

# Biotherapeutics

Vol: 4

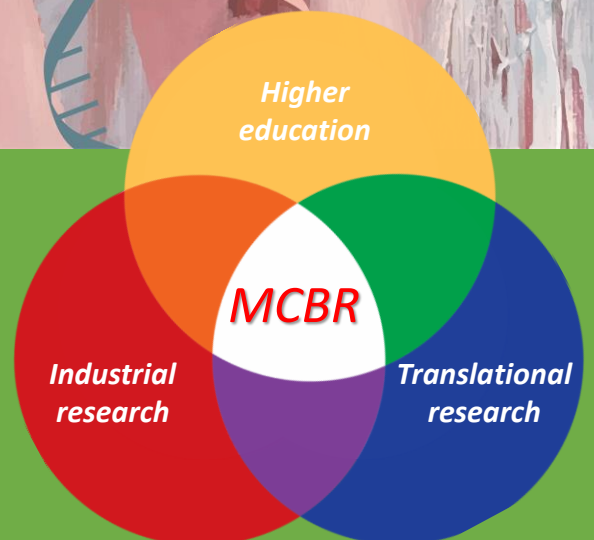
October-December, 2022

Quarterly Newsletter of Manipal Centre for Biotherapeutics Research, MAHE

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**MANIPAL**  
ACADEMY of HIGHER EDUCATION  
(Institution of Eminence Deemed to be University)



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## Contents

*Message from the Chief Editor*

*Celebration of the first anniversary  
of the establishment of MCBR*

*Activities at MCBR*

*Research progress*

*Invited lecture presentations*

*Notable visitors*

*Blogs*

*Global research update*

*Interactive events*

*Observance of Vijayadashami*

*Halloween and Christmas celebration*

*ArTure awareness activities*

*Off the trail club activities*

*Semester-end ceremony  
for MSc students*

*Fun moments:*

*Birthday celebrations at MCBR*

## *Message from the Chief Editor*



Dear friends and well-wishers of MCBR,

I am happy to present the last volume of *Biotheracues* for 2022. It covers events and progress that took place between October to December of this year.

This was by far the busiest quarter of the year for all of us. Full-fledged theoretical and practical classes were followed by weekly journal club presentations for the MSc students. Research activities also picked up courtesy of our research scholars and the efforts of the faculties. Overall, it was a productive and eventful three months for all of us. My best wishes to all the MSc students who are going to have a three-semester research internship in academia and industries.

Your feedback and suggestions are welcome to make the next newsletter issue more interactive.

Warm regards.

*Dr Souvik Dey*

## *Celebration of the 1<sup>st</sup> Anniversary of Establishment of MCBR*

On the 14<sup>th</sup> of October 2022, Manipal Centre for Biotherapeutics Research (MCBR), MAHE, Manipal, celebrated its first anniversary of establishment. MAHE Vice Chancellor Lt. Gen. (Dr) MD Venkatesh, Pro Vice Chancellor Dr. Venkatraya Prabhu and Registrar Dr. Narayana Sabhahit commended the achievements made by our team MCBR under the leadership of Dr. Raviraja NS. Our doctoral and master's students actively took part in this event – they sang the invocation song and shared their thoughts and experiences. Prof. Raviraja shared updates about our institute with the gathering. The event was followed by a brief photo session.



## Research Progress

Currently, MCBR has four doctoral research scholars and four research interns, who are likely to be joining their doctoral program in this center, soon. With the selection of one more faculty as Assistant Professor, the total faculty strength has become six.

Like earlier quarters, our faculties have submitted projects and Letters of Intent (LOIs) to different government funding agencies. 12 out of 13 of our MSc students are going to do their research work in pharma/biotech industries in next three semesters; the other student has been selected to carry out his research work in MCBR



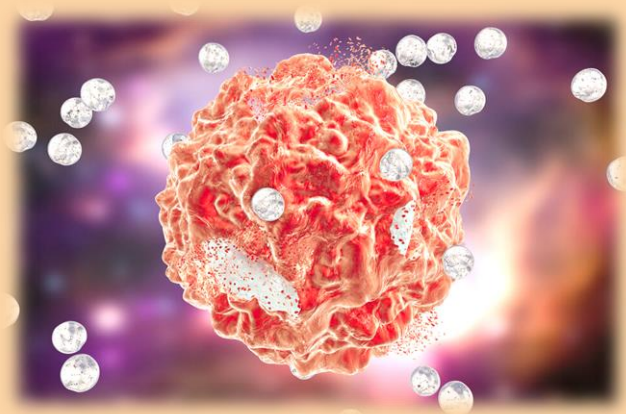
## Publications:

1. Maheedhar Kodali, Leelavathi N. Madhu, Roxanne L. Reger, Bojana Milutinovic, **Raghavendra Upadhya**, Jenny J. Gonzalez, Sahithi Attaluri, Bing Shuai, Daniel L.G. Gitai, Shama Rao, Jong M. Choi, Sung Y. Jung, and Ashok K. Shetty. Intranasally Administered Human MSC-derived Extracellular Vesicles Inhibit NLRP3-p38/MAPK Signaling after TBI and Prevent Chronic Brain Dysfunction. **Brain Behaviour and Immunity**, 2022. 108:118-134.doi:10.1016/j.bbi.2022.11.01 (Q1, IF 19.2).
2. Nampoothiri S, Dsouza JM, Yesodharan D, **Girisha KM**, Eapen M, Sivasankaran Nair S, Pillai BV, **Radhakrishnan P** (2022). A bi-allelic missense change c.638A >G in matrix metalloproteinase 15 in a patient with progressive familial intrahepatic cholestasis without cardiac anomalies. **Clin Genet**. (Q1\_IF: 4.296) doi: 10.1111/cge.14263.
3. Musyuni P, Bai J, Sheikh A, **Vasanthan KS**, Jain GK, Abourehab MA, Lather V, Aggarwal G, Kesharwani P, Pandita D. Precision Medicine: Ray of Hope in Overcoming Cancer Multidrug Resistance. **Drug Resistance Updates**. 2022 Nov 9:100889. (IF: 22.2)
4. **Meghana Kasturi, Vidhi Mathur, Prachi Agarwal**, Varadharajan Srinivasan, **Kirthanashri S Vasanthan**. 3D printing for Tissue regeneration in Advances in 3D printing ISBN: 978-1-80355-844-8, Intech open. 2022.
5. Daphne Norma Crasta, **Ramya Nair**, Sandhya Kumari, Rahul Dutta, Satish Kumar Adiga, Nagarajan Kannan, Guruprasad Kalthur. Haploid Parthenogenetic Embryos Exhibit Unique Stress Response to pH, Osmotic and Oxidative Stress. Accepted in **Reproductive Sciences**, December 2022.
6. Indrashis Bhattacharya\*# and **Souvik Dey**\*# (2023). Emerging concepts on Leydig cell development in fetal and adult testis. Accepted in **Front Endocrinol**. (Q1; IF: 6.05) doi: 10.3389/fendo.2022.1086276/. #Equal contributor; \*Corresponding author.
7. **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).

# Activities at MCBR

## Conference presentation

1. Ms. Jahnavy Joshi, DST-INSPIRE Fellow of MCBR made an oral presentation at the International Conference on Biomedical and Clinical Research (ICBMCR), held on the 21<sup>st</sup> & 22<sup>nd</sup> of November 2022 at SDM University, Dharwad. Her topic was ‘Mesenchymal Stromal Cell Secretome as a cell-free alternative for inflammatory diseases’.



2. Ms. Jahnavy Joshi also made a poster presentation titled ‘Mesenchymal Stromal Cell Secretome, an emerging alternative to cell therapy for inflammatory diseases’ at the Interdisciplinary Conference on Health and Technical Research (ICHTR), organized at MAHE, Manipal on 25<sup>th</sup> and 26<sup>th</sup> November 2022.



## Journal Club Presentation by MSc students

Faculties at MCBR took initiative to prepare our MSc students for public scientific talk. We conducted weekly *Journal Club* events. Each student would pick one journal research article- as per their area of interest, in consultation with a mentor (faculty) and weekly two of them would make a 20-min PowerPoint presentation followed by a ten minute Q &A round, where faculties, research scholars and even other MSc student would be interacting with them.



MCBR now has an Invitrogen make Power Blotter system which has significantly reduced both time and use of transfer buffer for the Western Blot process ( see image below).



## Invited lecture presentations

In the last quarter of 2022, MCBR organized two back-to-back invited talks on the 19<sup>th</sup> and 20<sup>th</sup> of October. Dr. Vishwas Kaveeshwar, Assistant Professor & Lab In-Charge, Shri Dharmasthala, Manjunatheshwara University, Dharwad delivered a captivating talk on “*Induced Pluripotent stem cells in disease modeling and drug discovery*” on the 19<sup>th</sup> of October (top panel). It was followed by another engrossing presentation on 20<sup>th</sup> October 2022 by Dr. Prashanth Hebbar, CEO & Research Scientist, Mbiomics LLC, USA on “*A comprehensive analysis of mRNA expression profiles of Esophageal Squamous Cell Carcinoma reveals downregulation of Desmoglein 1 and crucial genomic targets*” (bottom panel). Both talks were attended by faculties, researchers, and master’s students of MCBR.



## 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. Some of them can be seen in the photos below with our faculty and research scholars:

Most notable among them was definitely Dr. Sateesh Reddy, Adviser to Raksha Mantri, Ministry of Defence, GoI. His invaluable advice motivated all of us.



In December, we were visited by Dr. Raj Warriar, former Vice Chancellor, MAHE, an inspiring personality, famous oncologist, and a great administrator.

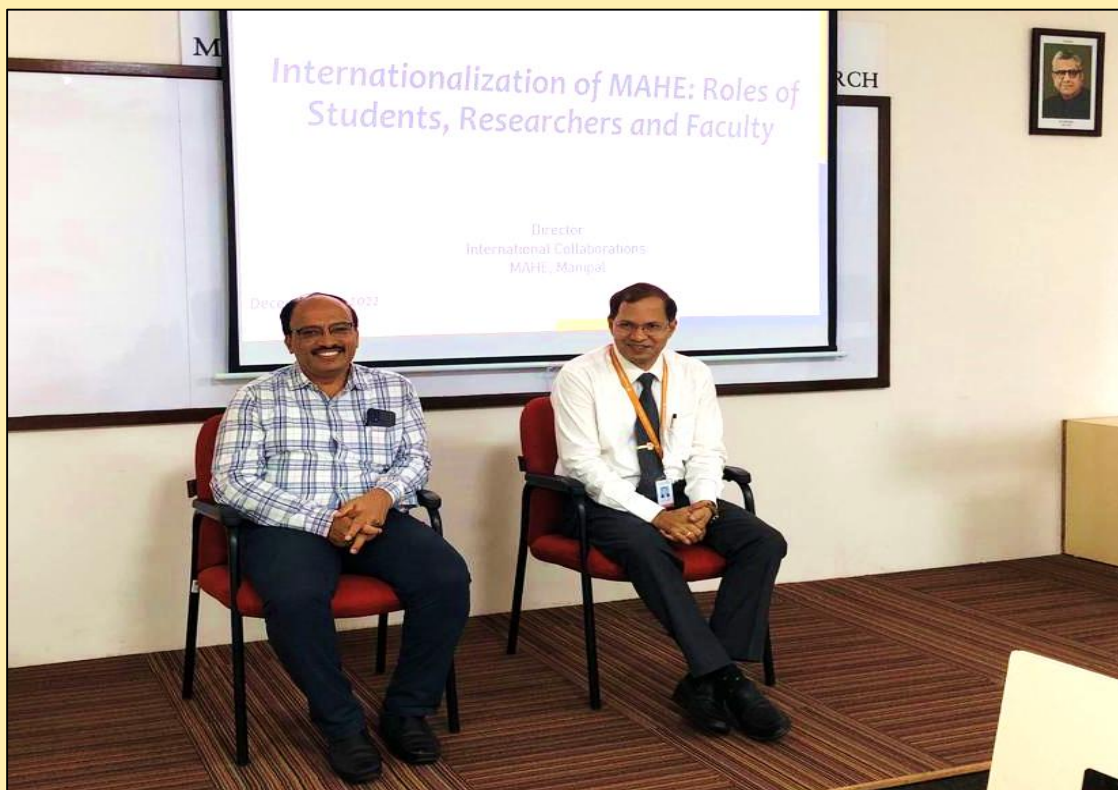




Air vice-marshal (Retd.) Dr. Dilip Chandra Agarwal, Vishist Seva Medel awardee and Dean & CEO - Manipal Education and Medical Group, Nepal inspired our students, as well as the faculties with his spirited words. His interaction with the MSc students was one of the highlights of this quarter.



Dr. Karunakar A Kotegar, Director- International Affairs and Collaborations, MAHE, Manipal delivered an invited talk on “Internationalisation of MAHE: Role of Students, Researchers and Faculty” at MCBR, MAHE, Manipal.





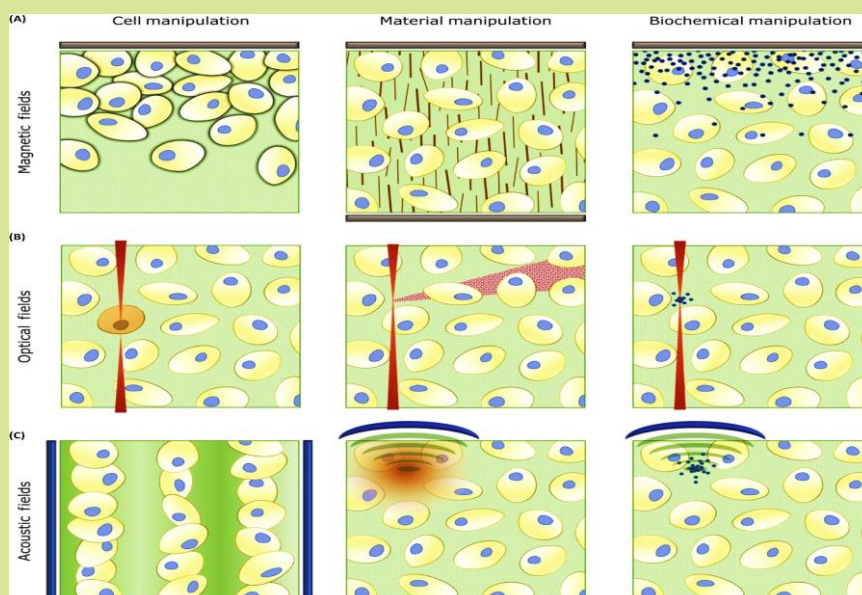
## Blogs

### Importance of single-cell manipulation technology

By Ms. Meghana Kasturi, Research Intern, MCBR, Manipal

The cells are the basic structural and functional unit of life. Hence, understanding the cellular processes is important to study different pathways and treat diseases. Most studies consider heterogeneity of cell populations. However, this approach can mask differences between individual cells. High-throughput single-cell analysis can bridge this gap and help analyse results to the minimal functional unit. Techniques such as 3D bioprinting, electrospinning, freeze drying can be used to fabricate scaffolds. These techniques are used to spatially organize components and initiate biochemical cues that can drive cell responses. An alternative approach is the use of externally applied forces (electrical or mechanical stimulation). Three common sources that are used for cell manipulation are optical fields, magnetic fields, and acoustic fields (**fig 1**). These are used to target cells and manipulate biomolecules for cell patterning, material assembly and biological stimulation. This kind of cell manipulation has shown a great control over epigenetics, gene expression and material degradation. These external forces - (i) assemble/move different components in a cell; (ii) initiate local responses like cell differentiation, proliferation, or material degradation/modification; (iii) exert responses like matrix fibre alignment; which can be applied to the entire tissue or an individual cell.

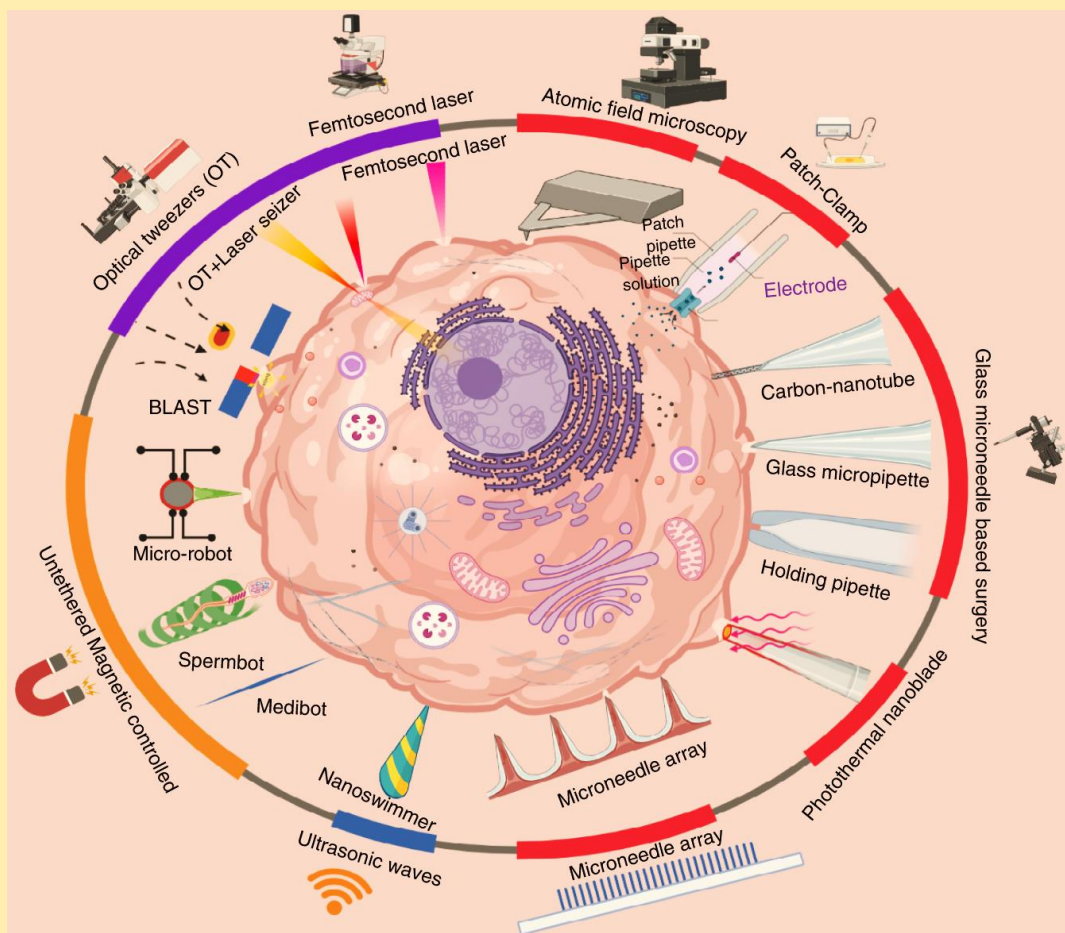
Cell manipulation can be done via encapsulation, sorting, trapping, isolation, rotation, pairing, patterning, stretching, transportation, lysis, and stimulation at a single cell level. Performing a single-cell analysis is more difficult than bulk-cell analysis in terms of the cell size and the concentrations of cellular components. However, it is also effective in targeting the desired cell rather than the entire chunk, example; drugs or biomolecules can be delivered only to the affected cell(s) rather than the whole chunk of cells in the surrounding area. Many tools and techniques like microfluidics, optical tweezers, ultrasound mediated delivery, di-electrophoresis etc., have been developed for this purpose (**fig 2**).



**Figure 1.** Effect of magnetic, optical, and acoustic fields on cells [1]

(A) Magnets (grey) manipulating the position of magnetized cells, aligning matrix fibers, and patterning growth factor gradients. (B) Optical fields (red) provide a high spatial resolution that can be used for optogenetic modulation of cells, photodegradation of materials, or local release of biochemical factors. (C) Acoustic fields can be generated by piezo transducers (blue) in order to pattern cell populations, modulate fiber microstructure, and locally release biochemical factors.

There is a need to study cells on both single and multi-cell levels to give researchers a balanced picture. Cell-to-cell variation occurs naturally in both healthy and diseased tissues which has implications in drug discovery and development, diagnostics, and prognostics. Generally, statistical analysis provides an average response across the entire cell population and does not give a clear picture on any one single cell including rare variants in the group. Hence, the average representation in the statistical studies may mask the response of a single cell. Such heterogeneity is a major challenge when attempting to develop accurate disease models, or elucidating patient responses to specific therapies. Therefore, analysis of individual cells enables the reduction of biological noise and offers the ability to investigate and characterize rare cells.



**Figure 2.** Tools and methods for single-cell manipulation [2]

#### References

1. Armstrong JPK, Stevens MM. Using Remote Fields for Complex Tissue Engineering. *Trends Biotechnol.* 2020 Mar 1;38(3):254–63.
2. Shakoor A, Gao W, Zhao L, Jiang Z, Sun D. Advanced tools and methods for single-cell surgery. *Microsyst Nanoeng.* 2022 Apr 29;8(1):1–21.
3. Luo T, Fan L, Zhu R, Sun D. Microfluidic Single-Cell Manipulation and Analysis: Methods and Applications. *Micromachines.* 2019 Feb 1;10(2):104.

# mRNA methylation and its therapeutic potential

by Ms. Neha Choudhari, Dr. TMA. Pai Research Fellow

Methylation modification of adenosine residue in mRNA is the most prevalent modification in eukaryotes. It involves various enzymes and complexes which regulate the process of mRNA translation, degradation, splicing, transport, and stability. Since the first discovery of methylation in mRNA in the 1970s, many researchers have explored the significance of this gene expression regulation in major diseases such as Type-2 diabetes, heart failure, viral infection, cancers, obesity, etc. The m6A on mRNA is installed by a writer complex containing methyltransferases such as METTL3 and METTL14 along with their cofactors and scaffolding proteins. This methylated mRNA is further processed accordingly with the help of readers i.e., the YTH-domain containing proteins. The reversal of this methylation is performed by the demethylases, FTO and ALKBH5. Many of these proteins have implications on disease development and are also found to regulate major biological processes such as tumor immunoregulation, inflammation, development of the central nervous system, spermatogenesis, glucose homeostasis, and progression of viral infections.

The first studies outlining the importance of methylation-regulated mRNA expression involved the enzyme METTL3/14. It was reported that loss of METTL3 in mammalian embryonic stem cells caused uncontrolled growth of the cells and affected their differentiation process. It was also observed that loss of METTL3 in mice caused death of the embryos before birth. METTL3 and METTL14 were further explored to play a major role in a variety of cancer types including acute myeloid leukemia, glioblastoma, and melanoma. Elevated levels of FTO and ALKBH5 have also shown to play oncogenic roles in acute myeloid leukemia cells, melanoma in mice and glioblastoma cells including gaining of resistance to various therapies such as tyrosine kinase inhibitor therapy and anti-PD-1 immunotherapy against melanoma.



More studies are being performed to understand the roles of these enzymes in major diseases and how their functions can be controlled to inhibit disease progression. Scientists are focusing on developing small molecule inhibitors against these enzymes and studies have proved that these might hold the therapeutic potential towards various disorders.

Epitranscriptomics, an emerging field in molecular biology, has enabled researchers to understand the essential target proteins that are regulated in the transcriptome and these relevant changes in protein expression can be compared with that observed in diseased conditions. Researchers believe that being able to understand and control mRNA modifications will open newer avenues for treating diseases. Epitranscriptomics involves the use of m6A antibodies to discover methylated mRNA transcripts which are then sequenced to find out the mRNA product of genes that are undergoing active translation during a disease condition. It has also enabled scientists to map the m6A modification in mRNA and reach to a conclusion that the modification takes place at a certain consensus sequence near stop codon and is not random. Although the field of epitranscriptomics is new and crude, it has provided useful insights into the world of disease regulation by mRNA modifications. Overall, the involvement of m6A in the pathogenesis of various human diseases suggests that this can be a potential therapeutic target and act as a viable treatment strategy.

## References:

- 1) He, P. C., & He, C. (2021). m6A RNA methylation: from mechanisms to therapeutic potential. *The EMBO journal*, 40(3), e105977.
- 2) Cross, R. (2019, Feb 18). "Epitranscriptomics: The new RNA code and the race to drug it." *C&en*, [Volume 97, Issue 7](https://cen.acs.org/business/start-ups/Epitranscriptomics-new-RNA-code-race/97/17). <https://cen.acs.org/business/start-ups/Epitranscriptomics-new-RNA-code-race/97/17>
- 3) Image courtesy: <https://www.stormtherapeutics.com>.



## Stem Cell Products: Recent Trends

Stem cells hold the property of self-replication and differentiation to various cell types. Due to these properties, they were considered wonder drugs to repair and regenerate diseased cell or tissues. Despite rapid increase in clinical trials, the hype that stem cells are magic bullets for all types of degenerative diseases are waning down over the past decade due to the lack of credible clinical evidence. However, it is important to note that there are some stem cell products available in Indian and international markets which have shown safety and efficacy in the clinical trials and have obtained marketing approval. The cost of manufacturing and the limitations with scaling up has made the allogeneic stem cell as favorite choice of companies developing stem cell drugs. A cursory look at the [www.clinicaltrials.gov](http://www.clinicaltrials.gov) reveals that Mesenchymal Stromal Cells (MSCs) are the preferred choice of stem cells for product development. Let us familiarize with some of the important allogeneic MSC products developed in the last decade.

**Prochymal:** Prochymal is an allogeneic bone marrow-derived MSC product developed by Osiris Therapeutics, conditionally approved in Canada in 2012. It is used to treat graft versus host disease (GvHD), a disease that occurs after transplantation, in which a patient's immune cells start attacking host tissues in pediatric patients. Now Mesoblast owns the Prochymal product.

**Alofisel:** Alofisel was developed by Takeda Pharma and approved in Europe and Switzerland since 2018. This is an adipose-derived MSC product that is used to treat perianal fistula in patients with Crohn's disease.

**TemCell:** Temcell HS was developed by JCR Pharmaceuticals and approved in Japan in 2015. It is an adult MSC product derived from healthy donors used to treat acute graft versus host disease (aGvHD) in children and adults.

**Cartistem:** Cartistem is a product developed by Korean company Medipost and approved in Korea in 2012. It is a human umbilical cord blood-derived MSC product used to treat knee articular cartilage defects.

**Regenacip:** REGENACIP® is a formulation of human bone marrow-derived allogeneic MSC product intended for intramuscular injection (IM) to treat Critical Limb Ischemia (CLI) due to Buerger's Disease (BD) and Peripheral Arterial Disease (PAD). The product is developed by Stempeutics Research Pvt Ltd and marketed in India by Cipla Ltd. This is the first allogeneic MSC product developed anywhere in the world for the treatment of CLI due to BD, which is an unmet medical need.

Stempeutics allogeneic MSC products are cryopreserved, off-the-shelf, derived from healthy adult donors using a patented pooling technology where patents have been issued in 16 countries (including US, Japan, and EU). Large scale manufacturing process ensures that one-time collection of bone marrow from three donors is sufficient to produce more than 1 million therapeutic doses.

**StemOne:** StemOne is an allogeneic MSC product derived from the human bone marrow MSCs for the Osteoarthritis of the knee. The product is developed by Stempeutics Research Pvt Ltd and marketed in India by Alkem Labs. It is the first allogeneic product developed in India for the treatment of Osteoarthritis. StemOne has the potential to provide best-in-class pain reduction, improve quality of life, has the potential to regenerate/maintain cartilage and to stall further disease progression for radiology Grade 2 & Grade 3 Osteoarthritis patients.

India is catching up with global companies as far as stem cell product development is concerned. We will witness an exciting time ahead in terms of new stem cell product launches.



## Interactive events

### Observance of Vijayadashami



### Halloween and Christmas celebration



Week-long *Secret Santa* game was arranged for the faculties, research scholars, and staff by the research scholars of MCBR starting a week prior to Christmas eve. Everyone participated and enjoyed this event thoroughly. Research scholars were way ahead in performing various fun tasks. The best part was revealing the surprise gifts for each other on the evening of the final day of this event.



Our MSc students put a lot of effort and came up with an innovative way to celebrate Halloween!



## 'ArTure' awareness activities



### Observance of the Drug Awareness week



Members of ArTure club of MCBR made a wonderful presentation to spread awareness against the abuse and intake of illegal drugs and how it has become a humanitarian crisis in today's societies across the globe.

### Celebration of Millets year



India is celebrating Millets year this time. ArTure members, Shreya, Nikshita, Madhu and Noman presented posters and explained the beneficial aspects of millets in our diet, especially for vegetarians.

# 'Off the trail' club activities

## Visit to Kapu beach



## Visit to Manipal End Point

You're Cordially Invited To  
*Visit to End Point*



Organized by  
*Off The Trail*

Team bonding activities like  
dumb charades, and  
photography

Faculty coordinator  
Dr. Manjunatha SM

President  
Rohan Janadri

07 December 2022  
4:00 pm - 7:00 pm





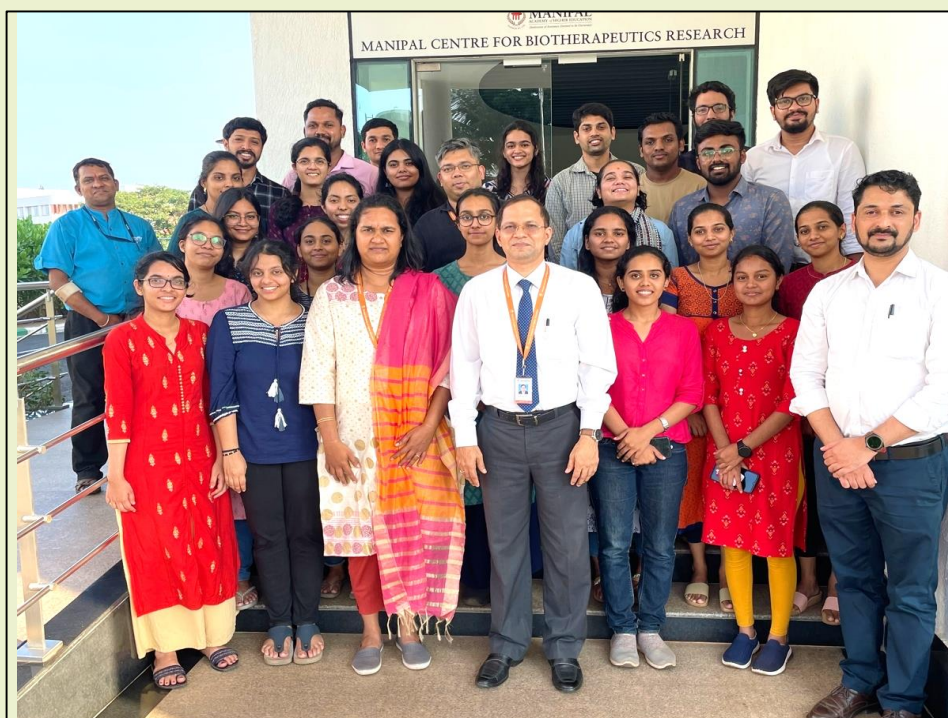
## *Semester-end ceremony for MSc students*



The first and only semester of academic activities ended for our maiden batch of MSc in Biotherapeutics students in the last week of December. A nice and brief semester-end ceremony was organized for them, mainly by our research scholars. Jahnvy played a soulful piece of music with the Indian traditional flute; Chetana assisted with her vocal music. Later on, all of us had a photo session.



Many of these students are going to do their upcoming three-semester research internships in the bio-pharma industries, while some will be developing expertise in academic research environments. We are thankful to all those companies and academic institutions who have offered these training facilities to our students.



*Fun moments:  
Birthday celebrations at MCBR*

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



11<sup>th</sup> November – Neha

14<sup>th</sup> November – Prachi

22<sup>th</sup> November – Kishore

19<sup>th</sup> December - Chethana

*Send your feedback and suggestions to [mabr.mahe@manipal.edu](mailto:mabr.mahe@manipal.edu)*



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