diagrammatically the organization of cell secretome. Meanwhile, Figure 3 summarizes the position of exosome as a part of EVs and clarify the organization of EVs in more detailed explanation based on some of the literature and guidelines from the International Society for Extracellular Vesicles in the Minimal Information for Studies of Extracellular Vesicles 2018 (MISEV2018) on nomenclature, isolation and characterization [26,27]. The secretome of individual cells and tissues is specific, and changes in response to fluctuations in physiological states or pathological conditions. The exosome is part of the EVs originating from the endosome with a size of 30–100 nm [28]. Exosomes are known to be an important substance to facilitate cellular communication by delivering functional cargos, for example, protein, mRNA and microRNA (miRNA), as described by Wang and

10.2144/fsoa-2021-0050

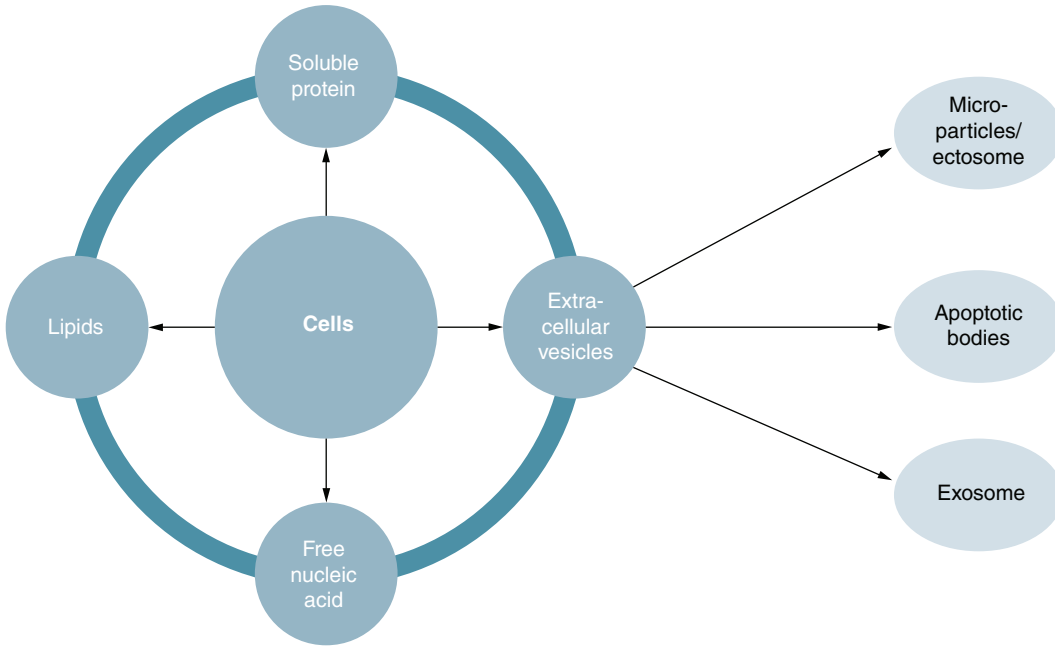


Figure 2. Cells secreted bodies into the extracellular space are called secretome, which contains soluble proteins, free nucleic acid, lipids and extracellular vesicles. The EVs can be divided into apoptotic bodies, microparticles and exosomes. Microparticles are also indicated with other names: nanoparticles, microvesicles, shedding vesicles or shedding bodies, exovesicles, secretory vesicles and oncosomes. Exosomes contains growth factors, cytokines and functional RNA.
EV: Extracellular vesicle.

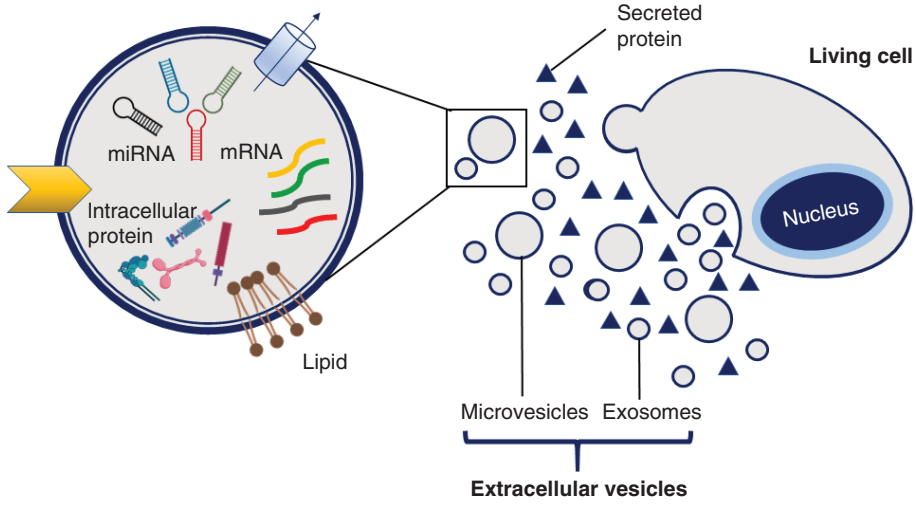


Figure 3. A living cell releases proteins and extracellular vesicles (microvesicles and exosomes) into extracellular spatial.

co-workers [29]. Exosomes from stem cells are composed of a lipid bilayer, with the ability to efficiently protect, transport, and deliver a wide variety of molecules contained in it [30]. Exosomes also play an irreplaceable role in normal physiological processes such as nerve function and neurodegenerative diseases.

The exosomes isolated from MSCs have a more effective therapeutic ability due to their small size and role in cell communication. According to Chopra and co-workers [31], the effectiveness of exosomes derived from MSCs may be due to its ability to migrate to the areas which need repair so that they are ideal for therapeutic use. At this point, it will be a potential method in regenerative treatment if MSCs derived exosomes are used because MSC

can be obtained from Wharton's Jelly which is a waste. Zhang *et al.* [32] proved that exosomes originating from MSCs can help repair cartilage. Exosomes can also help periodontal regeneration by increasing the migration and proliferation of the periodontal ligament cells [33]. However, the use of exosomes as a therapeutic agent currently still has obstacles, including the small number of exosomes produced [31,32,34].

Compared with stem cells or cell-based applications, the use of exosomes provides key advantages over cell-based therapy. The use of exosomes resolves several problems associated with the transplantation of living and proliferative cells population, which cannot be fully controllable *in vivo*. Besides, the immune compatibility, tumorigenicity, emboli formation and the transmission of infections can also be prevented. Moreover, the preparation prior to its applications can be evaluated for its safety, dosage and potency in a method analogous to the preparation of conventional pharmaceutical agents and the use of toxic cryo-preservative agent can also be avoided [35,36]. Eiro and co-workers [35] also predicted that mass production is possible through tailor-made cell lines under controlled laboratory conditions, allow it to provide off-the-shelf exosome therapies immediately.

Biogenesis, functions & potential of exosomes

As previously described, the secretome of MSC consists of soluble factors and EVs. The EV contains biologically active molecules, such as growth factors, cytokines and functional RNAs. Exosomes are released by MSC. At the time of this release, biological factors contained in the exosomes can exert an effect on the cells of the cellular environment or reach distant organs via the bloodstream, including the central nervous system, which processes depend on the permeability of the blood–brain barrier.

Exosomes are originated from endosomal and the size ranges from 30 to 100 nm [6,28], or 50 to 100 nm according to the Minimal Information for Studies of Extracellular Vesicles (MISEV) [26]. Its biogenesis is known to be regulated by specific cellular pathways [37]. Constitutive exocytosis, which occurs in almost all cell types and involved in the secretion of newly synthesized protein, triggers exosomes release. Exocytosis is initiated by invagination of endocytic vesicles that fused with early endosome, continued by endosomal formation [38]. In this way, exosomes are the result of the secretion process of the endosomal components of the cells.

Unlike the microvesicles or ectosomes and apoptotic bodies which are directly shed from the plasma membrane, exosomes are released upon the fusion of late endosomes and multivesicular bodies with the plasma membrane [39]. A highly dynamic endocytic pathway started the first step of exosomes release. The release is started by the accumulation of intraluminal vesicles (ILVs) as early endosomes mature into late endosomes. The ILVs sort and entrap proteins, lipids and cytosol within the late endosomes. The endosomal sorting complex required for transport (ESCRT) is found to control these initial steps of exosomes secretion [40]. The entrapment leads to morphological changes that result in multivesicular bodies (MVBs), as described in the previous studies [41–43]. In most cases, MVBs fuse with lysosome for the degrading and recycling their contents. Certain MVBs are patterned with specific proteins and markers to ensure the fusion with the plasma membrane, allow the release of their contents to extracellular space, and become known as exosomes. This mechanism is dependent, controlled by ESCRT and involves 30 different proteins which help sequester specific biomolecules in the MVBs and guide their releases through the plasma membrane as exosomes [39,43–45]. The diagrammatic cascade of exosomes biogenesis is shown in Figure 4.

Exosomes associate with the progression of diseases, among them are neurodegenerative disease, cardiovascular diseases and cancer. The association is related to the involvement of exosomes in many physiological processes such as antigen presentation, RNA transfer or tissue repair [31–35,46]. Evidence from the previous studies shows that exosomes have specialized functions and key roles in coagulation, intercellular signaling and waste products management. Their functions include immune regulation, vascular regeneration promoting, mediation of cell proliferation, differentiation, migration, and apoptosis, preserving the body physiological condition and partaking in disease processes [20].

MSC-derived exosomes (MSC-exosomes) exhibit high potential for cell-free-based therapy in regenerative medicine. Since MSCs derived exosomes have the characteristics of the resource cells, thus it can promote cell self-repair, regenerate tissue, restore homeostasis of the tissue and accelerate wound healing [47]. A lot of research shows that MSCs have a strong ability to produce exosomes [45–48] and MSCs derived exosomes are believed as the main effective paracrine component which plays almost equivalent biological effects to those of whole MSCs.

In comparison with the whole MSCs, exosomes fuse directly with the targeted cells, thus exhibit more intense biological effects. Exosomes derived from MSCs can be easily stored and transported at -70°C for a long time. Their main components are effectively protected by the exosome's plasma membrane which make them not easily

10.2144/fsoa-2021-0050

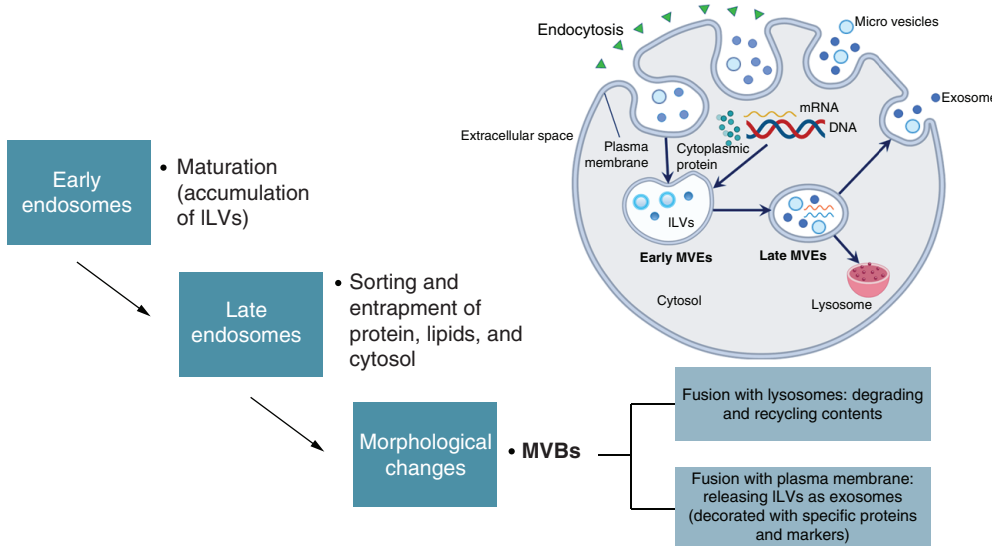


Figure 4. Biogenesis of extracellular vesicles. Microvesicles and apoptotic bodies are originated from plasma membrane, while exosomes are derived from the endosomal compartments. Through an ESCRT-dependent pathway, proteins, lipids, nucleic acids and other cargo are sequestered within the ILVs. The MVBs which fuse with plasma membrane will release ILVs into extracellular space as exosomes.
ESCRT: Endosomal sorting complex required for transport; ILV: Intraluminal vesicle; MVB: Multivesicular body.

destroyed. The concentration, dosage, route, and time of use are also easily controlled. Moreover, there is no risk of immune rejection and tumorigenesis caused by cell transplantation therapy [47].

Potential application of exosomes in regenerative dentistry

An engine search by MEDLINE (PubMed) database with relevant key words such as exosome, regenerative therapy, regeneration, tissue engineering and/or dentistry was used to search relevant articles to this review published up to 31 January 2021. When the terms 'exosome' AND 'dentistry' AND 'regeneration' were used, 60 articles were found. After the screening of the titles, among 60 there were 27 titles directly related or relevant to the study. Among 27, one article provided an experiment related to antibacterial activity of exosome, but after further reading, it was found that the authors only used exosome-liked vesicles from three bee products, in other words, honey, royal jelly and bee pollen [49]. A review article on the exosome derived from saliva [50] was also excluded from the study. Although the article [50] provided description on regeneration of wound healing by salivary exosome, but it was considered not directly relevant to this review. There were also other four review articles concerning exosome or cell-free-based tissue engineering, regenerative therapy and nanotechnology [51–54] which are not specifically related to regenerative dentistry. Therefore, we finally excluded them from the study, remaining 21 articles for further analysis. Table 2 summarizes search results from the 21 articles [55–75].

In his review, Cooper and co-workers [56] mentioned that exosomes carry with them informative cargo from the MSCs to targeted cells. The informative cargo is needed to regulate fundamental cellular processes for lineage-specific differentiation, migration and apoptosis. Regarding bone regeneration, key protein factors carried by exosomes will mediate a series of signaling pathway [76]. For example, an important transcription factor RUNX2 in exosome will promote differentiation of pluripotent stem cells into osteoblast and at the same time inhibit osteoblast maturation [77] or repress osteogenic transcription factors such as OPN, BSP, OSX, dan OCN [78]. Table 3 shows key bone regeneration factors mediated by protein carried by exosomes [76–106].

It is also notified that generally exosome enhanced regeneration by increasing cellular mobilization and proliferation. In case of PDL, Chew and co-workers used PDL cell cultures and found that exosome increased PDL migration and proliferation through CD73-mediated adenosine receptor activation of pro-survival AKT and ERK signaling [55]. Meanwhile, the mechanism of exosomes involvement in promoting bone regeneration process can be observed from the process in which proteins carried by exosomes upregulate bone regeneration factors, as depicted in Figure 5. For example, exosome may induce high expression of BMP2 which in turn promotes osteogenic differentiation and osteogenesis by cascade activation of OSX factor [107]. Similarly, when OPN or Type I collagen

Table 2. Summary of the search results from the MEDLINE (PubMed) database for the articles concerning the application of exosome in regenerative dentistry.

Functions in dentistry	Summary	Type of the study	Study	Ref.
To regenerate periodontal ligament (PDL)	MSC exosome-loaded collagen-sponge-enhanced periodontal regeneration in an immunocompetent rat periodontal defect model	*In vivo*	Chew *et al.*	[55]
To induce bone, cartilage, dentin, mucosa and pulp tissue formation	Functions of MSC exosome in relation to oral and craniofacial tissue engineering	Review	Cooper *et al.*	[56]
To repair critical size osteochondral defects	Exosome enhanced matrix synthesis and a regenerative immune phenotype in osteochondral defect	*In vivo*	Zhang *et al.*	[57]
	Exosome derived human embryonic MSCs promoted osteochondral regeneration	*In vivo*	Zhang *et al.*	[58]
To enhance angiogenesis in oral wounds	Possible implication of exosome for therapeutic induction of angiogenesis in the oral wounds	Review	Zimta *et al.*	[59]
To function as small molecule drug to enhance chondrogenesis	Exosome improved efficient delivery of kartogenin to synovial fluid derived MSCs for chondrogenic differentiation	*In vitro* and *in vivo*	Xu *et al.*	[60]
To treat OA (osteoarthritis) in TMJ (temporo mandibular joint)	Potential of exosome in regenerating cartilage and osseous compartments in TMJ, thus restoring injured, dysfunction, and pain tissues	Review	Lee *et al.*	[61]
	Exosome attenuated inflammation and restored matrix homeostasis	*In vitro*	Zhang *et al.*	[62]
To control dental-pulp derived pain and inflammation	Potential of exosome to modulate thermo-sensitive receptor potential cation channel in pain and inflammation management in everyday dental practices	Review	Schuh *et al.*	[63]
To promote oral mucosal wound healing	Exosome isolated from clinical grade production of oral mucosal epithelial cells stimulated epithelial regeneration and showed pro-regenerative effects on skin wound healing	*In vitro* and *in vivo*	Sjöqvist *et al.*	[64]
To enhance endodontics and pulp regeneration	Potential of exosome as an approach to enhance regenerative endodontics	Review	Tatullo *et al.*	[65]
	Potential of exosome to trigger pulp regeneration (including pulp angiogenesis), regulate proliferation, migration and differentiation and provide neuroprotection	Review	Yu *et al.*	[66]
	Exosome was isolated from DPCs culture supernatant and examined on its roles to HUVEC proliferation, pro-angiogenic factors expression and tubular formation. It was found that exosome-derived DPCs have vital roles in angiogenesis and tubular morphogenesis	*In vitro*	Xian *et al.*	[67]
To enhance cutaneous wound healing	Exosome from neonatal serum used to pre-treat MSCs improved MSCs biological functions in enhancing angiogenesis	*In vitro*	Qiu *et al.*	[68]
To enhance nerve regeneration, increase number and diameter of nerve fibers and promote myelin formation	Exosome was isolated from gingival MSCs, combined with biodegradable chitin conduits and applied to rat sciatic nerve defect. Number and diameter of nerve fibers increased significantly. There was also significant increased proliferation of Schwann cells and dorsal root ganglions by the treatment	*In vivo*	Rao *et al.*	[69]
To inhibit cancer growth	Potential of exosome to inhibit cancer growth since it may transduce apoptosis-inducing factors	Review	Stefanska *et al.*	[70]
To regulate bone remodeling and function as therapeutics agent in orthodontics	Potential of exosome to enhance communication networks integrating bone cells osteoblast, osteoclast, osteocyte) and linking bone to other tissues. These potentials are significant to augment bone remodeling associated with orthodontic force application or required for the repair of craniofacial bone	Review	Holliday *et al.*	[71]
To induce dentinogenesis in regenerative endodontics procedure	Stem cells from apical papilla derived exosomes were applied into the root fragment containing bone marrow MSCs and transplanted subcutaneously into immunodeficient mice. It was observed that dental-pulp like tissues were present and newly formed dentine was deposited onto the existing root canal. It was also observed that dentine sialophosphoprotein and mineralized nodule were significantly increased	*In vitro* and *in vivo*	Zhuang *et al.*	[72]
To regenerate and repair tissue through cell-free-based tissue engineering with sustained release capability	Potential of exosome as mediators for tissue regeneration. The review describes exosome involvement in a multitude of physiological processes, such as development, cell differentiation and angiogenesis	Review	Alqurashi *et al.*	[73]

DPC: Dental pulp cell; MSC: Mesenchymal stem cell.

10.2144/fsoa-2021-0050

Table 2. Summary of the search results from the MEDLINE (PubMed) database for the articles concerning the application of exosome in regenerative dentistry (cont.).

Functions in dentistry	Summary	Type of the study	Study	Ref.
To accelerate craniofacial regeneration when combined with three-dimensional block co-polymer	Exosome derived from human dental pulp stem cells loaded into biodegradable triblock copolymer microspheres of poly(lactic-co-glycolic-acid) or PLGA and poly(ethylene glycol) or PEG facilitated bone marrow stromal cells. It was also observed that direct insertion of the construct into calvaria defect of the mouse accelerated bone healing *in vivo*	*In vitro* and *in vivo*	Swanson *et al.*	[74]
To regenerate salivary gland	Potential of exosome to ameliorate salivary gland injury by combination of three-dimensional bioprinting or bio assembly spheroid or organoid cell transplantation	Review	Chansaenroj *et al.*	[75]

DPC: Dental pulp cell; MSC: Mesenchymal stem cell.

Table 3. Key bone regeneration factors mediated by protein or cytokine carried by exosomes.

Bone regeneration factor	Function	Study	Ref.
RUNX2	Key transcription factor for the differentiation of stem cells into osteoblast and inhibition of osteoblast maturation by suppression of OPN, BSP, OSX and OCN expression	Wang *et al.*; Deng *et al.*	[77,78]
PI3K-AKT	Key transcription factor with phosphatidylinositol 3-kinase (PI3K) and Akt/protein kinase B proteins involved. This signal transduction pathway promotes metabolism, proliferation, cell survival, growth and angiogenesis in response to extracellular signals	Xu *et al.*; Zhao *et al.*	[79,80]
Wnt	Key transcription factor for signaling pathway related to bone remodeling and repair. Wnt signaling system is also known to be a key factor to maintain bone mass	Komiya and Habbas; Issack *et al.*; Grigorie *et al.*; De Santis *et al.*	[81–84]
RANKL-RANK	Key signaling pathway responsible for homeostasis of bone metabolism determined by dynamic balance between osteoblast and osteoclast	Theoleyre *et al.*; Wada *et al.*; Leibbrandt *et al.*; Huynh *et al.*	[85–88]
BMP2	It is multi-functional growth factors which belong to superfamily TGF-β. The BMPs play critical roles in cartilage development, and specifically has been utilized for the therapeutics of bone defects, bone fractures, osteoporosis, spinal fusion and root canal surgery	Chen *et al.*	[89]
BMP9	BMP9 is known to have highest osteogenic potentials compared with other BMPs family. However, it is also revealed that BMP9 exerts broad range biological functions such as adipogenesis, angiogenesis, neurogenesis, oncogenesis and/or tumorigenesis and metabolism	Mostafa *et al.*; Bharadwaz and Jayasuriya	[90,91]
SPP1 (OPN)	SPP1 is also known as BSP1 or OPN. Among its diverse biological functions, OPN is known to regulate biomineralization because its calcium binding sites. As a member of SIBLING (Small Integrin-Binding Ligand, N-linked Glycoprotein) family, it can interact directly with extracellular matrix including fibronectin	Chen *et al.*; Mukherjee *et al.*; Fisher *et al.*; White *et al.*; Lund *et al.*; Singh *et al.*; Si *et al.*	[92–98]
OCN	Produced by osteoblast, OCN is the most abundant non-collagenous protein in bone. It regulates bone mineralization and coordinates mineral ions homeostasis. Bone quality is regulated by OCN because it aligns biological apatite parallel to the collagen fibrils	Wei and Karsenty; Komori	[99,100]
COL1	Type I collagen is the most abundant collagen and a key structural composition of bone tissue that is also expressed in almost all connective tissue as predominant component of interstitial tissue membrane	Henriksen and Karsdal	[101]
TGFβ1	TGFβ1 is abundant in bone, responsible for bone formation and resorption. It stimulates matrix protein synthesis and at the same time inhibits both osteoclast formation and activity	Bonewald and Mundy; Mundy	[102,103]
VEGF	This growth factor, VEGF belongs to PDGF super family. It regulates angiogenesis and vascular permeability	Risau; Shibuya	[104,105]
PDGF	When being activated, PDGF stimulates cell growth, changes cell shape by reorganization of actin filament and affects chemotaxis which directs cells motility. Its role is important during embryonic development and wound healing	Heldin and Westermark	[106]

The table is summarized from a chapter written by Yang *et al.* [76].
BMP: Bone morphogenetic protein; BSP: Bone sialoprotein; COL1: Type I collagen; OCN: Osteocalcin; OPN: Osteopontin; OSX: Osterix; SPP1: Secreted phosphoprotein 1

is upregulated by exosome, bone mineralization cascade will be activated followed by other bone regeneration processes. High expression of other bone regeneration factors such as BMP9, TGF-b1, VEGF and PDGF induced by exosomes will activate osteogenic differentiation and angiogenesis pathway to enhance bone regeneration [76]. In view of the potential of exosome in PDL and bone regeneration, the implication in regenerative dentistry can be clearly elaborated, such as for craniofacial regeneration, implant dentistry, oral-maxillofacial regeneration in

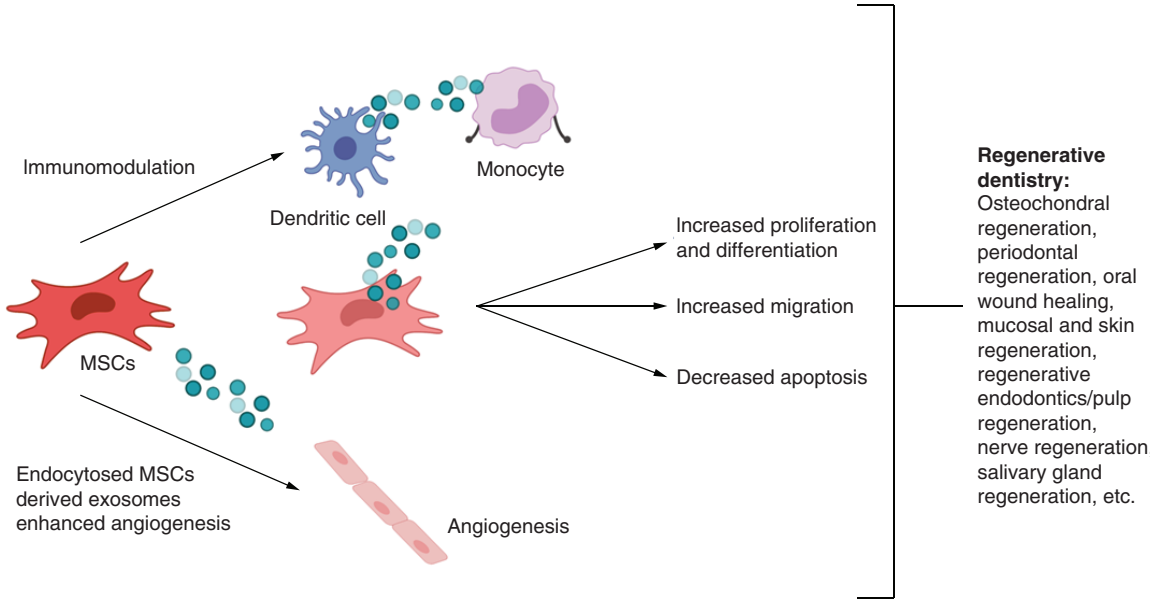


Figure 5. Mesenchymal stem cells derived exosomes with the potential to enhance regeneration in clinical dentistry.

general, PDL regeneration, and in orthodontics for application related to bone remodeling control to avoid relapse post orthodontics treatment.

Related to the role of exosome in cartilage regeneration, firstly it is known that cartilage is a connective tissue with limited capacity for intrinsic regeneration upon injury or lesions. Cartilage injury can also be further aggravated by several joint diseases such as osteoarthritis (OA) and rheumatoid arthritis (RA). In clinics, OA is characterized by joint pain, tenderness, crepitus, stiffness, limitation of movement due to occasional effusion with various degrees of local inflammation [108,109]. It is the most frequent chronic joint disease, with progressive breakdown of articular cartilage [110]. Meanwhile, RA is characterized by dysregulated inflammatory processes in the synovium of the joint. The inflammatory process eventually leads to the destruction of cartilaginous and bony elements of the joint, resulting pain and disability [111]. It is an autoimmune disorder in which dysregulated inflammation and T-cells induce pain and joint degradation [112].

Zhang *et al.* [58] demonstrated that weekly intra-articular injections of human embryonic MSC exosome has successfully induced an orderly cartilage regeneration and subchondral bone in a rat model, marked by the development of hyaline cartilage and underlying subchondral bone. The osteochondral defect repair is characterized by increased cellular proliferation and infiltration, enhanced matrix synthesis, and a regenerative immune phenotype [57,58]. The results of the study by Zhang and co-workers [58] corroborated with a previous study used exosome-derived synovial fibroblasts of RA patient which found that exosome from RA synovial fibroblast of patient (RASF) has a membrane bound form of TNF-a, which leads to apoptotic resistance of T-cells in RA because the lack of apoptotic machinery for T-cells progresses RA [113]. When apoptotic resistance of T-cells increases, there would be delayed onset of RA. In regenerative dentistry, these findings are relevant for the treatment of TMJ disorders because TMJ injury, dysfunction, and pain are closely related to the manifestation of OA and RA in dentistry [61,62].

Generally, during regeneration process, vascularization is essential because new blood vessel formation improves diffusion of oxygen and nutrients in the regeneration area. It has been demonstrated that exosome can stimulate proliferation, migration, and tube formation of endothelial cells (ECs) [114,115]. As it is widely known, angiogenesis is a process of blood vessel formation and stability which is controlled and dictated by VEGF [59,104,105]. Beside having action on vascular endothelial cells, VEGF also enhances bone development by stimulating vascular endothelial cells. Therefore, in some studies, it was known that osteogenesis is closely related to vascularization through cell-to-cell communication between vascular endothelial cells and osteoblasts. In other words, sufficient vascularization is considerably promoting osteogenesis [116–119]. Moreover, it is also revealed from the previous study that exosome-derived MSCs contained abundant levels of VEGF, which enhanced angiogenesis and contributed to periodontal tissue [73,120], oral epithelial [64], and dental pulp or endodontics [65] regenerations.

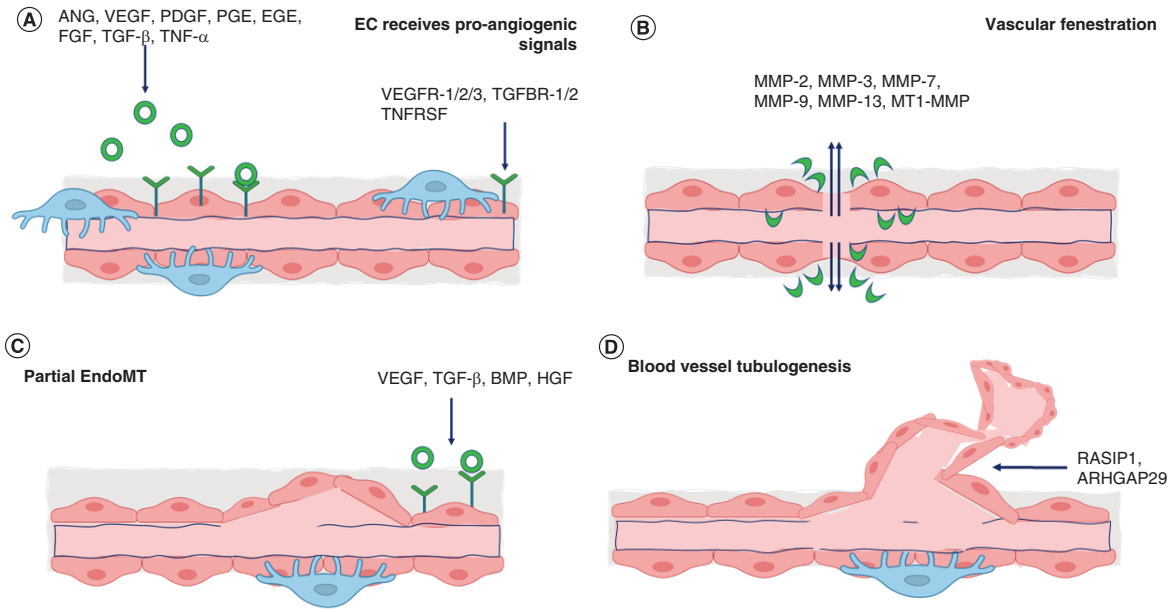


Figure 6. Angiogenesis is composed of several stages, as depicted schematically. The diagram is modified from and referred to the work Zimta *et al.* [59]. At first stage, pro-angiogenic factors, which bind to their corresponding receptors, are released by surrounding cells into local environment. **(A)** The ECs found at the outer surface of a blood vessel receive pro-angiogenic signals from ANG, VEGF, PDGF, PGF, EGF, FGF, TGF-β, and TTNF-α. On the surface of EC, there are several receptors corresponding to pro-angiogenic factors, for instance VEGFR1/2/3, TGFBR1/2, and TNFRSF. After signal transduction in the EC, cells start to proliferate and produce metalloproteinases (MMP). **(B)** Concurrently, blood vessel pores increase in size and fenestration happens. This will enable MMPs to escape from the blood vessels and degrade basement membrane. **(C)** The ECs start to migrate. This process is called partial endothelial to mesenchymal transition (partial EndoMT), proliferate at the fenestration area, and result a new blood vessel budding. **(D)** As the new tube forms, multiple signals from the environment such as RASIP1 and ARHGAP29 will enhance the development of 3D structure and organization of the newly formed network. By the final stage of the process, pericytes found at the exterior of the blood vessel responsible for blood vessel contraction begin to populate the newly formed network.
EC: Endothelial cell.

As depicted schematically in Figure 6, angiogenesis is composed of several stages [59]. Regarding angiogenesis which leads to neovascularization in regeneration area, exosomes are known as mediators for intercellular communication and can be used to maximize the local pro-angiogenic potential at the wound site. Abundant number of pro- and anti-angiogenic microRNAs were found [59] and this modulates the behavior of endothelial cells and could be included in the design of exosome delivery of pro-angiogenic factors. Exosome with its miRNA cargoes direct the process during neovascularization, for example miRNA-21 activates AKT and ERK pathway, thus leading to the VEGF-increased production. Besides, when generating exosomes, MSCs are maintained in hypoxic conditions. This hypoxic condition is predicted to stimulate enhancement of pro-angiogenic capacity of the exosomes [121]. The underlying mechanism is possibly due to overloading of exosomes with miR-135b which targets the factor inhibiting HIF-1 (FIH-1) gene, an inhibitor of hypoxia-inducible factor 1 (HIF-1), known as pro-angiogenic factor [122].

Beside cartilage, bone, oral mucosal, and PDL regenerations, nerve regeneration pays a lot of attention in dentistry due to prevalent cases of nerve injuries caused by oral-maxillofacial traumas and/or surgeries. From several studies, it was observed that exosome could stimulate Schwann cell proliferation and increased expression of cyclin Ki67 as an indication of exosome potentials in enhancing neurite length of dorsal root ganglion (DRG) neurons [69,123]. The capability of exosome in enhancing nerve regeneration is due to the presence of neuronal growth factors such as brain-derived neurotrophic factor (BDNF), insulin growth factor-1 (IGF-1), nerve growth factor (NGF), fibroblast growth factor-1 (FGF-1), and glial cell-derived neurotrophic factor (GDNF) [124,125]. Based on the presence of key neural growth factors, exosome could potentially provide new approaches to nerve regeneration in medicine and dentistry but further research to uncover underlying neurogenesis mechanism and roles of specific signaling molecules in relation to neural regeneration pathways are needed.

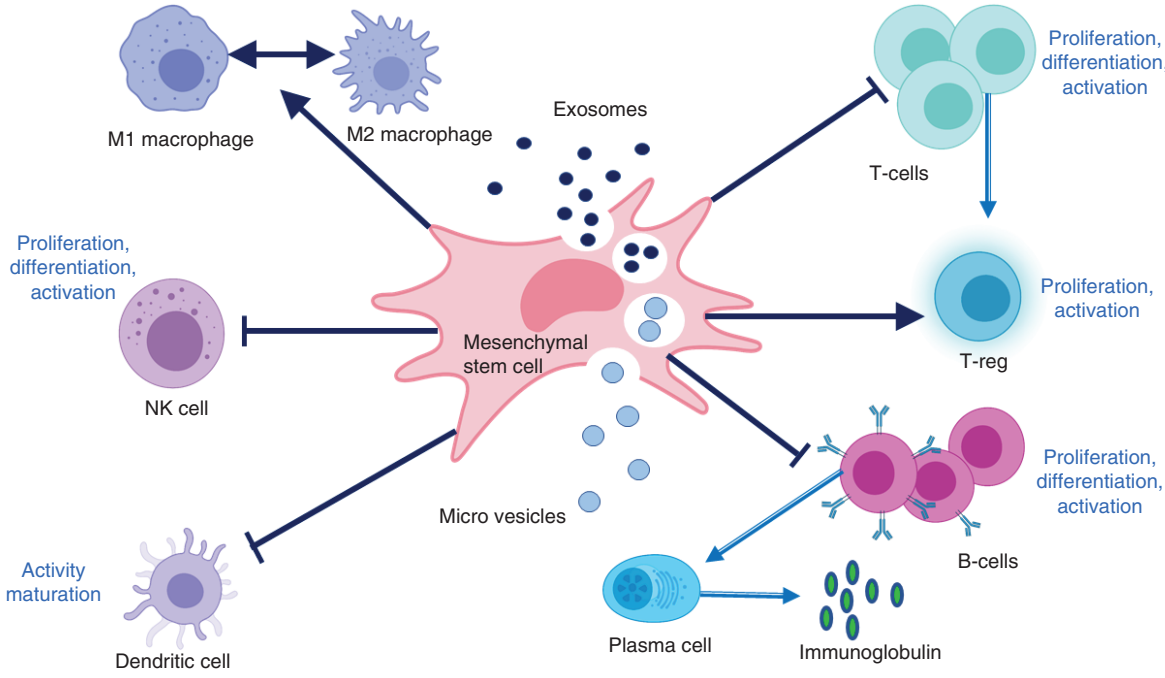


Figure 7. Exosomes and microvesicles (MSC's derived EV) exert immunomodulatory effect on innate and adaptive immune reactions mediated by many immune cells (T and B lymphocytes, natural killer cells, dendritic cells, and macrophages). Exosomes and microvesicles can inhibit the proliferation, differentiation, and activation of T, B, and natural killer cells and the pathogen-presenting function of dendritic cells and macrophages. Macrophage polarization can also be regulated under different microenvironment in accordance with EVs application. Figure was derived and further modified from Wang and co-workers [133].

Therapeutic potential of exosome in healing & regeneration process

From the previous description, it can be concluded that exosomes have potential in the process of regeneration, thus exosomes can be used as therapeutics agent in medicine and dentistry. These potentials cannot be separated from the three overlapping stages in regeneration process: inflammation, proliferation, and remodeling phases. Inflammation is a human body self-defense mechanism against harmful stimuli. It is a regulated acute response beneficial for wound healing [126]. If the inflammation phase were chronic and dysregulated, wound healing would be delayed and it would promote fibrosis, excessive scar formation, and inhibited proliferation or re-epithelization [127].

During the inflammation process, macrophages are a major component of the mononuclear phagocyte system and play critical roles in initiation, maintenance, and resolution of inflammation. Macrophage functions as antigen presenting cells and produce cytokine and growth factors for immunomodulation [128]. Macrophages are activated and deactivated during the inflammatory process. Activation of inflammation induces M1 phenotype to release signals, including cytokines such as interferon gamma (IFN-g), tumor necrosing factor (TNF), bacterial lipopolysaccharide (LPS), ECM proteins, and other chemical mediators. In concert with microbial products, such as LPS, and cytokines, such as TNF, IFN-g will activate M1 [129] indicated by high interleukin-12 (IL-12) and IL-23, as well as high toxic intermediates such as nitric oxide (NO) and reactive oxygen intermediates (ROI) productions [130]. Inflammation deactivation happens by removal of mediators to permit host to repair damage tissues in which M2 phenotype releases anti-inflammatory cytokines (interleukin 10 or IL-10 and TGF-b) and cytokines antagonist [128–130].

Since macrophages produce a wide range biologically active molecules to autoregulate in the inflammatory process, therapeutic interventions using exosome which targets macrophage may open new avenues for inflammatory disease control. Exosome can regulate activation, differentiation, and proliferation of B-lymphocytes and suppress T-lymphocyte proliferation at the same time. It can also convert activated T-lymphocytes into T-regulatory phenotype to exert immunosuppressive effects [126,131,132], as depicted in Figure 7, summarized from a review on the role of EVs in autoimmunity [133]. The regulation of inflammatory factors plays important roles in regeneration process. With the capacity to deliver a cargo of protein, lipids, nucleic acids, or other cellular components to neighboring or distant

Table 4. Possible mechanism of exosomes in immune regulation and inflammatory responses.

Target	Effect	Mechanism
$CD4^+$ and $CD8^+$ T-cells	Inhibiting differentiation toward effector or memory T-cell phenotypes	Mediated by anti-CD3/CD2/CD28 stimulation
T-cells in general	Inhibiting activation	Reduction of interferon-gamma (IFN-γ) secretion
Macrophage	Increasing mRNA levels of M2-related arginase-1 and interleukin-10 (IL-10)	
	Inducing macrophage polarization toward anti-inflammatory M2 phenotypes	Transactivation of arginase-1 by active signal transducer and activator of transcription 3 (STAT-3)
	Inhibiting macrophage inflammatory responses	Stimulated by lipopolysaccharide (LPS) and IFN-γ
Inflammatory response (*in vivo* in mouse model)	Regulating inflammatory responses	Reduction of inflammatory cytokines sech as IL-4, IL-23, IL-31, and tumor necrosis factor-alpha (TNF-α)
Inflammatory response (*in vivo* in mice after sepsis syndrome)	Improving survival and suppressing inflammatory responses	Increase inflammatory mediators such as MMP-9, macrophage migration inhibitory factor, TNF-α, nuclear factor kappa-B (NF kappa-B), and IL-1β

References [124,129–132] used as sources of information.

cells, exosomes may polarize the inflammatory response through down-regulation of pro-inflammatory enzymes like inducible NO, cyclooxygenase (COX)-2 and of cytokines such as TNF-a, IL-1b, monocyte chemoattractant protein (MCP)-1. Table 4 summarizes possible mechanism of exosomes in immune regulation and inflammatory responses, as the key points for therapeutics and regenerative treatment [124,129–132].

During proliferation phase, angiogenesis plays crucial roles in wound healing and repair. For this, MSCs derived exosomes are enriched with various angiogenesis related proteins and other miRNAs that could activate signaling pathways in endothelial cells, including up regulating angiogenesis related molecules found in vascular endothelial cells such as VEGF, VEGF receptor (VEGFR), FGF-1, E-selectin, angiopoetin-1 and endothelial nitric oxide synthase (eNOS), chemokine ligand 16 and IL-8 [126]. Furthermore, ECM reconstruction is the key point for tissue reconstruction during remodeling phase. It was observed that exosomes promoted synthesis of type I collagen, type III collagen and elastin during the early stage and inhibited collagen synthesis in the late stage of remodeling to inhibit scar tissue formation [126]. In this context MSCs derived exosomes will be potential candidate as a therapeutic agent to regulate inflammatory, proliferation and remodeling phase in tissue regeneration.

Moreover, because of their ideal native structure and characteristics, exosome is also indicated as a promising nanocarriers for clinical use due to its ideal small size to penetrate deep tissues, slightly negative zeta potential for long circulation, deformable cytoskeleton and similarity to cell membranes [133,134]. Exosomes can also exhibit an increased capacity to escape degradation or clearance by immune system [133].

Challenges & strategies

Based on the previous review, the MSCs derived exosomes and their potential as cell-free-based therapy in tissue engineering applied in dentistry, the challenges for the application include extensive research on the identification of the molecules involve in paracrine action of stem cells to open new therapeutics options using exosomes, the production, processing and manufacturing aspects, as well as strategies to develop the cost-effective system for clinical applications.

The initial challenges to be considered are exosome isolation, purification and characterization. In general, exosomes can be isolated from the conditioned media of cultured cells and almost any biological fluids [45]. Comprehensively, Li and co-workers wrote an update on various exosome isolation techniques and described the advantages and disadvantages of isolation techniques based on ultracentrifugation, size, immunoaffinity captured, precipitation and microfluidics [135]. To prepare clinical grade exosome, good manufacturing practices (GMPs) and quality control become an utmost important factor. In view of this, cell source and state including microenvironmental conditions must be kept uniform to provide consistent exosome quality and yield [45].

The development and translational framework of human EV-based therapeutics in general, or specifically exosomes, is regulated under biological medicinal products category [136]. A biological medicine contains one or more active substances made by or derived from biological cells, and to some extent equivalent to biologic drugs, biologicals or biopharmaceuticals [137–140]. Although regulatory framework for manufacturing and clinical trials exists in Europe, Australia and USA, but research related to establishment of special guidelines targeting EV-based therapeutics relevant to isolation, purification, characterization and their valorization is considered important area

to be investigated. In the context of exosome-based therapeutics valorization and clinical translation, mechanism of action (MoA) is essential and iterative because the dissection between exosome as an active substance and excipients are important to control the quality and safety of the exosome-based therapy. Further challenges related to the changes and differentiation of residing stem cells surrounding treatment area also need special attention since exosome may influence cell behavior [141,142] including the risk of factors transduction and other cell to cell communication [143]. For clinical application of exosomes in regenerative therapy, currently there has no standardized procedure yet. The isolation and storage are critical, even more the manufacturing requires adequate and appropriate technology with quality system for the safety of both donor and recipients.

In case of manufacturing for instance, although extensive research has been conducted, but still, the practical use of exosome is restricted by limited exosome secretion capability of cells [144]. Moreover, a large dose of exosome is required in actual clinical administration [136–140,144–146]. On the other hands, several studies show that increased intracellular calcium can lead to the formation and/or production of EVs [135]. In view of this, scaffold which contains calcium may resolve the problems by creating microenvironment with a capability to adjust cell exosome production. As shown in the previous study by Wu and co-authors [144], bioactive glass (BG) ceramic ion products significantly promoted MSCs to secrete exosome without changing the morphology, size distribution and internalization of the MSCs, and simultaneously improved their biological functions.

Typical BG is composed of SiO_2, Na_2O, CaO and P_2O_5 [147,148] which has been widely used for wound repair and regeneration [149–151]. As reported by Wu *et al.* [144], BG ion products significantly enhanced pathways that generate intracellular exosome vesicles and release mature exosome. Wu and co-authors [144] proposed the underlying mechanism that BG ion products enhanced MSCs to generate exosomes by upregulating the expression of nSMase2 and promoted MSCs to release exosomes by upregulating the expression of Rab27a. Simultaneously, the pathways will promote vascularization of the recipient cells by regulating the levels of miR-342-5p and miR-1290 in cargoes.

From the reports [34], it is known that ceramics-based scaffold can affect the behavior of single type of cells and cell–cell interactions to enhance exosome generation. Regarding this aspect, previous research have been extensively conducted to investigate synergetic effects of ceramics-based scaffold and exosome in regenerative treatment [3,17], however, they elaborated more on the therapeutics effects, not on the effect and mechanism on exosome generation by calcium containing construct such as ceramics-based scaffold.

In view of this, several ceramics-based scaffold can be explored and developed as an effective strategy to either enhance exosome production or yield and improve biological activity of the secreted exosomes. The use of ceramics-based scaffold can be a better alternative strategy to overcome limited exosome secretory from the cells when compared with modulation of cell culture conditions under hypoxia and low pH microenvironment, because it will be difficult to maintain healthy cells in such unfriendly conditions for large-scale clinical applications, as concluded diagrammatically in Figure 8. Therefore, a lot of ceramics-based scaffolds are awaiting to be investigated further as an alternative strategy to enhance exosome production from MSCs or other cells, such as hydroxyapatite, carbonate apatite, calcium carbonate, some calcium orthophosphate including biphasic calcium phosphate, tricalcium phosphate, bioactive glass [3,17] or other mineral-doped scaffold [152]. Specifically, ceramics-based scaffold can function as biomaterial for exosome retention and delivery vehicles for exosome to reach targeted cells. Meanwhile, in general challenges in cell-free-based tissue engineering therapy and therapeutics using exosomes in dentistry and medicine are summarized in Figure 9.

Conclusion

Clinical application on the use of MSC is limited due to its inherent heterogenicity, variation associated with cell expansion and risk of unwanted differentiation. Therefore, nowadays cell-free-based therapy with MSCs derived exosomes is considered an alternative treatment in dental tissue engineering. This is because exosomes carry with them informative cargos from the MSCs to targeted cells, which is needed to regulate fundamental cellular processes for lineage-specific proliferation, differentiation, migration, apoptosis and modulation of a series of signaling pathway. In the current state, exosome is found to be potential candidate as a therapeutic agent to regulate inflammatory, proliferation and remodeling phase in tissue regeneration. As a conclusion, exosomes could potentially provide new approaches to dental tissue engineering, but further research to uncover underlying mechanism and roles of specific signaling molecules in relation to dental tissue regeneration pathways are needed.

In addition to the first conclusion, currently there has no standardized procedure for the isolation, storage, and manufacturing technology with quality system for the safety of both donor and recipients in large-scale valorization. In case of manufacturing for instance, although extensive research has been conducted, but still, the practical use of

10.2144/fsoa-2021-0050

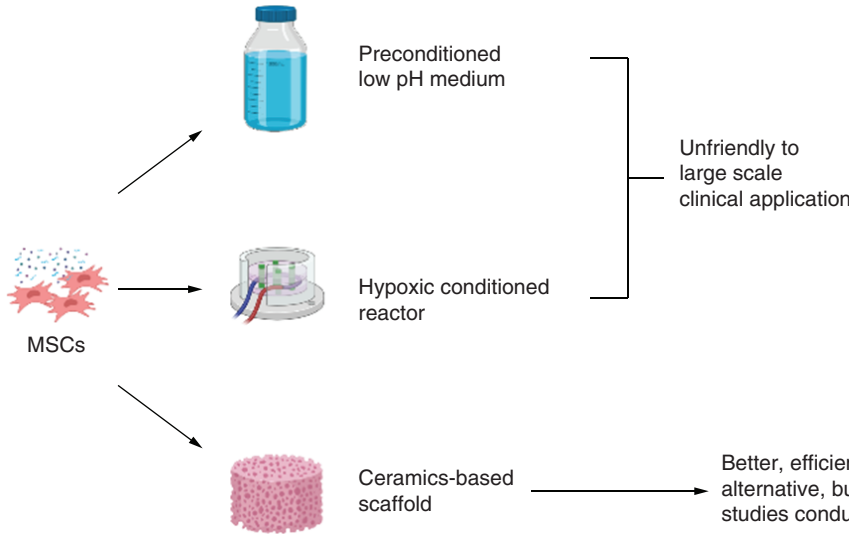


Figure 8. Although limited studies have been conducted, but ceramics-based scaffold has high potential to enhance exosome generation, production and secretion from MSCs due to the release of ion products from the construct such as calcium ions since the increased intracellular calcium can lead to the formation and/or production of extracellular vesicles. The use of ceramics-based scaffold is also beneficial for exosome retention and controlled release delivery system.

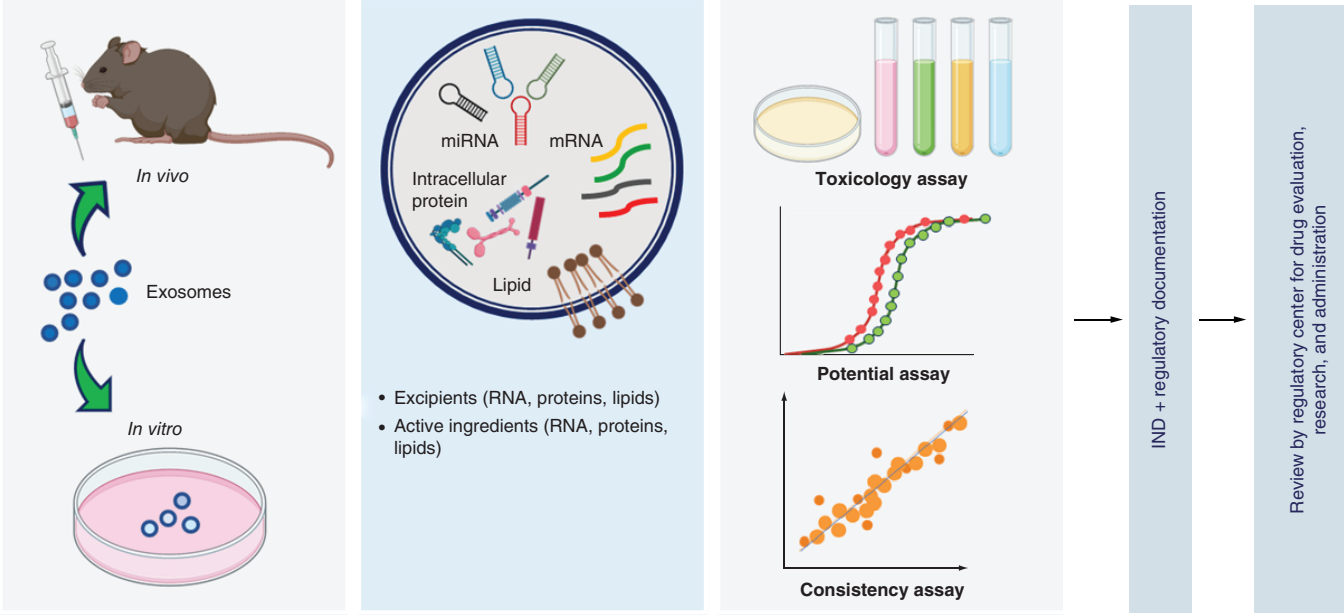


Figure 9. A lot of further *in vitro* and *in vivo* investigations are awaiting regarding isolation, characterization, production and storage of mesenchymal stem cells derived exosome for real clinical application. Mechanism of action, biosafety and biocompatibility on the use of exosomes for cell-free-based tissue engineering and new therapeutics approach are wide open area to be studied before translating exosomes as an investigational new drugs into clinical application.

exosome is restricted by limited exosome secretion capability of cells. The limitation on the application of exosome in clinics can be resolved by ceramics-based scaffold which can affect the behavior of single type of cells and cell–cell interactions to enhance exosome generation. Therefore, a lot of further investigations are awaiting to develop ceramics-based scaffold that functions in large-scale clinical application for cell-free-based therapy with exosomes to provide better alternative strategy to overcome limited exosome secretory from the cells, because ceramics-based scaffold produces important ions to enhance production and secretion of exosomes from the cells.

Future perspective

Exosomes are potential as an alternative future treatment in dental tissue engineering and in regenerative medicine. Exosomes carry with them informative cargos from the MSCs to regulate fundamental cellular processes for lineage-specific proliferation, differentiation, migration, apoptosis and modulation of a series of signaling pathway in the targeted cells. Because of that, exosomes are very potential for next generation therapeutic agent to regulate inflammatory, proliferation and remodeling phase in tissue regeneration. However, to date, there are still limited studies conducted to uncover underlying mechanism and roles of specific signaling molecules in relation to dental tissue regeneration pathways. There are also limited research involving exosomes for modulating extracellular signaling and intracellular reprogramming, which have been a significant approaches in tissue engineering.

On the other hands, advances in materials synthesis, protein engineering, molecular self-assembly, bio, micro and nanofabrication technology, nanotechnology as well as micro and nanopatterning technology have contributed to the high possibility of developing future therapy. When it is combined with exosomes technology, this could be resolution in regenerative therapy. Furthermore, progressive advancement in materials sciences may resolve problems and overcome limited capacity of the cells regarding production and secretion of EVs, including exosomes, because hybrid materials containing certain ions can also be designed and directed to enhance generation and secretion of exosomes for large-scale clinical applications.

To achieve future goals, better relevant and predictive *in vitro* or *ex vivo* models are needed to predict efficacy and safety of the cell-free-based therapy with exosomes. In this context, the development of microfluidic organ system known as 'organ-on-chip' may be crucial to capture phenomenon happens in body tissues and model diseases to provide accurate personalized medicine, involving a complex of exosomes and other biomolecules with hybrid biomaterials. A microfluidic system will allow researchers to study living tissues and organ in a more complex way and will contribute a lot to uncover underlying concept of exosomes as next generation therapeutic agent, including their novel delivery system. Interdisciplinary research to find out proper hybrid biomaterials to deliver, target, increase production, and increase secretion of exosomes involving bio-nanofabrication are significant to be conducted. Besides, standardized procedure for the isolation, storage, and manufacturing technology with quality system for the safety of both donor and recipients in large-scale valorization must be investigated. Their translational steps into dental clinics and, to large extent, into biomedical applications, are also important to be studied in the near future.

Executive summary

- In tissue engineering, the use of exosomes released have become a particular interest for cell-free regenerative therapy due to their epigenetic capacity and cargos.
- To valorize the use of exosomes in large-scale clinical setting, better relevant and predictive *in vitro* or *ex vivo* models are needed to predict efficacy and safety of the cell-free-based therapy with exosomes, as well as to capture phenomenon happens in body tissues and model diseases.
- Interdisciplinary research to find out proper hybrid biomaterials to deliver, target, increase production and increase secretion of exosomes involving bio-nanofabrication are significant to be conducted to uncover underlying concept of exosomes as next generation therapeutic agent.
- Their translational steps into dental clinics and biomedical applications are also important to be studied in the future.

Author contributions

ID Ana reviewed the literature, analyzed the literature, drafted the manuscript and prepared figures. A Barlian, AC Hidajah, CH Wijaya, HB Notobroto and TDK Wungu reviewed and edited the manuscript. All authors read and approved the manuscript.

Acknowledgments

Authors used BioRender to create some figures in this study.

Financial & competing interests disclosure

This study is supported by Indonesia Collaborative Research (RKI) Funding Scheme under World Class University Acceleration Program from the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia, with a contract number 810/UN1/Ditlit/Dit-Lit/PT/2020. The authors have no other relevant affiliations or financial involvement with any organization or

entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Caplan AI. Design parameters for functional tissue engineering. In: *Functional Tissue Engineering*. Guilak I, Butler DL, Goldstein SA, Mooney DJ (Eds). Springer-Verlag, Amsterdam, The Netherlands, 129–130 (2003).
2. Badylak S, Gilbert T, Myers-Irvin J. The extracellular matrix as a biologic scaffold for tissue engineering. In: *Tissue Engineering*. Van Blitterswijk CA, Thomsen P, Lindahl A *et al.* (Eds). Academic Press, CA, USA, 121–143 (2008).
3. Ana ID, Satria GAP, Dewi AH, Ardhani R. Bioceramics for clinical application in regenerative dentistry. In: *Novel Biomaterials for Regenerative Medicine.* Chun HJ, Park K, Kim CH, Khang G (Eds). Springer, Singapore, 309–316 (2018).
4. Badylak S. Xenogenic extracellular matrix as a scaffold for tissue reconstruction. *Transpl. Immunol.* 12(3–4), 367–377 (2004).
5. Farah-Carson MC, Wagner RC, Kiick KL. Extracellular matrix: structure, function, and applications to tissue engineering. In *Tissue Engineering.* Fisher JP, Mikos AG, Bronzino JD (Eds). CRC Press, FL, USA, 1–17 (2007).
6. Lopatina T, Deregibus MC, Cantaluppi V, Camussi G. Stem cell-derived microvesicles: a cell free therapy approach to the regenerative medicine. *Curr. Biotechnol.* 1, 11–22 (2012).
7. Togel F, Westenfelder C. The role of multipotent marrow stromal cells (MSCs) in tissue regeneration. *Organogenesis* 7(2), 96–100 (2011).
8. Rubina K, Kalinina N, Efmenko A. Adipose stromal cells stimulate angiogenesis via promoting progenitor cell differentiation, secretion of angiogenic factors, and enhancing vessel maturation. *Tissue. Eng. Part A* 15(8), 2039–2050 (2009).
9. Hare JM, Traverse JH, Henry TD. A randomized, double blind, placebo-controlled, dose-escalation study of intravenous adult human mesenchymal stem cells (prochymal) after acute myocardial infarction. *J. Am. Coll. Cardiol.* 54(24), 2277–2286 (2009).
10. Beyth S, Schroeder J, Liebergall M. Stem cells in bone diseases: current clinical practice. *Br. Med. Bull.* 99, 199–210 (2011).
11. Mingliang R, Bo Z, Zhengguo W. Stem cells for cardiac repair: status, mechanisms, and new strategies. *Stem Cells. Int.* 3, 109–128 (2011).
12. Casteilla L, Planat-Benard V, Laharrague P, Cousin B. Adipose derived stromal cells: their identity and uses in clinical trials, an update. *World. J. Stem. Cells* 3(4), 25–33 (2011).
13. Kunter U, Rong S, Boor P. Mesenchymal stem cells prevent progressive experimental renal failure but mal differentiate into glomerular adipocytes. *J. Am. Soc. Nephrol.* 18(6), 1754–1764 (2007).
14. Michalopoulos GK. Liver regeneration. *J. Cell. Physiol.* 213(2), 286–300 (2007).
15. Yokoo T, Matsumoto K, Yokote S. Potential use of stem cells for kidney regeneration. *Int. J. Nephrol.* 5, 917–931 (2011).
16. Zakrzewski W, Dobrzyński M, Szymonowicz M, Zbigniew R. Stem cells: past, present, and future. *Stem Cell. Res. Ther.* 10(68), 1165–1186 (2019).
17. Mahanani ES, Ana ID, Bachtiar I. Human mesenchymal stem cells behavior on synthetic coral scaffold. *Key. Eng. Mater.* 696, 205–211 (2019).
18. Wang J, Ye F, Cheng L *et al.* Osteogenic differentiation of mesenchymal stem cells promoted by overexpression of connective tissue growth factor. *J. Zhejiang Univ. Sci. B* 10(5), 355–367 (2009).
19. Breitbach M, Bostani T, Roell W. 2007. Potential risks of bone marrow cell transplantation into infarcted hearts. *Blood* 110(4), 1362–1369 (2009).
20. Gomzikova MO, Rizvanov AA. Current trends in regenerative medicine: from cell to cell-free therapy. *Bio. Nano. Sci.* 7, 240–245 (2017).

•• **Clarifies the importance, advantages and future perspective of cell and cell-free based therapy.**

21. Inchingolo F, Tatullo M, Marrelli M *et al.* Regenerative surgery performed with platelet-rich plasma used in sinus lift elevation before dental implant surgery: a useful aid in healing and regeneration of bone tissue. *Eur. Rev. Med. Pharmacol. Sci.* 16(9), 1222–1226 (2012).
22. Ge R, Lv Y, Li P, Xu L, Feng X, Qi H. Upregulated microRNA-126 induces apoptosis of dental pulp stem cell via mediating PTEN-regulated Akt activation. *J. Clin. Lab. Anal.* 35(2), e23624 (2021).
23. Madrigal M, Rao KS, Riordan NH. A review of therapeutic effects of mesenchymal stem cell secretions and induction of secretory modification by different culture methods. *J. Transl. Med.* 12, 260–270 (2014).
24. Hutmacher D, Woodfield T, Dalton P, Lewis J. Scaffold design and fabrication. In: *Tissue Engineering*. Van Blitterswijk CA, Thomsen P, Lindahl A *et al.* (Eds). Academic Press, CA, USA, 404–454 (2008).

25. Beer L, Mildner M, Ankersmith HJ. Cell secretome based drug substances in regenerative medicine: when regulatory affairs meet basic science. *Ann. Transl. Med.* 5, 170–172 (2017).
26. Théry C, Witwer KW, Aikawa E. 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* 7(1), 1535750 (2018).
27. Witwer KW, Van Balkom BWM, Bruno S *et al.* Defining mesenchymal stromal cell (MSC)-derived small extracellular vesicles for therapeutic applications. *J. Extracell. Vesicles* 8(1), 1609206 (2019).
28. Sun B, Peng J, Wang S *et al.* Applications of stem cell-derived exosomes in tissue engineering and neurological diseases. *Rev. Neurosci.* 29(5), 531–546 (2018).
29. Wang B, Xing D, Zhu Y, Dong S, Zhao B. The State of exosomes research: a global visualized analysis. *Biomed. Res. Int.* 2019, 1–11 (2019).
30. Maguire G, Friedman P, Mc Carthy D, Friedman R, Maniotis A. Stem cell released molecules and exosomes in tissue engineering. *Procedia. Eng.* 59, 270–278 (2013).
31. Chopra N, Dutt Arya B, Jain N *et al.* Biophysical characterization, and drug delivery potential of exosomes from human wharton's jelly-derived mesenchymal stem cells. *ACS Omega* 4(8), 13143–13152 (2019).
32. Zhang S, Chuah SJ, Lai RC, Hui JHP, Lim SK, Toh WS. MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis, and modulating immune reactivity. *Biomaterials* 156, 16–27 (2018).
33. Chew JRJ, Chuah SJ, Teo KYW *et al.* Mesenchymal stem cell exosomes enhance periodontal ligament cell functions and promote periodontal regeneration. *Acta Biomater.* 15(89), 252–264 (2019).
34. Phan J, Kumar P, Hao D, Gao K, Farmer D, Wang A. Engineering mesenchymal stem cells to improve their exosome efficacy and yield for cell-free therapy. *J. Extracell. Vesicles* 7(1), 1522236 (2018).
35. Eiró N, Sendon-Lago J, Seoane S *et al.* Potential therapeutic effect of the secretome from human uterine cervical stem cells against both cancer and stromal cells compared with adipose tissue stem cells. *Oncotarget* 5, 10692–10708 (2014).
36. Vizoso FJ, Eiro N, Cid S, Schneider J, Perez-Fernandez R. Mesenchymal stem cell secretome: toward cell-free therapeutic strategies in regenerative medicine. *Int. J. Mol. Sci.* 18, 1852–1875 (2017).
37. Théry C, Ostrowski M, Segura E. Membrane vesicles as conveyors of immune responses. *Nat. Rev. Immunol.* 9(8), 581–593 (2009).
38. Melliana A, Dewi NM, Wijaya A. Mesenchymal stem cell secretome: cell-free therapeutic strategy in regenerative medicine. *Indones. Biomed. J.* 11(2), 113–124 (2019).
39. Van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles. *Nat. Rev. Mol. Cell. Biol.* 19, 213–228 (2018).
40. Simons K, Gerl MJ. Revitalizing membrane rafts: new tools and insights. *Nat. Rev. Mol. Cell. Biol.* 11(10), 688–699 (2010).
41. Simons M, Raposo G. Exosomes – vesicular carriers for intercellular communication. *Curr. Opin. Cell Biol.* 21(4), 575–581 (2009).
42. Thery C, Zitgovel L, Amigorena S. 2002. Exosomes: composition, biogenesis, and functions. *Nat. Rev. Immunol.* 2, 569–579 (2009).
43. Hessvik NP, Liorente A. Current knowledge on biogenesis and release. *Cell. Mol. Life Sci.* 75, 193–208 (2018).
44. Colombo M, Raposo G, Thery C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. *Annu. Rev. Cell. Dev. Biol.* 30, 255–289 (2014).
45. Ramasubramanian L, Kumar P, Wang A. Engineering extracellular vesicles as nanotherapeutics for regenerative medicine. *Biomolecules* 10, 48–70 (2020).
46. Lai RC, Yeo RW, Lim SK. Mesenchymal stem cell exosomes. Semin. *Cell. Dev. Biol.* 40, 82–88 (2015).
47. Yeo RW, Lai RC, Zhang B, Tan SS, Yin Y, The BJ. Mesenchymal stem cell: an efficient mass producer of exosomes for drug delivery. *Adv. Drug. Deliv. Rev.* 65(3), 336–341 (2013).
48. Lu K, Li HY, Yang K, Wu JL, Cai XW, Zhou Y. Exosomes as potential alternatives to stem cell therapy for intervertebral disc degeneration: invitro study on exosomes in interaction of nucleus pulposus cells and bone marrow mesenchymal stem cells. *Stem Cell. Res. Ther.* 8(1), 108–118 (2017).
49. Schuh CMAP, Aguayo S, Zavala G, Khoury M. Exosome-like vesicles in *Apis mellifera* bee pollen, honey and royal jelly contribute to their antibacterial and pro-regenerative activity. *J. Exp. Biol.* 222, 1–7 (2019).
50. Brand HS, Veerman EC. Saliva and wound healing. *Chin. J. Dent. Res.* 16(1), 7–12 (2013).
51. Haque N, Widera D, Govindasamy V, Soesilawati P, Abu Kasim NH. Extracellular vesicles from stem and progenitor cells for cell-free regenerative therapy. *Curr. Mol. Med.* (epub ahead of print) (2021).
52. Kayambashi P, Iyer J, Pillai S, Upadhyay A, Zhang Y, Tran SD. Hydrogel encapsulation of mesenchymal stem cells and their derived exosomes for tissue engineering. *Int. J. Mol. Sci.* 22(2), 684 (2021).
53. Niedermair T, Lukas C, Li S *et al.* Influence of extracellular vesicles isolated from osteoblasts of patients with Cox-Arthrosis and/or osteoporosis on metabolism and osteogenic differentiation of BMSCs. *Front. Bioeng. Biotechnol.* 8, 615520 (2020).
54. Jin GZ. Current nanoparticle-based technology for osteoarthritis therapy. *Nanomaterials (Basel)* 10(12), 2368 (2020).

55. Chew JRJ, Chuah SJ, Teo KYW *et al.* Mesenchymal stem cell exosomes enhance periodontal ligament cell functions and promote periodontal regeneration. *Acta Biomater.* 89, 252–264 (2019).
56. Cooper LF, Ravindran S, Huang CC, Kang M. A role of exosome in craniofacial tissue engineering and regeneration. *Front. Physiol.* 10, 1569 (2020).
57. Zhang S, Chuah SJ, Lai RC, Hui JHP, Lim SK, Toh SW. MSC exosomes mediate cartilage repair by enhancing proliferation, attenuating apoptosis and modulating immune reactivity. *Biomaterials* 156, 16–27 (2018).
58. Zhang S, Chu WC, Lai RC, Lim SK, Hui JHP, Toh SW. Exosomes derived from human embryonic mesenchymal stem cells promote osteochondral regeneration. *Osteoarthr. Cartil.* 24(12), 2135–2140 (2016).
59. Zimta AA, Baru O, Badea M, Buduru SD, Berindan-Neagoe I. The role of angiogenesis and pro-angiogenetic exosome in regenerative dentistry. *Int. J. Mol. Sci.* 20(2), 406–427 (2019).
60. Xu X, Lian Y, Li X *et al.* Exosome-mediated delivery of kartogenin for chondrogenesis of synovial fluid-derived mesenchymal stem cells and cartilage regeneration. *Biomaterials* 269, 120539 (2019).
61. Lee YH, Park HK, Auh QS *et al.* Emerging potential of exosomes in regenerative medicine for temporomandibular joint osteoarthritis. *Int. J. Mol. Sci.* 21(4), 1541 (2020).
62. Zhang S, Teo K, Chuah SJ, Lai RC, Lim SK, Toh WS. MSC exosomes alleviate temporomandibular joint osteoarthritis by attenuating inflammation and restoring matrix homeostasis. *Biomaterials* 200, 35–47 (2019).
63. Schuh CMAP, Benso B, Aguayo S. Potential novel strategies for the treatment of dental pulp-derived pain: pharmacological approaches and beyond. *Front. Pharmacol.* 10, 1068 (2019).

• **An interesting study which describes novel strategy for the treatment of dental pulp-derived pain with exosomes.**

64. Sjöqvist S, Ishikawa T, Shimura D *et al.* Exosomes derived from clinical-grade oral mucosal epithelial cell sheets promote wound healing. *J. Extracell. Vesicles* 8(1), 1565264 (2019).
65. Tatullo M, Marelli B, Palmieri F *et al.* Exosomes from human periapical cyst-MSCs: theranostic application in parkinson's disease. *Int. J. Environ. Res. Public. Health* 17(1), 3001 (2020).
66. Yu S, Chen H, Gao B. Potential of exosomes in regenerative endodontics. *Arch. Oral Biol.* 120, 104946 (2020).
67. Xian X, Gong Q, Li C, Guo B, Jiang JH. Exosomes with highly angiogenic potential for possible use in pulpregeneration. *J. Endod.* 44(5), 751–758 (2018).
68. Qiu X, Liu J, Zheng C *et al.* Exosomes released from educated mesenchymal stem cells accelerate cutaneous wound healing via promoting angiogenesis. *Cell Prolif.* 53(8), e12830 (2020).
69. Rao F, Zhang D, Fang T *et al.* Exosomes from human gingiva-derived mesenchymal stem cells combined with biodegradable chitin conduits promote rat sciatic nerve regeneration. *Stem Cells Int.* 2019, 2546367 (2019).
70. Stefańska K, Mehr K, Wieczorkiewicz M *et al.* Stemness potency of human gingival cells-application in anticancer therapy and clinical trials. *Cells* 9(8), 1916 (2020).
71. Holliday LS, McHugh KP, Zuo J, Aguirre JI, Neubert JK, Rody WJ Jr. Exosomes: novel regulators of bone remodeling and potential therapeutic agents for orthodontics. *Orthod. Craniofac. Res.* 20(Suppl. 1), 95–99 (2017).
72. Zhuang X, Ji L, Jiang H *et al.* Exosomes derived from stem cells from the apical papilla promote dentine-pulp complex regeneration by inducing specific dentinogenesis. *Stem Cells Int.* 2020, 5816723 (2020).
73. Alqurash H, Ortega A, Lambert DW. The emerging potential of extracellular vesicles in cell-free tissue engineering and regenerative medicine. *Tissue Eng. B* 2020, 0222 (2020).
74. Swanson WB, Zhang Z, Xiu K *et al.* Scaffolds with controlled release of pro-mineralization exosomes to promote craniofacial bone healing without cell transplantation. *Acta Biomater.* 118, 215–232 (2020).
75. Chansaenroj A, Yodmuang S, Ferreira J. Trends in salivary gland tissue engineering: from stem cells to secretome and organoid bioprinting. *Tissue Eng. Part. B* 2020, 0149 (2020).
76. Yang J, Zhu W, Lu J, Xie K, Fang S, Kan L. Potential therapeutic applications of exosomes in bone regenerative medicine. *In book: Osteogenesis and Bone Regeneration.* IntechOpen, 1–21 (2018).
77. Wang KX, Xu LL, Rui YF *et al.* The effect of secretion factors from umbilical cord derived mesenchymal stem cells on osteogenic differentiation of mesenchymal stem cells. *PLoS ONE* 10, e120593 (2015).
78. Deng Y, Zhou H, Gu P, Fan X. Repair of canine medial orbital bone defects with miR-31 modified bone marrow mesenchymal stem cells. *Invest. Ophthalmol. Vis. Sci.* 55, 6016–6023 (2014).
79. Xu W, Yang Z, Lu N. A new role for the PI3K/Akt signaling pathway in the epithelial-mesenchymal transition. *Cell Adh. Migr.* 9(4), 317–324 (2015).
80. Zhao B, Xie Z, Wang Y. Exosomes/tricalcium phosphate combination scaffolds can enhance bone regeneration by activating the PI3K/Akt signaling pathway. *Stem Cell Res. Ther.* 7(1), 136 (2016).
81. Komiya Y, Habas R. Wnt signal transduction pathways. *Organogenesis* 4(2), 68–75 (2008).

82. Issack PS, Helfet DL, Lane JM. Role of Wnt signaling in bone remodeling and repair. *HSS J.* 4(1), 66–70 (2008).
83. Grigorie D, Lerner UH. The crucial role of the Wnt system in bone remodeling. *Acta Endocrinol. (Buchar).* 14(1), 90–101 (2018).
84. De Santis M, Di Matteo B, Chisari E *et al.* The role of Wnt pathway in the pathogenesis of OA and its potential therapeutic implications in the field of regenerative medicine. *Biomed. Res. Int.* 2018, 7402947 (2018).
85. Theoleyre S, Wittrant Y, Tat SK, Fortun Y, Redini F, Heymann D. The molecular triad OPG/RANK/RANKL: involvement in the orchestration of pathophysiological bone remodeling. *Cytokine Growth Factor Rev.* 15(6), 457–475 (2004).
86. Wada T, Nakashima T, Hiroshi N, Penninger JM. RANKL-RANK signaling in osteoclastogenesis and bone disease. *Trends Mol. Med.* 12(1), 17–25 (2006).
87. Leibbrandt A, Penninger JM. RANK/RANKL: regulators of immune responses and bone physiology. *Ann. NY Acad. Sci.* 1143, 123–150 (2008).
88. Huynh N, VonMoss L, Smith D *et al.* Characterization of regulatory extracellular vesicles from osteoclasts. *J. Dent. Res.* 95, 673–679 (2016).
89. Chen D, Zhao M, Mundy GR. Bone morphogenetic proteins. *Growth Factors* 22(4), 233–241 (2004).
90. Mostafa S, Pakvasa M, Coalson E *et al.* The wonders of BMP9: from mesenchymal stem cell differentiation, angiogenesis, neurogenesis, tumorigenesis, and metabolism to regenerative medicine. *Genes Dis.* 6(3), 201–223 (2019).
91. Bharadwaz A, Jayasuriya AC. Osteogenic differentiation cues of the bone morphogenetic protein-9 (BMP-9) and its recent advances in bone tissue regeneration. *Mater. Sci. Eng. C* 120, 111748 (2021).
92. Chen Y, Bal BS, Gorski JP. Calcium and collagen binding properties of osteopontin, bone sialoprotein, and bone acidic glycoprotein-75 from bone. *J. Biol. Chem.* 267(34), 24871–24878 (1992).
93. Mukherjee BB, Nemir M, Beninati S *et al.* Interaction of osteopontin with fibronectin and other extracellular matrix molecules. *Ann. NY Acad. Sci.* 760, 201–212 (1995).
94. Fisher LW, Torchia DA, Fohr B, Young MF, Fedarko NS. Flexible structures of SIBLING proteins, bone sialoprotein, and osteopontin. *Biochem. Biophys. Res. Commun.* 280(2), 460–465 (2001).
95. White FJ, Burghardt RC, Hu J, Joyce MM, Spencer TE, Johnson GA. Secreted phosphoprotein 1 (Osteopontin) is expressed by stromal macrophages in cyclic and pregnant endometrium of mice but is induced by estrogen in luminal epithelium during conceptus attachment for implantation. *Reproduction* 132(6), 919–929 (2006).
96. Lund SA, Giachelli CM, Scatena M. The role of osteopontin in inflammatory processes. *J. Cell. Commun. Signal.* 3(3–4), 311–322 (2009).
97. Singh A, Gill G, Kaur H, Ahmed M, Jakhu H. Role of osteopontin in bone remodeling and orthodontic tooth movement: a review. *Prog. Orthod.* 19(1), 18 (2018).
98. Si J, Wang C, Zhang D, Wang B, Zhou Y. Osteopontin in bone metabolism and bone diseases. *Med. Sci. Monit.* 26, e919159 (2020).
99. Wei J, Karsenty G. An overview of the metabolic functions of osteocalcin. *Rev. Endocr. Metab. Disord.* 16(2), 93–98 (2015).
100. Komori T. Functions of osteocalcin in bone, pancreas, testis, and muscle. *Int. J. Mol. Sci.* 21(20), 7513 (2020).
101. Heriksen K, Karsdal MA. Type I collagen. *In book: Biochemistry of Collagens, Laminins and Elastin*. Academic Press, 1–11 (2016).
102. Bonewald LF, Mundy GR. Role of transforming growth factor-beta in bone remodeling. *Clin. Orthop. Relat. Res.* 250, 261–276 (1990).
103. Mundy GR. The effects of TGF-beta on bone. *Ciba. Found. Symp.* 157, 137–143 (1991).
104. Risau W. Mechanisms of angiogenesis. *Nature* 386(6626), 671–674 (1997).
105. Shibuya M. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for anti- and pro-angiogenic therapies. *Genes Cancer* 2(12), 1097–1105 (2011).
106. Heldin CH, Westermark B. Mechanism of action and *in vivo* role of platelet-derived growth factor. *Physiol. Rev.* 79(4), 1283–1316 (1999).
107. Martins M, Ribeiro D, Martins A, Reis RL, Neves NM. 2016. Extracellular vesicles derived from osteogenically induced human bone marrow mesenchymal stem cells can modulate lineage commitment. *Stem Cell Rep.* 6, 284–291 (2016).
108. Pereira D, Ramos E, Branco J. Osteoarthritis. *Acta Med. Port.* 28(1), 99–106 (2015).
109. Xia B, Chen D, Zhang J, Hu S, Jin H, Tong P. Osteoarthritis pathogenesis: a review of molecular mechanisms. *Calcif. Tissue Int.* 95(6), 495–505 (2014).
110. Bertrand J, Cromme C, Umlauf D, Frank S, Pap T. Molecular mechanisms of cartilage remodeling in osteoarthritis. *Int. J. Biochem. Cell Biol.* 42(10), 1594–1601 (2010).
111. Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: a synopsis. *Am. J. Manag. Care* 20(Suppl. 7), S128–S135 (2014).
112. Burke J, Hunter M, Kolhe R, Isales C, Hamrick M, Fulzele S. Stem cell-derived exosomes: a potential alternative therapeutic agent in orthopedics. *Stem Cells Int.* 2016, 5802529 (2016).

113. Zhang HG, Liu C, Su K *et al.* A membrane form of TNF-alpha presented by exosomes delays T-cell activation-induced cell death. *J. Immunol.* 176(12), 7385–7393 (2006).

114. Takeuchi R, Katagiri W, Endo S, Kobayashi T. Exosomes from conditioned media of bone marrow-derived mesenchymal stem cells promote bone regeneration by enhancing angiogenesis. *PLoS ONE* 14(11), e0225472 (2019).

115. Zhang W, Wray LS, Rnjak-Kovacina J *et al.* Vascularization of hollow channel-modified porous silk scaffolds with endothelial cells for tissue regeneration. *Biomaterials* 56, 68–77 (2015).

116. Dicarlo M, Bianchi N, Ferretti C, Orciani M, Di Primio R, Mattioli-Belmonte M. Evidence supporting a paracrine effect of IGF-1/VEGF on human mesenchymal stromal cell commitment. *Cells Tissues Organs* 201(5), 333–341 (2016).

117. Rouwkema J, Rivron NC, van Blitterswijk CA. Vascularization in tissue engineering. *Trends Biotechnol.* 26(8), 434–441 (2008).

118. Saran U, Gemini PS, Chatterjee S. Role of angiogenesis in bone repair. *Arch. Biochem. Biophys.* 561, 109–117 (2014).

119. Rouwkema J, Khademhosseini A. Vascularization, and angiogenesis in tissue engineering: beyond creating static networks. *Trends Biotechnol.* 34(9), 733–745 (2016).

120. Kawai T, Katagiri W, Osugi M, Sugimura Y, Hibi H, Ueda M. Secretomes from bone marrow-derived mesenchymal stromal cells enhance periodontal tissue regeneration. *Cytotherapy* 17(4), 369–381 (2015).

121. Fan GC. Hypoxic exosomes promote angiogenesis. *Blood* 123(25), 3669–3670 (2014).

122. Bian S, Zhang L, Duan L, Wang X, Min Y, Yu H. Extracellular vesicles derived from human bone marrow mesenchymal stem cells promote angiogenesis in a rat myocardial infarction model. *J. Mol. Med. (Berl.)* 92(4), 387–397 (2014).

123. Bucan V, Vaslaitis D, Peck CT, Strauß S, Vogt PM, Radtke C. Effect of exosomes from rat adipose-derived mesenchymal stem cells on neurite outgrowth and sciatic nerve regeneration after crush injury. *Mol. Neurobiol.* 56(3), 1812–1824 (2019).

124. Hong P, Yang H, Wu Y, Li K, Tang Z. The functions and clinical application potential of exosomes derived from adipose mesenchymal stem cells: a comprehensive review. *Stem Cell Res. Ther.* 10, 242 (2019).

125. Zhu Z, Kalyan BS, Chen L. Therapeutic potential role of exosomes for ischemic stroke. *BSA* 5(2), 128–143 (2020).

126. Hu P, Yang Q, Wang Q *et al.* Mesenchymal stromal cells-exosomes: a promising cell-free therapeutic tool for wound healing and cutaneous regeneration. *Burn Trauma* 7, 38 (2019).

127. Landén NX, Li D, Ståhle M. Transition from inflammation to proliferation: a critical step during wound healing. *Cell. Mol. Life Sci.* 73, 3861–3885 (2016).

128. Adams DO, Hamilton TA. The cell biology of macrophage activation. *Annu. Rev. Immunol.* 2, 283–318 (1984).

129. Fujiwara N, Kobayashi K. Macrophages in inflammation. *Curr. Drug Targets Inflamm. Allergy* 4(3), 281–286 (2005).

130. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol.* 25(12), 677–686 (2004).

131. Sugimoto MA, Sousa LP, Pinho V, Peretti M, Teixeira MM. Resolution of inflammation: what controls its onset? *Front. Immunol.* 7, 160 (2016).

132. Koh TJ, DiPietro LA. Inflammation and wound healing: the role of the macrophage. *Expert Rev. Mol. Med.* 13, e23 (2011).

133. Wang JH, Liu XL, Sun JM, Yang JH, Xu DH, Yan SS. Role of mesenchymal stem cell derived extracellular vesicles in autoimmunity: a systematic review. *World J. Stem Cells* 12(8), 879–896 (2020).

134. Vader P, Mol EA, Pasterkamp G, Schiffelers RM. Extracellular vesicles for drug delivery. *Adv. Drug. Deliv. Rev.* 106, 148–156 (2016).

135. Luan X, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. *Acta Pharmacol. Sin.* 38, 754–763 (2017).

•• **The potential of exosomes for next-generation therapeutic agents are well described in this study.**

136. Li P, Kaslan M, Lee SH, Yao J, Gao Z. Progress in exosome isolation techniques. *Theranostics* 7(3), 789–804 (2017).

137. Lener T, Gimona M, Aigner L *et al.* Applying extracellular vesicles-based therapeutics in clinical trials - an ISEV position paper. *J. Extracell. Vesicles.* 4, 30087 (2015).

138. Ilic N, Savic S, Siegel E, Atkinson K, Tasic L. 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.* 1, 898–908 (2012).

139. Ilic N, Savic S, Siegel E, Atkinson K, Tasic L. 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.* 1, 909–920 (2012).

140. Reiner AT, Witwer KW, Van Balkom BWM *et al.* Concise review: developing best-practice models for the therapeutic use of extracellular vesicles. *Stem Cells Transl. Med.* 6(8), 1730–1739 (2017).

141. Marrelli M, Codispoti B, Shelton RM, *et al.* Dental pulp stem cell mechanoresponsiveness: effects of mechanical stimuli on dental pulp stem cell behavior. *Front. Physiol.* 26(9), 1685 (2018).

142. Ballini A, Boccaccio A, Saini R, Van Pham P, Tatullo M. dental-derived stem cells and their secretome and interactions with bioscaffolds/biomaterials in regenerative medicine: from the *in vitro* research to translational applications. *Stem Cells Int.* 2017, 6975251 (2017).

143. Inchingolo F, Tatullo M, Abenavoli FM *et al.* Non-Hodgkin lymphoma affecting the tongue: unusual intra-oral location. *Head Neck Oncol.* 3, 1 (2011).

144. Wu Z, He D, Li H. Bioglass enhances the production of exosomes and improves their capability of promoting vascularization. *Bioact. Mater.* 6(3), 823–835 (2021).

•• **Since the production and secretion of the exosomes from cells are still a challenge, this study provides solution to resolve the problem based on the role of calcium-containing scaffold.**

145. Watson DC, Yung BC, Bergamaschi C *et al.* Scalable, cGMP-compatible purification of extracellular vesicles carrying bioactive human heterodimeric IL-15/lactadherin complexes. *J. Extracell. Vesicles* 7(1), 1442088 (2018).

146. Patel DB, Luthers MJ, Fisher JP, Steven MJ. Enhanced extracellular vesicle production and ethanol-mediated vascularization bioactivity via a 3D-printed scaffold-perfusion bioreactor system. *Acta Biomater.* 95, 236–244 (2019).

• **Technology to enhance extracellular vesicle production is described in this study, and this can be a good reference for the application of tissue engineering with exosome and biomaterials.**

147. Hench LL. The story of bioglass. *J. Mater. Sci. Mater. Med.* 17, 967–978 (2006).

148. Ana ID, Anggraeni R. Development of bioactive resin modified glass ionomer cement for dental biomedical applications. *Heliyon* 7(1), e05944 (2021).

149. Dong X, Chang J, Li H. 2017. Bioglass promotes wound healing through modulating the paracrine effects between macrophages and repairing cells. *J. Mater. Chem. B* 5, 5240–5250 (2017).

•• **This study is an interesting study to elucidate the mechanism of Bioglass in enhancing wound healing by switching of macrophages and paracrine effects between the macrophages and repairing cells in wound healing, thus is beneficial in understanding the roles of calcium in wound healing and regeneration in combination with cells or their secretomes.**

150. Xu Y, Peng J, Li H, Chang J. Combined chemical and structural signals of biomaterials synergistically activate cell-cell communications for improving tissue regeneration. *Acta Biomater.* 55, 249–261 (2017).

•• **This is a good study to be referred related to signals important for cell–cell communications, including the role of exosome in combination with biomaterials.**

151. Li H, Xue N, Kong K, Chang J. Silicate bioceramics enhanced vascularization and osteogenesis through stimulating interactions between endothelia cells and bone. *Biomaterials* 35, 3803–3818 (2014).

•• **This study clearly described the roles of biomaterials in cell–cell interaction, thus important to further studies employing biomaterials and exosomes.**

152. Tatullo M, Spagnuolo G, Codispoti B *et al.* PLA-based mineral-doped scaffolds seeded with human periapical cyst-derived MSCs: a promising tool for regenerative healing in dentistry. *Materials (Basel).* 12(4), 597 (2019).