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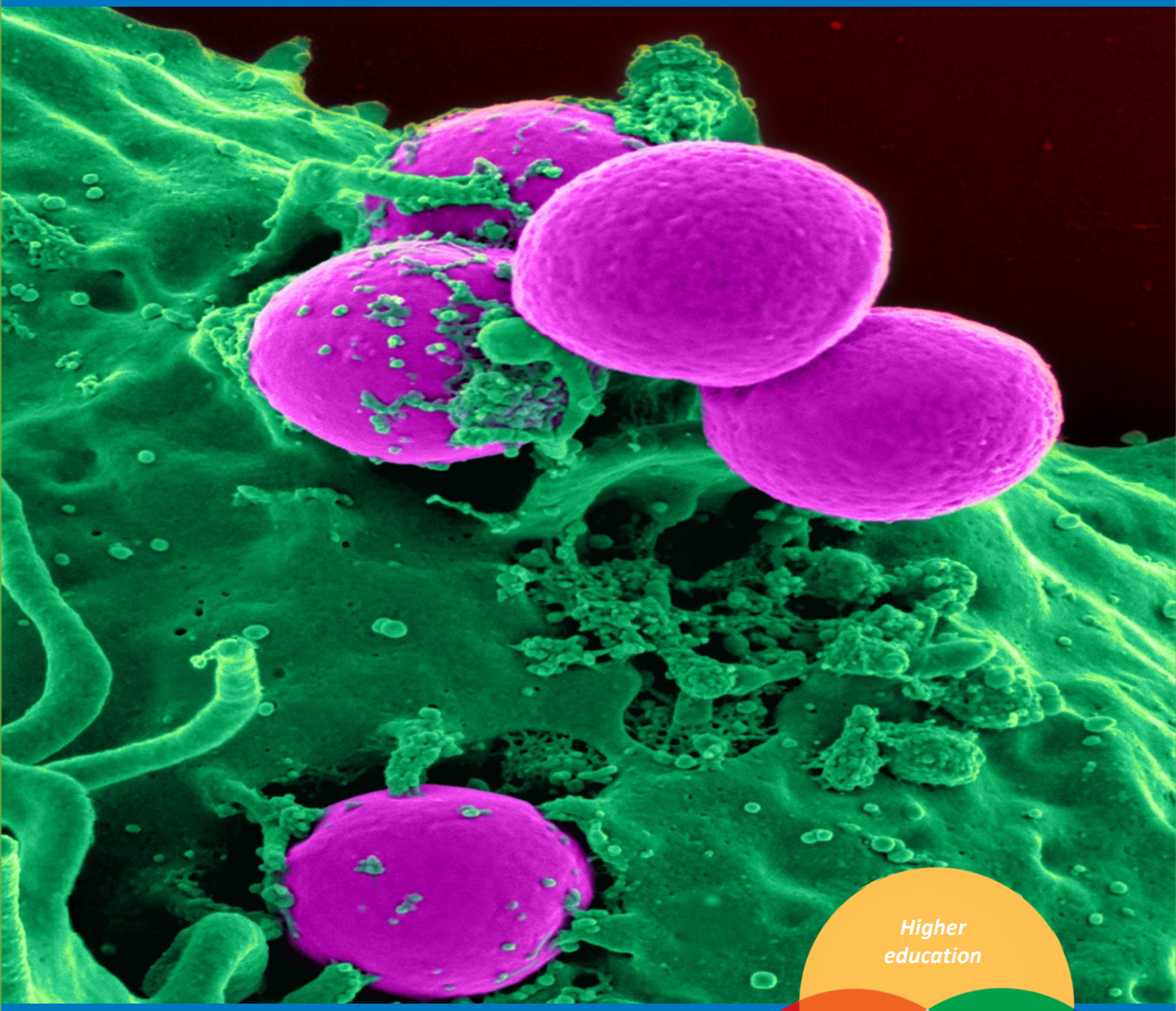
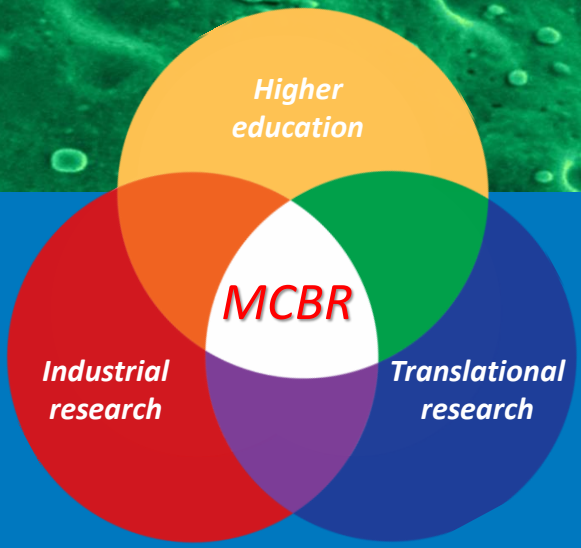
Biotheracues

Quarterly Newsletter of Manipal Centre for Biotherapeutics Research, MAHE





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ACADEMY of HIGHER EDUCATION
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Contents

Message from the Chief Editor

Dear friends and well-wishers of MCBR,

I am pleased to present you with the first issue of our newsletter for 2023. We have introduced a new section titled '*article under focus*' from this volume.

During this quarter, our first batch of MSc students completed their first and only academic semester at MCBR and proceeded to the three-semester-long research internship period. While most of them chose to do research in industrial set-up, two students are pursuing academic research for their internship.

The current issue of *Biotheracues* is going to provide us with the different facets of academic progress made by MCBR; the installation of the 3D-Bioprinting facility under the supervision of Dr. Kirthanashri is one of the landmark events that happened during this period. Besides that, a five-day long workshop on stem cell culture, characterization, and assays was successfully organized under the supervision of Dr. Manjunatha and Dr. Raghavendra. Students and professionals across the MAHE campuses took part in that. I express my appreciation to Mr. Liston Augustine, an internship student for his help in re-designing the internal pages of this newsletter.

Your feedback and suggestions are always welcome to enhance the quality of our newsletter.

Warm regards.

Dr. Souvik Dey

Inauguration of 3D Bioprinting Facility

Manipal Centre for Biotherapeutics Research (MCBR), Manipal, a constituent unit of Manipal Academy of Higher Education (MAHE), inaugurated the 3D Bioprinting and Tissue Culture Facility which was unveiled by Lt. Gen. (Dr) M. D. Venkatesh, Vice Chancellor, MAHE**, Dr Sharath K. Rao**, Pro Vice-Chancellor (Health Sciences), MAHE, **Mrs. Nirali Vora,** CSR Head of Genesis Packaging, along with **Mr. Kaushal Vora**, Director, Genesis Packaging. Dual nozzle 3D bioprinter (Anga Pro, Alfatek Systems) was procured from the CSR funds contributed by Genesis Packaging Pvt. Ltd., Udupi.

*While inaugurating the facility **Lt. General (Dr) M.D. Venkatesh, Vice-Chancellor, MAHE** said "3D Bioprinting is the promising area of research where significant progress is being made in printing human tissues and organs. I am glad to inaugurate the 3D Bioprinting and Tissue Culture facility at MCBR and I look forward to seeing pathbreaking research to emerge from this facility ultimately benefitting healthcare at large".*

Mrs. Nirali Vora, CSR Head of Genesis Packaging said *"I am honoured and humbled to be felicitated by MAHE leadership. MCBR is a world-class research facility, and we are extremely happy to contribute CSR funding to procure the 3D Bioprinter. We wish MCBR and MAHE researchers all the best in their research using the Bioprinter". MAHE and Alfatek signed an agreement to collaborate on skill development and innovative research in the area of 3D Bioprinting."*

***Mr Sumant Bhutoria, CEO of Alfatek Systems Pvt. Ltd., Kolkata**, "spoke about the progress on 3D Bioprinting in India and the promises it holds."*

The event was presided by Dr Raviraja N S, Professor and Coordinator of MCBR welcomed the gathering and shared the vision of MCBR. Dr Kirthanashri SV, Associate Professor, and Team Leader 3D Bioprinting, MCBR, presented the research highlights in the area of 3D bioprinting at MCBR. Air Vice Marshal Dr D C Agarwal, Dr B S Satish Rao, Dr Sathish B Pai, Dr Sajan D George, and others were present. Ms. Prachi Agarwal anchored the program and Ms. Vidhi Mathur proposed the vote of thanks.

ACTIVITIES AT MCBR

MCBR organized a five day (20th – 24th Feb, 2023) workshop on **Stem Cell Culture, functional characterization, and potency assay**. There was also an ***Open House*** event in between the days of workshop (22nd Feb) for potential students and industry collaborators. Stalls from various companies dealing with life sciences research were put in the courtyard of MCBR to showcase their products. MAHE members and participants of the workshop interacted with them.

MCBR conducted its first workshop on the topic 'Stem Cell Culture, Functional Characterization, and Potency Assays' from 20th February to 24th February 2023 under the leadership of Dr. Raviraja N S as organizing Chairman, along with Dr. Manjunatha S Muttigi, Workshop Convener and Dr. Raghavendra Upadhya, Workshop Co-convenor. The inaugural function was graced by the presence of Dr. V R Ravi, Mr. Manohar B N, Dr. H S Ballal, and Dr. Sharath K Rao, along with department heads, researchers, and Heads of various Institutions from MAHE. A keynote address was delivered by Dr. VR Ravi, Director, Mothercell regenerative Centre Pvt. Ltd discussed the past, present and future opportunities of using stem cells in clinical scenarios.

A total of 12 participants were from various institutes of MAHE, including MCOPS, KMC and Jamshedpur Campus. The workshop included cell culture basics theory, hands-on cell culture techniques, Transfection experiments, development of potency assays, MTT Assay, Flow Cytometry technique for cell cycle analysis, and surface marker expression. There was also a hands-on session on Real-Time quantitative PCR for gene expression studies and Secretome analysis using ELISA. Observation of trilineage differentiation and its staining was also included. In cell culture experiments initiated the cultures of Mesenchymal stem cells, and surface marker analysis of these cells was done using flow cytometry. The workshop also provided an opportunity for the participants to interact with the application scientists from companies of Stempeutics Research Pvt Ltd, ThermoFisher Scientific, Applied BD Biosciences, and talks from scientists of Himedia, Eppendorf. Dr. Udaykumar K, Vice President, Technical Operations, Stempeutics Research Pvt. Ltd spoke on 'Cell Therapy workflows- Chemistry, Manufacturing and Controls' and answered any doubts. Dr. Raviraja N S delivered a talk on 'Stem Cell Product Development in India', Dr. Suresh Kannan, principal scientist, Stempeutics Research Pvt Ltd, delivered a talk on 'Potency Assay Development for Stem Cell Therapy Products', followed by a Q and A session.

The workshop sponsors- Stempeutics Research Pvt. Ltd, Himedia, AIC Enterprises Pvt Ltd, Thermofisher Scientific, Eppendorf, Sri Durga Lab equipment, Alkeme – the complete lab solutions, Roshtec Life Science, SV Scientific Pvt. Limited had an interesting interactive session with talks about their products and the basics of the instruments and respective techniques.

The valedictory function was held on 24th February with Dr. Satish Rao BS, Director Research, MAHE, as guest of honor and chief guest Dr. Niti Nipun Sharma, Pro Vice-Chancellor - Strategy & Planning, MAHE. Participants shared their positive and insightful feedback. The successful completion of this workshop paves way for many more such academic activities at MCBR.

Student Achievements

Hearty Congratulations Ms. Nikshitha K (MSc Biotherapeutics student at MCBR), for being one among 100 recipients of the prestigious Bayer Fellowship Program - MEDHA, awarded by Bayer CropScience Limited and the committee- Office of the Principal Scientific Adviser to the Government of India. We are proud of you.

Research Progress

Publications:

- Crasta DN, **Nair R**, Kumari S, Dutta R, Adiga SK, Zhao Y, Kannan N, Kalthur G. Haploid Parthenogenetic Embryos Exhibit Unique Stress Response to pH, Osmotic and Oxidative Stress. ***Reproductive Sciences***. 2023 Jan 23:1-5.

- Indrashis Bhattacharya*# and **Souvik Dey*# (2023).** Emerging concepts on Leydig cell development in fetal and adult testis. ***Frontiers in Endocrinology*** (**Q1; IF: 6.05**) doi: 10.3389/fendo.2022.1086276/. #Equal contributor; *Corresponding authors.

- Prachi Agarwal, Gargi Arora, Vidhi Mathur, Amit Panwar, Varadharajan Srinivasan, Deepti Pandita, **Kirthanashri S Vasanthan.** Diverse applications of 3D printing in biomedical engineering: A review, 3D printing and additive manufacturing. Jan 2023 **(IF:5.35).**

- Sayali Pravin Metkar, Gasper Fernandes, Ajinkya Nitin Nikam, Soji Soman, Sumit Birangal, **Raviraja N Seetharam**, Manjunath Bandu Joshi and Srinivas Mutalik. Mannosylated-Chitosan-Coated Andrographolide Nanoliposomes for the Treatment of Hepatitis: In Vitro and In Vivo Evaluations. ***Membranes.*** 2023, 13, 193. https://doi.org/10.3390/membranes13020193 (**Q2; IF: 4.562**)

- Jahnavy Madhukar Joshi, Manjunatha S. Muttigi, Raghavendra Upadhya & **Raviraja N Seetharam**. An overview of the current advances in the treatment of inflammatory diseases using mesenchymal stromal cell secretome. ***Immunopharmacology and Immunotoxicology.*** 2023, DOI: 10.1080/08923973.2023.2180388 (**Q2; IF: 3.24**)

Faculty Updates

Dr Vadiraja B Bhat, PhD, Country Biopharma Business Development Manager, Agilent Technologies India Pvt. Ltd. Bengaluru, has been appointed as the Adjunct Faculty at Manipal Centre for Biotherapeutics Research, MAHE, Manipal. Congratulations Dr Vadi Sir. MCBR is looking forward to your guidance and mentorship.

On 1st March 2023, Dr. Raviraja, Director of MCBR, was also given a new position of Director of Planning and Monitoring

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Brain Behavior and Immunity

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Intranasally administered human MSC-derived extracellular vesicles inhibit NLRP3-p38/MAPK signaling after TBI and prevent chronic brain dysfunction

Maheedhar Kodali [a], Leelavathi N. Madhu [a], Roxanne L. Reger [a], Bojana Milutinovic [a,1], Raghavendra Upadhya [a,2], Jenny J. Gonzalez [a], Sahithi Attaluri [a], Bing Shuai [a], Daniel L.G. Gitai [b], Shama Rao [a], Jong M. Choi [c], Sung Y. Jung [d], Ashok K. Shetty [a,*]

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Intranasally Administered Human MSC-derived Extracellular Vesicles Inhibit NLRP3-p38/MAPK Signaling after TBI and Prevent Chronic Brain Dysfunction

Traumatic brain injury (TBI) is associated with chronic neuroinflammation characterized by activation of the nucleotide-binding domain leucine-rich repeat and pyrin domain-containing receptor 3 (NLRP3) inflammasome in microglia. This study investigated whether a single intranasal (IN) administration of human mesenchymal stem cell-derived extracellular vesicles (hMSC-EVs) naturally enriched with microglia-modulating miRNAs can prevent chronic adverse outcomes of traumatic brain injury (TBI). Small RNA sequencing validated the enrichment of microRNAs with the ability to modulate activated microglia in hMSC-EV cargo. Injection of hMSC-EVs into adult mice 90 minutes after inducing a unilateral controlled cortical impact injury resulted in their incorporation into neurons and microglia in both the injured and uninjured hemispheres.

A single treatment with a higher dose of hMSC-EV inhibited NLRP3 inflammasome activation following TBI, as indicated by decreased levels of NLRP3, microglia of TBI mice administered hMSC-EVs. hMSC-EV treatment at a higher dose inhibited the chronic activation of the p38 mitogen-activated protein kinase`(MAPK) signaling pathway induced by IL-18, thereby reducing the release of proinflammatory cytokines. Inhibition of chronic activation of NLRP3-p38/MAPK signaling following TBI also prevented long-term cognitive and emotional deficits. Notably, animals receiving higher doses of hMSC-EVs after TBI exhibited superior cognitive and emotional function on all behavioral tests compared to animals receiving the vehicle. A lower dose of hMSC-EV improved cognitive and emotional function to a lesser degree. Thus, an optimal intravenous (IV) dose of hMSC-EVs naturally enriched with activated microglia-modulating miRNAs can inhibit chronic activation of NLRP3-p38/MAPK signaling following TBI and prevent long-term brain dysfunction.

BLOGS

Evolution of Cell Culture Media

*-**Jahnavy M Joshi,** Research Scholar, MCBR, MAHE*

Since the development of Ringer's solution by Sydney Ringer in 1882, scientists have been working towards ways to culture cells *in vitro*. The first successful attempt was by Ross Harrison in 1907 where he could study nerve fibres of frogs in frog lymph fluid for weeks. This paved the way towards establishing more such combinations of defined and natural components to grow cells *in vitro*. Margaret Reed is known to be the first person to grow guinea pig bone marrow samples and culture mammalian somatic cells. A noble prize winner, Alexis Carrel is credited to be the first person to introduce the now culture flasks to maintain aseptic environment in 1912. The discovery that adding plasma and/or chicken embryonic extract is more suitable than only lymph furthered the cell culture options. However, the natural components containing media had unknown composition. This led to characterization of such components, to prepare a more chemically defined solution. In 1911, Locke-Lewis solution, made up of balanced salts along with amino acids, bouillon, and glucose is better for chick embryo growth. Another solution, called Baker's medium showed to be more effective as in addition to basic components, it also has vitamins. Nevertheless, it was found that addition of some sort of natural part was a necessity. Though such medias supported *in vitro* cell culture, the quest to compose a chemically defined medium still continued. Fischer, through using dialysed plasma, developed a new way to compose media. On this basis, in 1955, Harry Eagle developed a media composed of minimum amounts of components necessary to HeLa and mouse L cells, which was fine-tuned to produce minimum essential medium (MEM) which is used till date. Using Fischer's dialysis principle, Thomas McCoy discovered the role of pyruvate in carcinosarcoma cell and during same time, Rosewell Park Memorial Institute calibrated the McCoy's 5A media to produce RPMI 1640 which was used extensively in lymphocyte culture. Another approach to developing cell culture medium was the synthetic approach wherein serum-free culture was demonstrated. In this regard, though a few formulations like CMRL1066, NCTC109, and MB 752/1, Ham's F-12 have been developed, these have known to pose major drawbacks to serum containing media, and are very specific to particular cell lines. The latter part can be used to advantage, it can be tailored according to the cells of interest. Supplements are being formulated based on known compositions as per requirements. For example, Insulin Transferrin Selenium (ITS) is a widely used supplement for various differentiation experiments. The growth in regenerative medicine and biotherapeutics guarantees the development of many such media compositions, which will lead to more innovations.

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- Jedrzejczak-Silicka, M. (2017). History of Cell Culture. New Insights into Cell Culture Technology. doi: 10.5772/66905

Stem Cell Therapy For Infertility

*-**Dr. Rmaya Nair,** Postdoctoral Fellow, MCBR, MAHE*

Infertility is a major health concern that has a physical, physiological, and economic impact on the individual, family, and community. Stem cell therapy has provided new hope for infertility treatment. Stem cells have the ability to divide and differentiate into many cell types, giving them a great therapeutic value. Mesenchymal stem cells (MSCs) derived from bone marrow (BM), Wharton's jelly (WJ), umbilical cord (UC), amniotic fluid (AF), menstrual stem cells, adipose tissue, and endometrial cells have been shown to be effective at reversing infertility and resulting in live births (1). Stem cells from ovaries, endometrium, decidua, and testis are pluripotent in nature and serve as repair machinery for maintaining tissue homeostasis (2). VSELs (Very Small Embryonic-like Stem Cells) can be used as autologous pluripotent stem cells for infertility and improve egg quality. MSCs serve as paracrine providers of cytokines, growth hormones, signalling lipids, mRNAs, and miRNAs that help tissue cells differentiate into specific cell types (3). They are bioresource-free therapeutic models for infertility and serve as a model for tissue engineering, regenerative medicine, and reproductive medicine. Figure 1 depicts the possible mode of treatment available for treating female and male infertility issues by stem cell therapy.

Female Reproductive issues addressed by Stem Cell Therapy:

It is an emerging field in reproductive biology, with preclinical and clinical trials showing that MSC injections can revive the activity and functioning of the ovarian, uterine, and endometrial systems. The restoration of paracrine activities in ovaries following MSCs infusion, with increased follicle growth and the revival of hormone activity (4–6), as well as differentiation into oocyte-like structures, giving hope to postmenopausal and premature ovarian syndrome women (7). MSC immunomodulatory actions have been reported to be beneficial in the PCOS model for the recovery of the estrous cycle and maturation of follicles and corpus luteum with a decreased cystic follicle (8) along with activity of miRNA-323-3p. Cell free therapy has also been found to improve the ovarian system, with

miRNA-derived exosomes increasing oestrogen levels and decreasing FSH levels, and programmed cell death protein (PDCD4) and phosphatase tension homolog (PTEN) downregulated. Microinjections of autologous ADSC mitochondria into immature oocytes improved oocyte quality, embryo development, and fertility in elderly mice. MSCs derived from WJ and BM improved tubal factor infertility by decreased inflammation during salpingitis and increased healthy follicles in mice, leading to an increase in the pregnancy rate during the natural estrous cycle.

Endometrial damage repair by stem cells is being investigated as a potential treatment for diseases such as endometriosis and Asherman's syndrome. Preclinical and clinical trials are underway to improve physiological reproductive functions through the use of stem cells in decidualization, implantation, pregnancy maintenance, and postpartum uterine remodelling. Endometrial disruption caused by uterine disorders or endometriosis has been shown to regenerate using bone marrow mesenchymal stem cells. Exosomes have been shown to reduce apoptosis and promote endometrial repair via the TGF-1/Smad signalling pathway. Uterine fibroids have also been found to shrink and disappear after stem cell injections into these fibroids. Fibrosis during endometrial damage was found to improve the condition in the IUA model via miRNA 29 and 340.

Male Reproductive issues addressed by Stem Cell Therapy:

Stem cell therapy can be useful in treating azoospermic individuals, as preclinical studies have shown successful differentiation of spermatogonial stem cells to create new sperm cells. Holstein–Friesian calves have given a new ray of hope after autologous transplantation of SSC, and autologous cryopreserved spermatogenic stem cells in pubertal and prepubertal macaques have resulted in enhanced spermatogenesis. Mesenchymal Stem cells from neonatal testis of rats have been found to differentiate into Leydig cells, which can secrete androgen. The immunosuppressive effect of bone marrow-derived MSCs on anti-sperm antibody production was reported in mice, and exosomes protect the sperm genomic integrity by decreasing cell membrane injury, decreasing ROS and DNA damage. In male diabetic animal model, infertility due to erectile dysfunction was ameliorated by ADC-derived exosomes. Stem cell therapy has ushered in a new era of cell-based infertility treatment, with its effectiveness far greater than traditional treatment systems. However, there are technical obstacles to overcome before it can be widely used, such as efficiency and risk of anti-donor immune response. Long-term planning and evaluation are needed to ensure the quality and safety of these procedures during their implementation.

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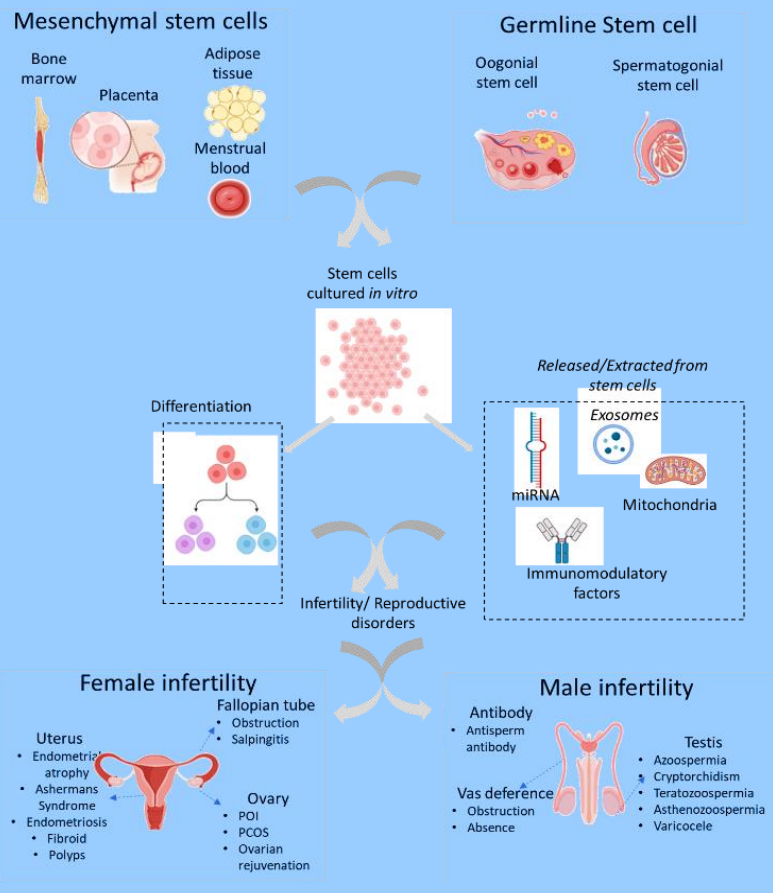

Figure 1: Possible role of stem cell therapy in treating various male and female infertility-related diseases (1).

AGING REVERSAL: NOT A SCIENCE FICTION, ANYMORE

Aging is a complex process that is best described as chronic dysregulation of cellular processes leading to tissue and organ degeneration. Although, aging cannot be prevented, its impact on the lifespan and health-span in elderly may be mitigated through interventions by restoring these cellular processes to optimal function. There have been many investigations on reversing the aging process in mice. One such promising approaches is the use of "senolytic" medications that target and kill senescent cells (cells that have stopped dividing and accumulate in the body as we age). When these cells are destroyed, inflammation decreases and regeneration of healthy cells improve. Other techniques include genetic modification of mTOR system in mice changes certain aging mechanisms that affects cell development and metabolism. These techniques have demonstrated encouraging results in prolonging the lifespan of mice and lowering lowering age-related illnesses. It is essential to emphasize, however, that additional research is required to discover whether these procedures can be safely and efficiently applied to humans. A 2019 study published in ***Cell*** led by Prof. David Sinclair of Harvard Medical School demonstrated that a mixture of molecules termed Yamanaka factors (OCT4, SOX2, and KLF4; OSK) could cure aging in mice by repairing the thymus gland, which plays a crucial role in immunity. The study demonstrated that therapy with Yamanaka factors might regenerate the thymus in aged mice, resulting in enhanced resistance to infection. A follow-up study by the David Sinclair group published in 2020 in the journal ***Nature*** demonstrated that the OSKM (OCT4, SOX2, KLF4, and c-MYC) cellular reprogramming approach could correct age-related epigenetic alterations in mice, resulting in longer lifespan and enhanced health. The study demonstrated that therapy with OSKM might reverse age-related DNA methylation alterations and restore the youthful condition of multiple tissues in aged mice, hence enhancing their physical fitness, organ function, and cognitive abilities. Another group of researchers in their 2023 communication to pre-print repository ***bioRxiv*** claimed that systemically administered AAVs (Adeno-associated virus; used as vectors) encoding an inducible OSK system extend the median *remaining lifespan* of 124-week-old mice by more than two folds relative to wild-type controls and improved certain health parameters. Importantly, they also observed a significant improvement in frailty scores (a measure of the health status of older individuals), indicating that the intervention was able to simultaneously increase the health span and lifespan of these mice. In addition, they observed significant epigenetic markers of age reversal in human keratinocytes expressing exogenous OSK, suggesting potential reregulation of genetic networks to a younger, potentially healthier state. These findings may have significant implications for the development of interventions that use partial reprogramming to reverse age-related diseases in the elderly. While these studies demonstrate encouraging outcomes in reversing aging in mice, additional research is required to discover whether they can be safely and efficiently applied to humans.

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NOTABLE VISITORS

Some prominent personalities including industrialists, scientists, and administrators visited MCBR during the last three months. MCBR thanks all of them profusely for their visit.

Dr. Giridhar Kini and Dr. Jayavanath Kamath visited MCBR on 20th Jan 2023 and interacted with the faculty, research scholars, and interns of MCBR.

Dr. Sohum Sohoni from the University of New Brunswick, visited MCBR on 2nd Feb 2023, and provided insights on various aspects of research.

Dr. Sadhna Joglekar, Senior Vice President and Head, Global Drug Development, Hyderabad, Novartis visited MCBR on 11th Feb 2023, and gave insights on how MCBR could contribute in the area of health care and commercializing various products.

Dr. Harish Madhyastha, Assistant Professor of Cardiovascular Physiology, Department of Medical Sciences, School of Medicine, Faculty of Medicine, University of Miyazaki, Japan, visited MCBR and gave his insights on Metal Nano Medicine.

Prof. Aaron Russel from Australia visited MCBR his area of interest is stem cells and had an interactive session with members of MCBR

INTERACTIVE EVENTS

MCBR OBSERVES VOTER'S DAY ON 27TH JANUARY

MCBR CELEBRATES HOLIKA DAHAN ON 7TH FEBRAURY

FUN MOMENTS

MCBR celebrated the birthdays of our research scholars and staff with cakes and claps!

Mrs Sujata –

7th January

Dr Manjunatha –

28th January

Mr Prasad –

3rd March

Mr Avinash –

8th February

Dr Raviraja –

4th March

Dr Raghavendra

&

Ms Jhanavy –

23rd March

Ms Mrunmayi –

16th March

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