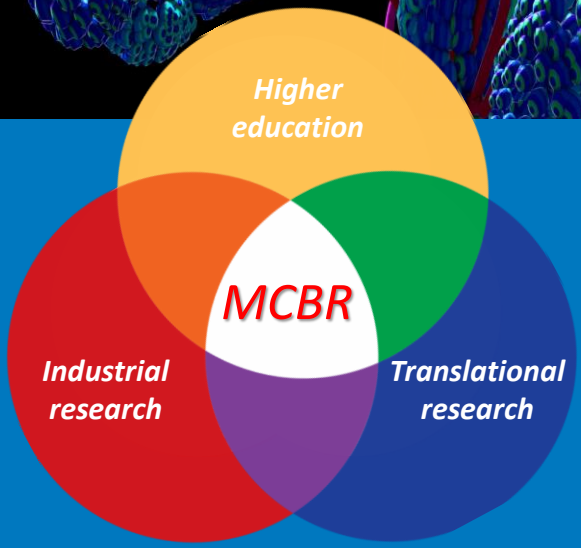
Vol: 3 July-September, 2022

Biotheracues

Quarterly Newsletter of Manipal Centre for Biotherapeutics Research, MAHE



MANIPAL
ACADEMY of HIGHER EDUCATION
(Institution of Eminence Deemed to be University)
INSPIRED BY LIFE

Contents

Message from the Chief Editor

Dear friends and supporters of MCBR,

I am delighted to present the July-September, 2022 Issue of our newsletter to you.

This quarter was particularly a busy one, pleasantly so, as a bunch of young and enthusiastic masters students joined MCBR on the 1st of August. I am happy to inform you that we got an almost full capacity of students in the inaugural year of this course itself.

The present issue of *Biotheracues* will give you a prevue of the research accomplishments and the academic interactions that occurred during this period. You will also learn about our initiatives on industry outreach and promotion of bonhomie through art & culture and outbound activities.

Your opinion and ideas are always welcome to improve our newsletter.

Warm regards.

Dr. Souvik Dey

Inauguration of MSc course in Biotherapeutics

On 1st August 2022, **MAHE Vice Chancellor Lt. Gen. (Dr) M D Venkatesh** inaugurated India's first "MSc (By Research) in Biotherapeutics" program at Manipal Centre for Biotherapeutics Research, MAHE, Manipal. This course will impart students with contemporaneous knowledge in theory and the practical uses of molecular tools and techniques in the discovery and development of cell, gene, protein, and other biomolecular novel drug candidates relevant to biotherapeutics. The course curriculum involves one-semester classroom training coupled with practical and three-semester extensive research training where learning will be hands-on in the areas of biotherapeutics discovery and development, process development, product characterization, delivery mechanisms, scale-up technologies, *in vitro* and preclinical research, and a fair knowledge of the regulatory framework.

The inauguration event received wide media coverage across Karnataka and outside. This ceremony was followed by a week-long orientation program for the masters students supervised by expert personnel from some key departments of MAHE.

Orientation program for the Masters' students

MUTBI CEO **Dr. Shrihari Upadhyaya**, Manipal-GOK Bioincubator CEO **Dr. Manesh Thomas** and MAHE Chief Innovation Officer **Dr. Mohammad Zuber** interacted with MSc (by Research) in Biotherapeutics students of MCBR. MCBR thanks CEOs and CIO for sharing their rich experience in the Incubation and Innovation space.

Dr. Vinod V Thomas, Registrar Evaluation, MAHE, Manipal, interacted with the first batch of MSc (by Research) in Biotherapeutics Students, Research Scholars and Faculty as a part of MSc orientation program. MCBR thanks Dr Vinod Thomas for his thoughts, insights and inspiring words.

Dr. Geetha Maiya, Director- Students Affairs, MAHE, Manipal, interacted with the first batch of students of MSc (by Research) in Biotherapeutics as a part of the Orientation Program. Students were inspired by her talk and felt happy about the support system available at MAHE. MCBR thanks Dr Geetha Maiya wholeheartedly for such a cordial interaction.

Activities at MCBR

Research Progress

In the last three months, MCBR continued its way toward scientific advancement as well as infrastructural development. Dr. Kirthanashri joined our Centre as an Associate Professor. Dr. Ramya Nair joined MCBR as a postdoctoral fellow. A new intern also started working here during this period.

Publications

1. Vidhi Mathur, Amit Panwar, **Prachi Agarwal**, Varadharajan S, **Kirthanashri SV**, Facet of 4D Printing in Biomedicine. Journal of Materials Research. Accepted. October 2022.

2. Debasish Kumar Ghosh, Shruti Pande, Jeevan Kumar, Dhanya Yesodharan, SheelaNampoothiri, **Periyasamy Radhakrishnan**, Chilakala Gangi Reddy, Akash Ranjan, **Katta M Girisha.** The E262K mutation in Lamin A links nuclear proteostasis imbalance to laminopathy-associated premature aging. ***Aging Cell. 2022. (IF: 11.0).*** doi: 10.1111/acel.13688.

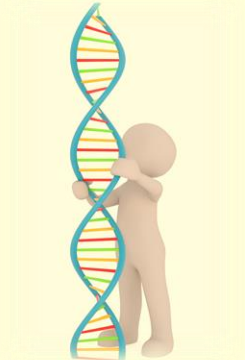
A new inclusion to MCBR instrumental repertoire, ***Synergy H1 multimode reader, BioTek.***

Conference Presentations

1. Dr. Raviraja NS, Professor and Coordinator, MCBR, MAHE, Manipal, delivered an invited talk titled "Biotherapeutics: Future of Medicine" at Manipal Pharmaceutics Conference 2022 (MPCON 2022) held between 22-24 Sept. 2022.

2. Dr. Souvik Dey, DBT-RLSF & Asst. Professor, MCBR delivered an oral presentation on the topic entitled "A Regulatory Loop between Cyclic AMP and Glycogen Synthase Kinase 3 functions in Mammalian Spermatozoa" at the 39th Annual Meeting of SRBCE and International Conference On "Reproductive Biology, Comparative Endocrinology & Development, held at CSIR-CCMB, Hyderabad from 14-16 September 2022.

3. Prof. Raviraja NS delivered an invited talk titled "Topical Growth Factors in Cosmetic Dermatology: A Bird's Eye View" at the 20th Annual Conference of Association of Cutaneous Surgeons (I) held at Vythiri Village Resort, Wayanad, Kerala from 15-17 September 2022.



Hosting of webinar

MCBR arranged an Invited Talk entitled, "*Advancements in Nanopharmaceuticals for Drug and Gene Delivery*", by **Dr. JC Bose Rajendran**, Senior Scientist (Biomedical and Translational Medicines), Masonic Medical Research Institute: Utica, NY, US, This event was organized in collaboration with *Manipal School of Pharmaceutical Sciences (MCOPS)* on *25th August 2022* using a virtual platform. Dr. Rajendran received his doctoral degree the School of integrative Engineering/Biomedical Engineering, Chung-Ang University, Seoul, KR. He is also an alumnus of the Center for Cancer Nanotechnology, Department of Radiology, Stanford University, CA, USA

Dr. Usha Nayak, Associated Professor, MCOPS co-moderated the webinar. Professor C. Mallikarjuna Rao, Principal of MCOPS at MAHE, and Professor Raviraja N.S., Coordinator of MCBR at MAHE, were the Chief Guests for this webinar. Neha Choudhari, Dr. TMA Pai PhD Scholar was M.C. for this event. Attendees included professors and PhD students from both MCBR and MCOPS. After Dr. Rajendran's talk, a Q&A session was held.

Industry outreach initiative

MCBR, MAHE, Manipal, invited Pharma/Biopharma companies to partner with us to co-develop next-generation Biotherapeutics. Partnering companies can benefit from equipped GMP facilities, skilled manpower, expert advice, etc.

Launch of Art & Culture And Outbound Activity Clubs

Culture plays an important role in the development of any institution. It represents a set of shared attitudes, values, goals and practices and thus helps in developing bonhomie among its stakeholders. **Prof. Raviraja,** Coordinator, MCBR envisions this centre to become a role model in this respect and believes that a cohesive and relaxed atmosphere is key to any kind of collective creative output.

We must thank and congratulate **Dr. Kithanashri,** our Cultural Coordinator, for taking a very proactive and resourceful role in setting up the MCBR student Clubs "ArTure" (Art and Culture) and "Off the Trail" (Outbound Activity). The students, research scholars, faculties and staff of MCBR were all looking enthusiastic about this initiative.

Dr. Venkatraya M Prabhu, Pro Vice Chancellor, MAHE, Manipal inaugurated "ArTure" and "Off the Trail" clubs on 21st September 2022 at MCBR, MAHE, Manipal. Ms. Nikshita and Mr. Rohan Janadri were elected as Presidents *ArTure* and *Off The Trail*, respectively. Dr. Prabhu shared his experience and expressed trust in the centre.

Notable visitors

Throughout the past three months, MCBR has welcomed a plethora of prominent figures from the business, scientific, and administrative communities. In the following images, you can see some of them mingling with our faculty and research scholars:

Dr. Kaladhar Kamalasanan, Associate Professor at Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham, Kerala visited us recently.

Dr. Prashant M Vishwanath, Director (Research) I/C, **Dr. Akila Prashant, Dr. MVSST Subbo Rao**, both Professors, and **Dr. Rajesh Kumar T,** Associate Professor in Dept. of Biochemistry, **Dr. Madhu B.,** Dy. Director (Research), **Dr. Saravana Babu. C,** Professor, Dept. of Pharmacology, JSS Academy of Higher Education & Research, Mysuru, Karnataka had intense scientific interaction with faculties of MCBR. We are looking forward to a collaborative research effort by these two institutions.

Blogs

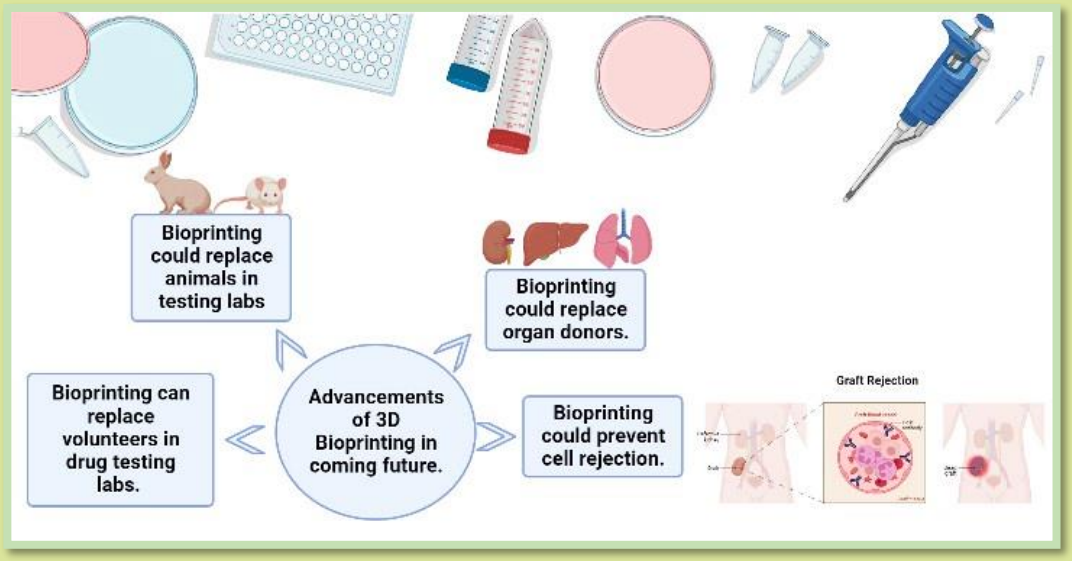
THE ESCALATING ADVANCEMENT OF 3-D BIOPRINTING IN THE COMING FUTURE

by ***Mrunmayi A. Gadre***, *Dr TMA Pai PhD Scholar*

With a lot of cutting-edge innovations that have blown scientist minds, 3D bioprinting may have been the most astonishing one. Many experiments, which were once science fiction such as the manufacturing of live organs like hearts and lungs and replacements of damaged skin, bioprinting may one day become life-altering innovation. Few examples to prove that this remarkable technology may influence on the leading science researchers in the future:

Replacement of organ donors by bioprinting - Statistically many patients register for the organ transplant queue, but unfortunately only 18% receive the organ required to survive. A few of them don't make it while the others keep waiting and hoping for their turn to come. Using the 3D Bioprinting, leading scientists in the field are researching the development of organs like livers, kidneys, lungs, and other organs which the human body demands for survival. There is a prediction that the organ transplant shortage could be reduced or for that matter completely eliminated provided the success of the experiments. Skin being the most abundant and delicate organ, tests are being carried out to help make the wound healing quicker and easier.

Prevention of rejection by host body - Manufacturing biomaterial mimicking the human tissues/ organs is not an easy assignment, but on the other hand finding a donor with same compatibility is not very high either. Transplant from donor may seem to be very practical in books but in practice it brings a lot of rejection by host's body. In real the transplants come along with lot of complications and rejections, but with the 3D Bioprinting, the cultured cells may be taken from the host's (patient) body itself which will avoid all the complications which arises from donor's sample.



Replacements of test animals - With an increase in the number of diseases and human needs, there has been an increase in the number of testing drugs/ products on lab animals leading to sacrificing a huge number of animals. Recently L'Oreal became the first cosmetics company to test its product on bioprinted tissue. If there is an increase in the production of bio-printed materials, there will be an increase in availability for the various tests that are now been conducted worldwide on test animals, giving an opportunity for an alternative method on hand.

Replacements of volunteers in drug testing labs (clinical trials) - There is a high possibility for the replacement of volunteers from drug testing facilities, reducing the risks poses to the health and safety of volunteers in such tests. 3D bioprinting platform can become the most practical and safest method for testing new advancing drugs.

Having so many 3D Bioprinting applications, there is still a long way ahead for applying the knowledge for practical use. There are many cases where the testing phase is still on for products obtained from 3D bioprinting. Researchers all around the globe are working hard towards perfecting the technology. Highlighting the difficulty faced by the innovation when it comes to printing skin are – the requirement of detailed cell composition in order to produce organ functional inside the body of a human. Other factors involved which are crucial include space distribution, but also growth factors, cell concentration, drop volume and so the list keeps going on.

REFERENCE - https://info.izumiinternational.com/advantages-of-bioprinting

Ethical Considerations Surrounding Embryonic Stem Cells – A Morally Grey Area

*by **Jahnavy Joshi**, DST-INSPIRE Fellow*

Turning the pages of history, humankind has been working towards providing hope for a variety of diseases using stem cell therapies. One such therapy uses embryonic stem cells (ESCs). Embryonic stem cells are found in the blastula in a developing embryo. The blastulas used in research are taken from fertility clinics wherein the non-implanted ones are used in research instead of discarding them. The science part related to ESC in research and therapy is undergoing massive developments, providing alternative possible remedies in near future. But, the moral and ethical dilemma surrounding it is not so clear. The two faces of this dilemma lie in human's two basic responsibilities- One is to protect human life in its basic form, and the other is to contribute towards the greater good. The former opinion defends the right to live whereas supporters consider that destroying the blastula is equivalent to ending a life. The latter, however, argue that the surplus blastula produced in *in-vitro* fertility clinics can be used to ameliorate the medical field and add to the pool of knowledge regarding various cellular mechanisms. The complexity of the basic question – "when does a human being start to exist?", is virtually impossible to answer.

In India, ICMR has issued National guidelines for stem cell research(2017), which direct the use of blastocysts for ESC derivation. The guidelines are framed in a way wherein the research using ESCs is permitted, and its acquisition has to be only after donor consent. The donor can withdraw the consent till the cells are cultured. Such guidelines try to encompass and consider all the ethical sides regarding ESCs. Clearly, there is no definite answer to the question of ethics and morals attached to the use of ESCs in research and therapy, and the laws regarding it will have to be modified according to the situations pertaining to the different cases. Needless to say, the usage of ESCs for research will always be an open-ended question.

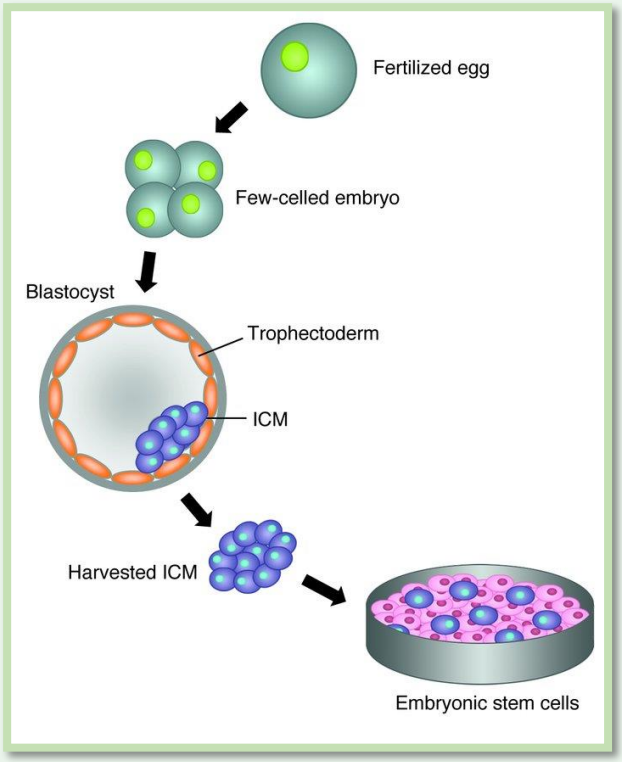


Figure: ESC isolation from blastocyst

References:

•Indian Council for Medical Research. (2017) *National Guidelines for Stem Cell Research*

•Landry DW, Zucker HA. Embryonic death and the creation of human embryonic stem cells. J Clin Invest. 2004 Nov;114(9):1184-6. doi: 10.1172/JCI23065. PMID: 15520846; PMCID: PMC524233.

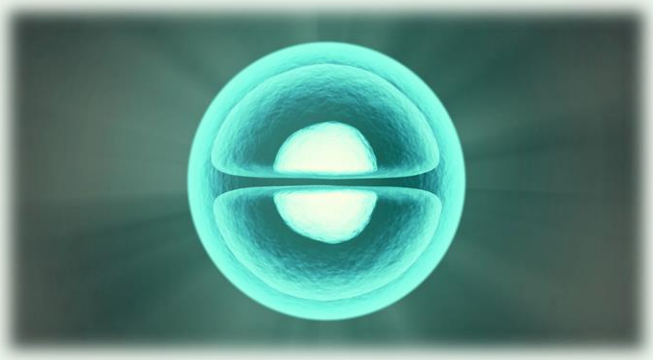


Figure: A dividing cell

CAR-T Therapy: Progress to enhance the efficacy

Cancer therapy has made significant strides in recent years, but the condition is still hard to cure. The unsatisfactory therapeutic effects of conventional cancer treatments like chemotherapy, radiotherapy, and surgery highlight the priority of using cutting-edge therapies like immunotherapy. One of its most popular kinds is the chimeric antigen receptor T cell, which was designed to drive T lymphocytes toward tumors (CAR-T cells) *(Mehrabadi, A. Z. et al., Biomedicine & pharmacotherapy, 2022)*. Several clinical trials have demonstrated CAR-T cell therapy's potential in treating various hematological tumors. But unfortunately, in solid tumors, it is still challenging. The safety and effectiveness of the treatment may be impacted by target antigen evasion, immunosuppressive-TME, and other adverse effects. Patients experiencing refractory hematologic malignancies often seek treatment with chimeric antigen receptor (CAR)-T cells. Unfortunately, many patients develop low CAR-T cell cytotoxicity and durability, which can lead to the escape of tumor cells and disease relapse. Kim MY *et al.*, demonstrated that the fusion of a prolonged-functional prototype of recombinant human interleukin-7 (IL-7) along with hybrid Fc (rhIL-7-hyFc) enhances the human CAR-T cell proliferation or expansion, tenacity, and its cytotoxicity lead prolonged tumor-free survival. A customizable clinic-ready adjunct rhIL-7-hyFc describes the potential for improving CAR T cell functionality *(Kim, M.Y, Nat Commun. 2022)*. Despite the successful application of CAR-T cells in treating various hematological tumors, it is less effective in eradicating solid tumors. Such tumors often thrive in high immunosuppressive settings, which are more challenging to target, due to the absence of tumor-specific antigen expression and other contributing factors.

Xie YJ *et al.*, demonstrated using a single-domain antibody (VHH)-associated with CAR-T cells to identify the tumor markers within their tumor milieu, and their strategy to target several solid tumor types. This strategy targets the tumor-based microenvironment either via immune checkpoint receptors i.e., PD-L1, or via stromal & ECM biomarkers for targeting solid tumors in syngeneic, immunocompetent animal models *(Xie, Y. J at al, PNAS, 2019)*. In a preclinical investigation conducted by Qi C *et al.*, CAR T cells were directed against claudin18.2 (CLDN18.2), a gastric-specific isoform of respective CLDN-18 protein, which demonstrated remarkable potency against gastric cancer (GC). CT041 constitutes genetically modified autologous T-cells that expressed the CLDN18.2 - targeted CAR. Henceforth, the final results signified that CT041 exhibits the potency to form an essential therapeutic modality for patients suffering from advanced GC *(Jiang H et al, J Natl Cancer Inst. 2019)*. Further implying, a similar kind of CAR-T cell therapy benefits patients with hematologic malignancies and those with solid tumors.

As stated by the American Cancer Society, glioblastoma (GBM), one of the most prevalent types of brain tumor, ranks among humans' deadliest forms of cancer. Treatment is especially challenging due to the tumors' rapid spread all across the brain. Tumour diversity is still a significant obstacle even though CAR-T cells have shown evidence of therapeutic efficacy against glioblastoma (GBM). Wang D *et al.*, devised a peptide comprising CAR to target GBM in extensive and effective manner, exploiting the ability of chlorotoxin (CLTX), a component of snake venom in binding GBMs. Patient-derived glioblastoma xenograft regression was achieved by CLTX-CAR T cells in mice without any signs of antigen escape.

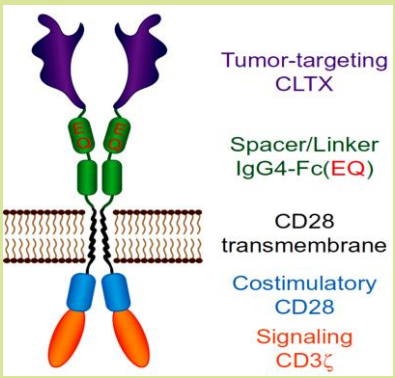


Figure: CAR incorporating a CLTX tumor-targeting domain, an IgG4-Fc spacer domain with EQ mutations, a CD28 transmembrane domain, and intracellular costimulatory and signalling domains (CD28 and CD3ζ) Reproduced from Science translational medicine, 2020.

Such toxin-deployed CAR T cells differ from conventional CAR designs and may someday be applied to treat glioblastoma by poisoning it *(Wang, D. et al, Science translational medicine, 2020)*. Additionally, Larson RC et al., carried out a genome-wide CRISPR knockdown assay in glioblastoma, a condition for which CAR-T cells have shown only marginal efficacy. They discovered that glioblastoma and other solid tumors became more refractory to being killed by CAR-T cells in both the in vitro and in vivo when genes in the interferon-γ receptor (IFN-γR) signal transduction pathway (IFNGR1, JAK1 or JAK2) were lost. Further, it showed that solid and liquid cancers interact with CAR-T cells independently in a different manner, and it implies that strengthening the binding interactions amongst T cells and cancer cells may optimize therapeutic responses in overall tumors *(Larson, R.C. et al, Nature 2022)*.

Additionally, explicit knowledge of CAR-T and tumor tissues is crucial to developing future therapy to enhance anti-tumor efficacy and decrease the frequency of adverse effects.

***Acknowledgment**: The above piece of article is contributed by Dr. Manjunatha SM, Assistant Professor, MCBR, MAHE*

Interactive events

Teachers' Day celebration

MCBR celebrated Teachers' Day on 5th September. Research scholars organized a quiz event where all the faculties and staff took part. It was followed by a cake-cutting ceremony.

Observance of Onam And Navaratri

Onam, an annual Indian harvest festival was observed on September 8. All the Masters' students and research scholars participated in the celebration; they made a beautiful floral design.

ArTure Club of MCBR arranged Navaratri, an annual and one of the most revered Hindu festivals observed in the honor of Goddess Durga. It spans over nine nights (and ten days), in the month of Sharada. It is observed for different reasons and celebrated differently in various parts of the Hindu-Indian cultural sphere. Celebrations include worshiping nine goddesses for nine days, stage decorations, recital of the legend, enacting of the story, and chanting of the scriptures of Hinduism. This year it was observed from September 26 through October 4. Students made a *Rangoli* of Goddess Durga.

Participation in Leadership Summit

Ms. Shreya Bhat, an M.Sc. Student from MCBR participated in the Leadership training workshop conducted by MAHE.

It was a very interactive and innovative session about leadership and personality development which will shape us for the future.

Fun moments:
Birthday celebrations at MCBR

At MCBR, we like to celebrate the birthdays of our scholars and staff with cake and applause!

11th August – Shweta Verma

20th September – Preethesh Poojary

Send your feedback and suggestions to mcbr.mahe@manipal.edu

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