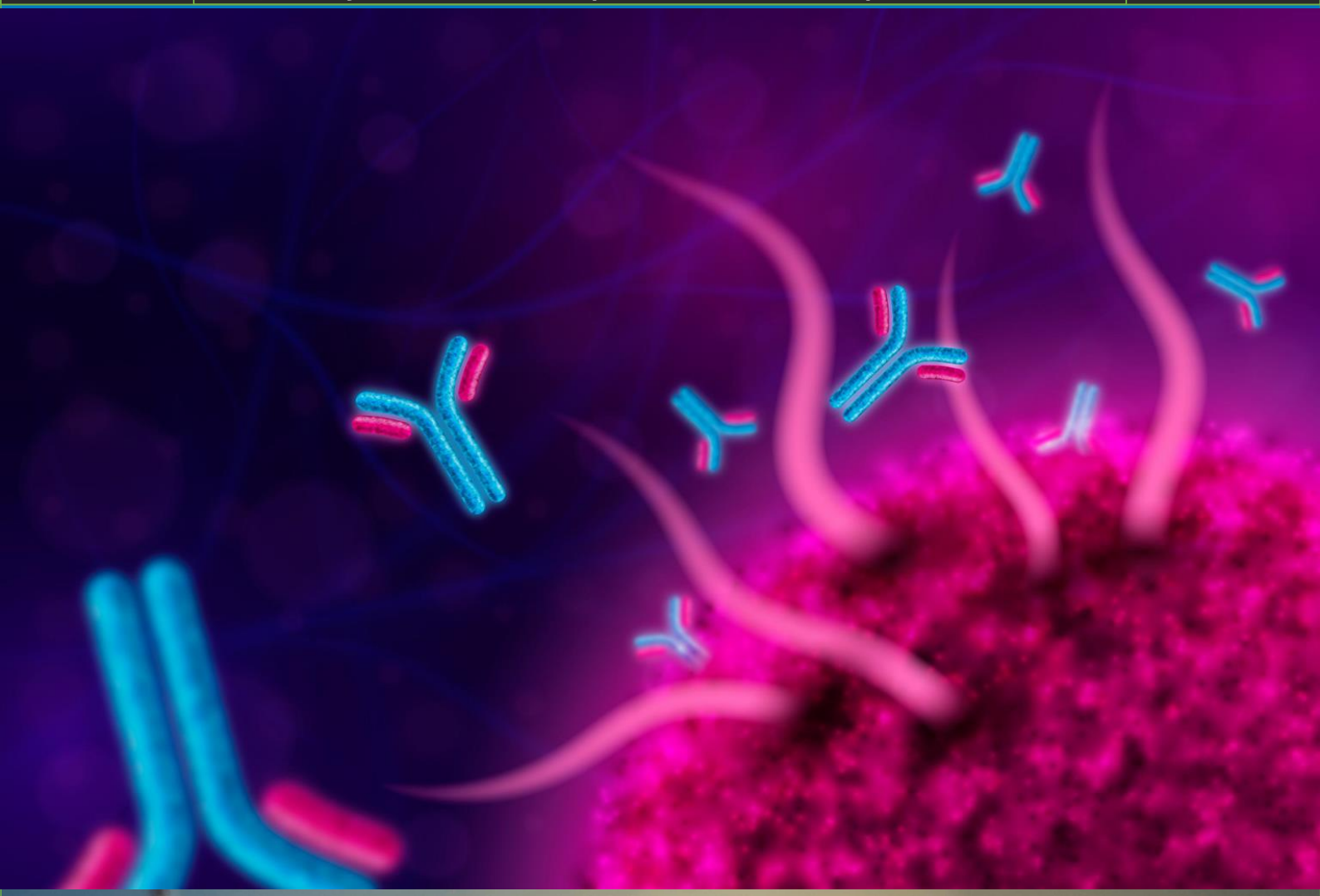
Vol: 9 January-March 2024

Biotheracues

Quarterly Newsletter of Manipal Centre for Biotherapeutics Research



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

Contents

Message from the Chief Editor

Dear friends and well-wishers of MCBR,

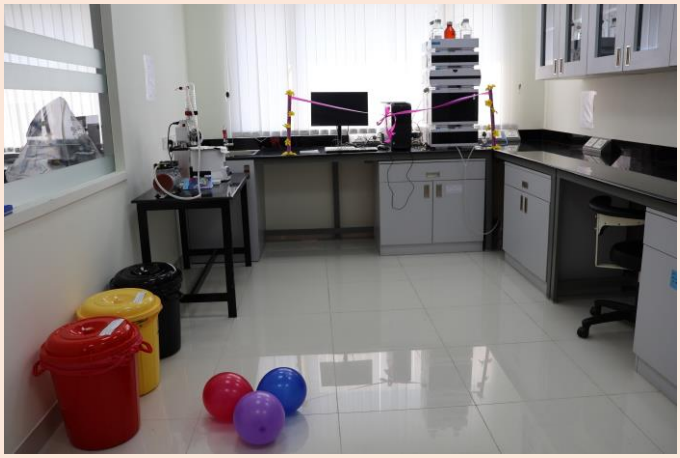
I am pleased to present you with the ninth edition of *Biotheracues*. With this edition, I am assuming the role of Chief Editor. But before I say anything, let me convey my sincere thanks to Dr. Souvik Dey who has been Chief Editor of *Biotheracues* for almost two years. I am very much grateful to Dr. Raviraja N.S. (Coordinator, MCBR) for trusting and nominating me for this role. Dr. Souvik has done wonderful job in maintaining the high standards of our newsletter which has been appreciated by the higher leadership of MAHE. I promise you all that I will do my best to maintain its quality and raise its standards even higher during my tenure. With your support and well wishes, I am ready to take this responsibility and do my best to fulfill my duties.

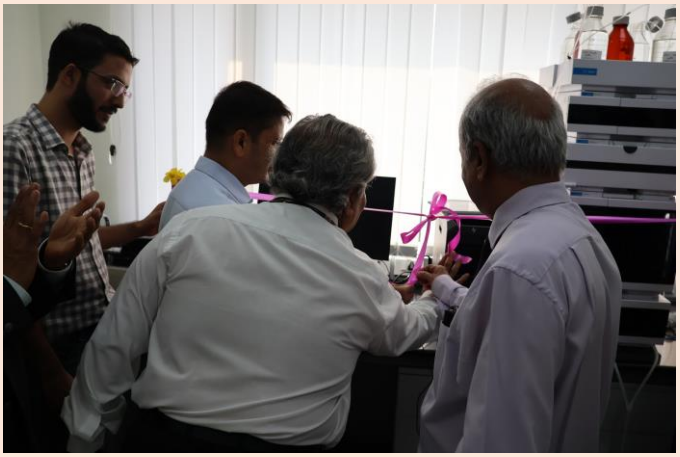
The last quarter has been productive in terms of research output and grants for MCBR. Among all, I would like to highlight CRG-SERB grant to Dr. Abhishek Kumar Singh and DST-NIDHI PRAYAS grant to Dr. Kirthanashri S. V. Kudos to both of our esteemed faculties!! There is no fun in science without memorable joyful moments!! This quarter, we also had fun moments while celebrating science day, women's day, and Holi at MCBR. Science day was especially a great success and students from various schools who visited MCBR had great interaction with all our faculty members and research scholars. Within this quarter, we – MCBR – as a family grew even further. I would like to welcome Dr. Mahendra Rao (Adjunct faculty) and Dr. Kanupriya Singh (Asst. Professor) and I wish them the best for their future endeavors at MCBR.

Finally, I would like to thank again to Dr. Raviraja N. S. and all the faculty members of MCBR for supporting me for Chief Editor role. As always, I welcome all the suggestions and recommendations from you to make this newsletter a better read for all of you.

Dr. Abhayraj S. Joshi

Inauguration of Central Bio-LC Facility at MCBR





The **Bio-LC (Ultra High Performance Liquid Chromatography (UHPLC))** facility was inaugurated as a part of MAHE – Core Research Facility on 27th March 2024 by the MAHE Vice Chancellor, Lt. Gen. Dr. M. D. Venkatesh, Dr. Sharath Rao, Pro Vice Chancellor (Health Sciences) in R & D lab 3 of MCBR, MAHE. Dr. B. S. Sathish Rao and Dr. Vadiraja Bhat were the guests of honor. Prof. Dr. Raviraja N. S., the coordinator of MCBR, welcomed the gathering. Dr. Souvik Dey, the coordinator of Bio-LC facility, gave the insights of this facility and its capabilities which entire MAHE can use to carry our state-of-the-art research. Dr. Raghavendra Upadhya, co-coordinator of Bio-LC facility, proposed vote of thanks. Whole MCBR family and MAHE campus thank Dr. Vadiraja Bhat, the business development manager for Country Biopharma, and scientist from Agilent Technologies, Bengaluru, who made the dream of Bio-LC facility a reality.

Inauguration of Central Bio-LC Facility at MCBR

ACTIVITIES AT MCBR

Faculty recruitment

Dr Mahendra Rao has been appointed as the Adjunct Faculty at the Manipal Centre for Biotherapeutics Research (MCBR), MAHE, Manipal, effective from 15th February 2024. He received his MD (MBBS) from Bombay University in India and his PhD in Developmental Neurobiology from the California Institute of Technology. He is internationally known for his research involving human embryonic stem cells (hESCs) and iPSC as well as other somatic stem cells and has worked in the stem cell field for more than 25 years with stints in academia, government and regulatory affairs and industry. Dr Mahendra is the Chief Scientific Officer-Vita Therapeutics and CEO of PanCELLa. He is the Board member and advisor for several companies across the globe. MCBR wholeheartedly welcomes Dr Mahendra Rao and looks forward to getting benefitted from his rich experience.

Faculty recruitment

Dr. Kanupriya Singh joined Manipal Centre for Biotherapeutics Research (MCBR), Manipal Academy of Higher Education (MAHE) as Assistant Professor on 11th March 2024. She completed her Ph.D. from the National Centre for Cell Science (NCCS), Pune and got a US patent for her Ph.D. work. She also worked as an Institute Post-doctoral Fellow (IPDF) in the department of Biosciences and Bioengineering (BSBE), at Indian Institute of Technology Bombay. She has three-year industrial experience in CAR T cell therapy. Her research interests include application of CAR T based cell therapy for curing of B cell leukemias and lymphomas as well as solid tumor. She also works in the area of osteo-immunology.

RESEARCH PROGRESS

Publications:

- Meghana Kasturi & **Kirthanashri S Vasanthan**. Harvesting decellularized liver extra cellular matrix from rodents for 3D scaffold fabrication. ***Artificial Cells, Nanomedicine, and Biotechnology***. (Jan 2024). Accepted. (IF: 5.8).

- Mrunmayi Gadre, Meghana Kasturi, Prachi Agarwal, **Kirthanashri S Vasanthan**. Decellularization and their significance for tissue regeneration in the era of 3D bioprinting. ***ACS Omega*** (Jan 2024). Accepted. (IF: 4.1).

- J. K. Sinha, A. Trisal, S. Ghosh, S. Gupta, K. K. Singh, S. S. Han, M. Mahapatra, M. M. Abomughaid, A. M. Abomughayedh, R. Bhaskar, P. C. Mishra, S. K. Jha, N. K. Jha, **Abhishek Kumar Singh** (2024), Psychedelics for Alzheimer's Disease-Related Dementia: Unveiling Therapeutic Possibilities and Pathways. **Ageing Research Reviews**, 2024; 96: 102211. (IF 13.1).

Grants:

- **CRG SERB grant (Rs. 54 lakh)** to Dr. Abhishek Kumar Singh - Understanding the protective effect of chlorogenic acid in rat embryonic neural stem cells prenatally exposed to air particulate matter: A transcriptome-based approach.

- **DST Nidhi Prayas grant (Rs. 7.5 lakh)** to Dr. Kirthanashri S. V. , Vidhi Mathur, Dr. Raviraja N. S.: Formulation of Gelatin methacrylamide ink suitable for 3D bioprinting.

Online talks:

- Dr. Anand Singh – a staff scientist at National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD, USA – delivered a talk on **"A novel peptide-based miRNA nanoparticle-hydrogel composite attenuates mesothelioma tumor growth"** on 11th March 2024.

RESEARCH PROGRESS

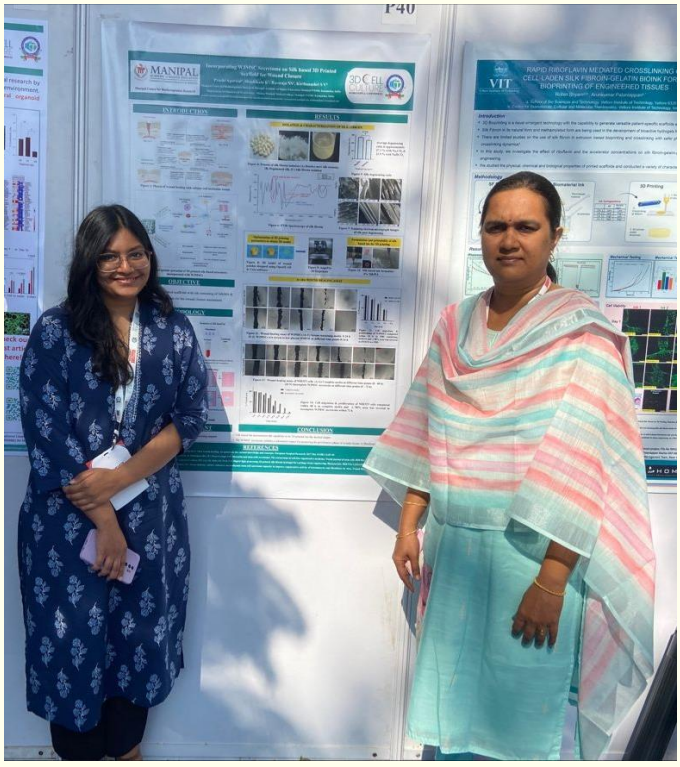
Dr. Abhishek Kumar Singh, Associate Professor, MCBR, MAHE is attending and delivered oral presentation titled "Fisetin as a Caloric Restriction Mimetic Confers Neuroprotection Against Aging-Induced Oxidative Stress, Mitochondrial Dysfunction, and Neurodegeneration in Old Rats" at the Young Scientists Conference, India International Science Festival 2023 in one of the technical sessions i.e. Translational Research. This prestigious event, hosted by the Government of India and Government of Haryana at DBT-THSTI, Faridabad from 17th to 20th January 2024, featured a highly competitive selection process, with Dr. Singh's abstract among the 120 chosen for oral presentations out of 2552 submissions.

Dr. Souvik Dey, Assistant Professor & DBT-Ramalingaswami Fellow, MCBR, MAHE, Manipal, delivered an 'Invited Talk' on 31st January 2024, at the 46th Meeting of the Environmental Mutagen Society of India (EMSI 2024). This talk was focused on his lab's ongoing research work on the role of m6A methylation of RNA in mouse spermatogenesis. Central University of Kerala hosted this event in its Periya, Kasaragod campus.

RESEARCH PROGRESS

Dr. Souvik Dey, Assistant Professor & DBT-Ramalingaswami Fellow, MCBR, MAHE, Manipal presented an 'Invited Talk' on 2nd February 2024, at the 9th Meeting of the Society for Molecular Signaling (SMS) and International Conference on Molecular Signaling (ICMS 2024). This talk titled, "Role of FTO, a RNA-specific Demethylase, In Spermatogenesis" was delivered at the auditorium of the School of Life Sciences, University of Hyderabad, an Institute of Eminence, Hyderabad.

Dr. Kirthanashri S. V., Associate Professor and **Ms. Prachi Agarwal**, Dr. TMA Pai Research Scholar, MCBR, MAHE attended the international conference on “Advances in 3D cell culture” on 2nd and 3rd February 2024 at Taj The Trees, Mumbai, organized by ICT Mumbai. The team also presented their poster entitled "Incorporating WJMSC secretome on silk based 3D printed scaffolds for wound healing". The conference had several startups and leading biopharma companies participating and the MCBR team had several interactions, which has opened up the possibility of MCBR collaborating with the industry for technology transfer.



RESEARCH PROGRESS

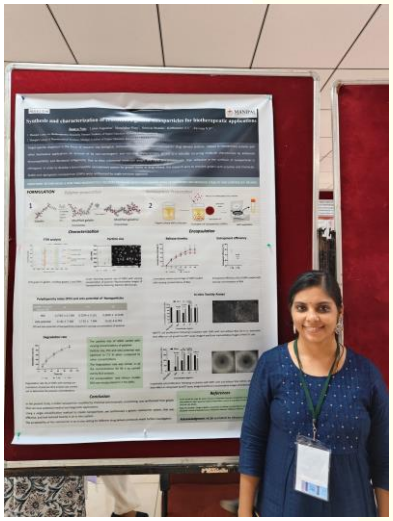
Dr. Raviraja N. S., Professor and Coordinator of MCBR, was a Panelist at "SACT 2024 Asia Pacific Cell Therapy Conference", themed "Series of Advancements in the Cell Therapy," organized by the CAR-T & Cell Therapy Centre at Tata Memorial Centre, Mumbai, India on 2nd and 3rd February 2024. The Panel discussion was on "Planning Better for Faster Approvals" in the MANUFACTURING TRACK - "How To Elevate Early Your Process Optimization & Analytics For Faster Approval".

Ms. Mrunmayi Gadre and **Ms. Shweta** along with **Dr. Vardharajan** (Coordinator, IPTTO, MAHE) attended the workshop held by ASSOCHAM and Ministry of Micro Small & Medium Enterprises, Government of India on 13th and 14th February 2024 at Mangalore.

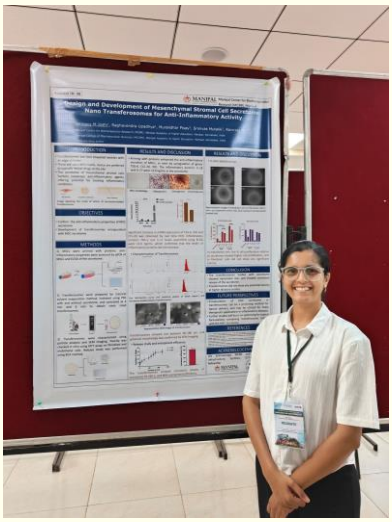
RESEARCH PROGRESS

Dr. Souvik Dey, Assistant Professor & DBT-Ramalingaswami Fellow at Manipal Centre for Biotherapeutics Research (MCBR), MAHE, Manipal, presented an invited talk, titled "Deciphering the Contribution of FTO in Mammalian Spermatogenesis" at the International Conference on Reproductive Health: Innovations, Integration, and Implementation & 34th Annual Meeting of the Indian Society for the Study of Reproduction and Fertility. This event was hosted by Indian Institute of Chemical Technology (CSIR-IICT), Hyderabad, on 23rd to 25th February 2024.

Ms. Mrunmayi Gadre and **Ms. Vidhi Mathur** attended the event held by American Chemical Society (ACS) entitled "It's what you know and who you know" at MAHE. The event involved interactions with ACS editors in order to improve publications on 28th February 2024 at Manipal.



Dr. Ramya, Postdoctoral research fellow, and **Mrs. Jahnavy**, DST-INSPIRE fellow presented their posters at the International conference on nanoscience and nanotechnology held from 29th February 2024 to 1st March 2024 at Manipal.



ARTICLE UNDER FOCUS

ARTIFICIAL CELLS, NANOMEDICINE, AND BIOTECHNOLOGY
2024, VOL. 52, NO. 1, 175–185
https://doi.org/10.1080/21691401.2024.2319893

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Harvesting decellularized liver extracellular matrix from rodents for 3D scaffold fabrication

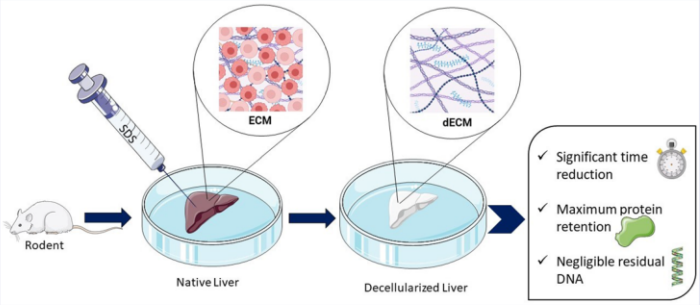
Meghana Kasturi[a] and Kirthanashri S. Vasanthan[b]

[a]Department of Mechanical Engineering, University of MI, Dearborn, USA; [b]Manipal Centre for Biotherapeutics Research, Manipal Academy of Higher Education, Karnataka, India

ABSTRACT

Decellularization is a process to harvest the decellularized extra cellular matrix (dECM) that helps develop 3D scaffolds which mimic the native tissue composition. The decellularized tissues retain the structural and functional properties of the extracellular matrix (ECM) by an efficient decellularization process that retains tissue-specific biochemical and biophysical cues for tissue regeneration. In this study, we report an injection-based decellularization method, without perfusion setup. This study also compares the efficiency of the proposed protocol in the two animal models viz rat and mice. This method harvests rat and mice liver dECM using ethylenediamine tetra acetic acid (EDTA) and sodium dodecyl sulphate (SDS) within 08 h and 02 h respectively and preserved significant amount of ECM proteins. We reported that the harvested mice decellularized extracellular matrix (mdECM) and rat decellularized extracellular matrix (rdECM) had significant reduction in their DNA content (~97%) and retained structural architecture resembling their native tissue counterparts. The total protein content retained in mdECM was ~39% while that retained in rdECM was ~65%. It was also found that the sGAG (sulphated glycosaminoglycan) content showed a no List of Figures.

GRAPHICAL ABSTRACT



ARTICLE HISTORY
Received 5 September 2023
Revised 6 February 2024
Accepted 12 February 2024

KEYWORDS
Decellularization; decellularized extracellular matrix; 3D scaffolds; liver tissue engineering

This article describes a novel method for efficient decellularization of liver extracellular matrix and its use for 3D scaffold fabrication. Authors have proved that decellularization process not only maintain structural and functional properties of extracellular matrix, but also ensures retention of liver-specific biochemical and biophysical cues. Upon decellularization, the extracellular matrix retained significant proportion of proteins with negligible amount of DNA. Proposed method provided a time-saving and cost-effective methodology that can be employed in future for similar other tissues to harvest their extracellular matrix for the purpose of scaffold fabrication. This scientific report from our research centre signifies an advanced step in the field of biomaterial science.

The Promise of PROTACs in Targeted Protein Degradation

Mr. Rounak Roy, *Dr. TMA Pai Scholar, MCBR, MAHE*

Targeted protein degradation (TPD) has attracted substantial attention due to its potential of successfully altering proteins which were previously been difficult to target using conventional small molecule methods. Certain proteins provide difficulties because their active sites have broad, superficial pockets, making harder to interact with small molecules. Furthermore, certain proteins have surfaces that are smooth and restricted sites of attachment for small molecule. Despite these difficulties, many of these targets play critical roles in illnesses such as cancer, preserving their value for therapeutic intervention regardless of their resistance to small molecule inhibitors.

Protease-targeting chimaera (PROTAC) protein degraders are a class of molecule, which can modulate challenging proteins via TPD. These compounds consist of two ligands connected by a linker: (1) one interacts with the protein of interest (POI), and (2) the other interacts to an E3 ubiquitin ligase. This dual interaction triggers ubiquitylation of the POI, which leads to its destruction by the ubiquitin-proteasome system (UPS), after which the PROTAC is regenerated to target new POI. PROTACs operate via a catalytic mechanism, distinguishing them from traditional inhibitors, which typically have a one-to-one interaction with the POI. Additional types of targeted protein degraders, like molecular glues, were discovered incidentally following observations with thalidomide and its derivatives. Unlike PROTAC molecules, molecular glues do not possess heterobifunctional properties. Instead, they contribute in the ubiquitylation of a POI by increasing a protein-protein interaction (PPI) between a possible substrate and a ligase (Ito et. al., 2010).

Over the previous two decades, since scientists initially reported PROTACs in research publications (Sakamoto et. al., 2001), this technology has made its way from academic labs to the industry. Numerous biotech and pharmaceutical companies have initiated programs focusing on preclinical and early clinical development. In 2019, the initially approved PROTAC compounds began clinical trials, which by 2020 offered the first clinical validation for this modality against two recognised cancer targets: the androgen receptor (AR) and estrogen receptor (ER) (Petrylak et al., 2020). With these milestones achieved, the field of TPD is now primed to address previously untargeted proteins and other challenging classes of protein targets.

In conclusion, the development of TPD technologies, illustrated by PROTACs and molecular glues, represents a transformative shift in drug discovery and therapeutic intervention. With the ability to modulate challenging proteins resistant to traditional small molecule inhibitors, TPD offers promising approaches for targeting diseases such as cancer. The successful translation of TPD from academic research to clinical application underscores its potential to revolutionize treatment strategies and advance precision medicine. As TPD evolves, collaboration among academics, industry, and regulatory authorities will be critical for maximising its therapeutic potential and enhancing patient outcomes.

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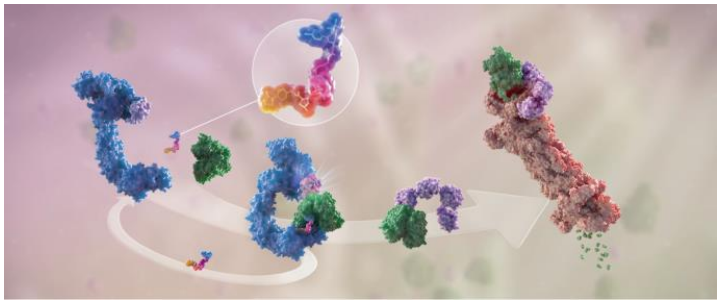

GENE EDITING: TRANSFORMING THE REALM OF THERAPEUTICS

Mr. Noman Bakshi *, Research Intern, MCBR, MAHE*

In the current era of precision medicine, the focus of research has changed towards development of highly targeted therapies taking molecular phenotype of patient into consideration. This approach has led us towards developing therapies carrying minimum side effects and maximum therapeutic efficacy. Here, a combination approach of gene editing and immunotherapy is being investigated showing positive signs in preclinical studies. Recent success achieved by this approach to treat sickle cell disease and β-Thalassemia, where BCL11A edited CD34+ cells were transplanted into a β-Thalassemia and sickle cell disease carrying patient showing highly encouraging outcomes leading to remission of disease. This research has further been fuelled into cancer therapeutics where approaches such as targeted lipid nanoparticle mediated gene editing showed encouraging results in pre-clinical studies for ovarian cancer. Further, recent approach towards cytosine base editing leading to development of quadruple edited allogenic CAR-T cells against T ALL has opened an exciting area to work on for further enhancement of CAR-T therapies.

While the future with precision medicine is bright, there are still challenges to overcome. Delivering gene editing tools safely and efficiently to target cells remains as a problem we are still to overcome. Researchers are actively exploring delivery mechanisms, including viral vectors, nanoparticles, and electroporation, to address this problem. Additionally, minimizing unintended edits is crucial and techniques like using high-fidelity Cas9 enzymes or base editing, which modifies single nucleotides instead of double-strand breaks, are used to counter this problem.

In future, this field is ripe for further exploration. Editing multiple genes simultaneously could hold promise for tackling complex diseases like cancer with multiple driver mutations. Research into both ex-vivo editing and in vivo editing is ongoing, each offering unique advantages and limitations. Finally, as gene editing continues to evolve, ethical considerations around germline editing need to be carefully addressed to ensure responsible development and application of these powerful tools.

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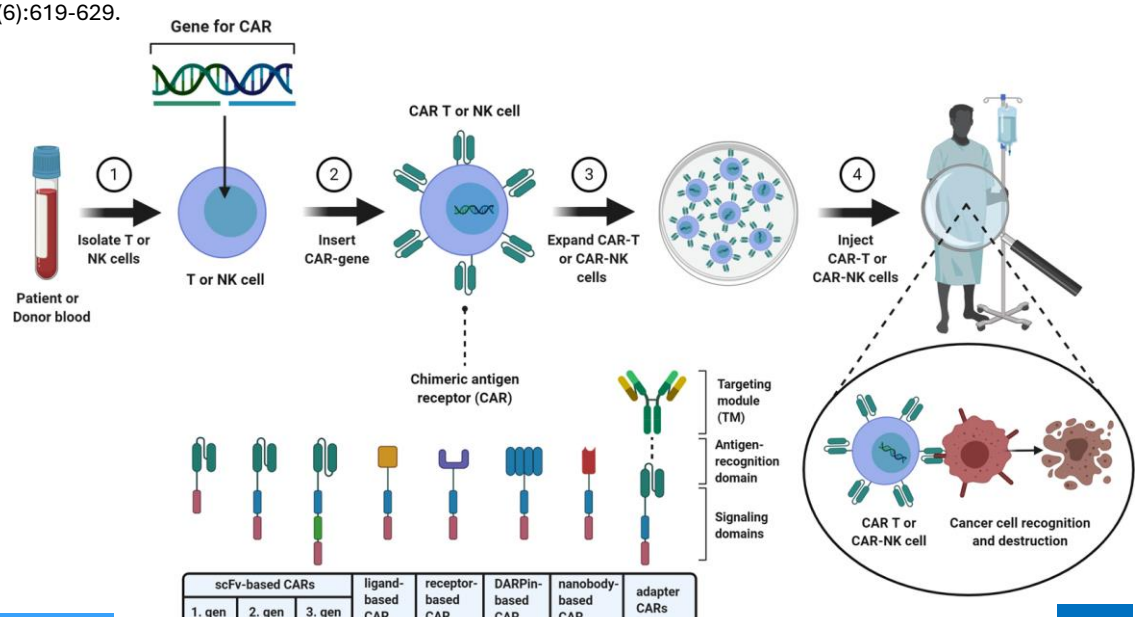
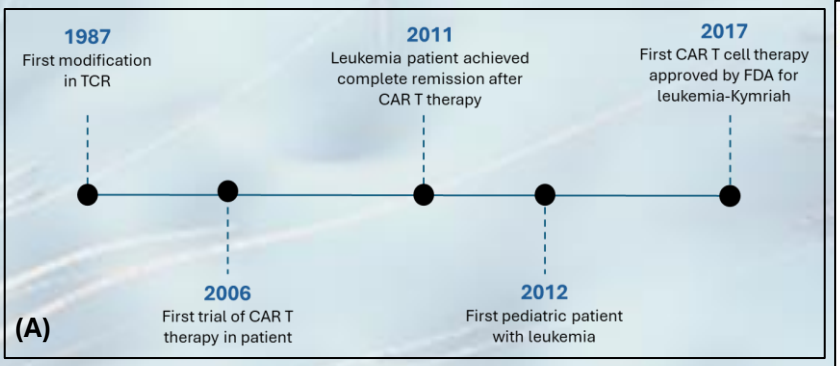


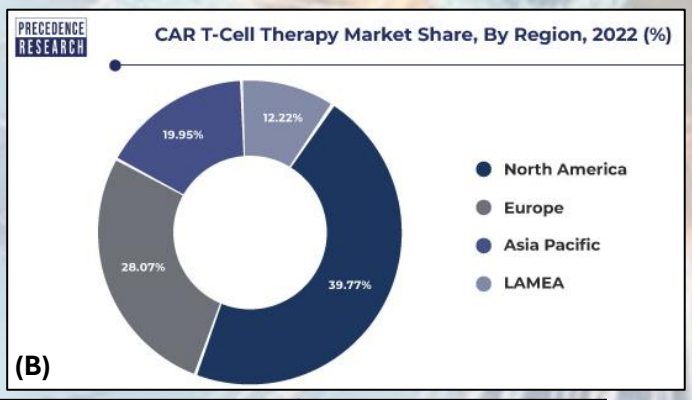
GLOBAL RESEARCH UPDATE

CAR T cell therapy- Where we are standing globally?

Dr. Kanupriya Singh, *Assistant Professor, MCBR, MAHE*

Chimeric antigen receptor T-cell (CAR-T) based cell therapies are one of the most cutting-edge immunotherapies for the treatment of cancer in the present times. Currently in this therapy, T cells are isolated from cancer patients and genetically modified in such a way that these genetically modified T cells can recognize and kill the cancer cells. The fascinating journey of CAR-T cell development started nearly 30 years back when genetic modifications were successfully achieved in T cell receptor in 1987 (Kuwana Y, et. Al; 1987). From the start of TCR modification to the first approval by FDA as a therapy it took about thirty-years of hard work of experts and researchers in this field to achieve this feat. That said, KYMRIAH (Tisagenlecleucel) was the first CAR-T cell therapy which was approved by the FDA in August 2017 (Figure 1A). This CAR-T cell therapy uses the CD19 molecule as a target molecule and is used for adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and young adult patients up to age 25 with relapsed or refractory acute lymphoblastic leukemia (ALL). So far, total of six products have been approved by the FDA for ALL and Multiple Myeloma (MM) (Table). These approvals opened the door of hope for those cancer patients who have lost their hope with the existing conventional cancer treatments. With these approvals, we entered in the new world of cell therapy. Worldwide, huge number of research and clinical personnel started working on the improvement and development of more efficacious with fewer side effects and cost-effective CAR-T cell therapies for various types of cancers. However, North America still dominates the market of CAR-T cell therapies by contributing approximately 40% of the overall world growth (Figure 1B). In 2023, CAR-T cell therapy market value was about 4 US billion dollars, which is expected to grow up to 90 US billion dollars by the year 2032 indicating the huge potential of CAR-T cells in the field of cancer research and treatment.





Brand Name	Scientific Name	Year of approval	Target Molecules
KYMRIAH	tisagenlecleucel	August 2017	CD19
YESCARTA	axicabtagene ciloleucel	October 2017	CD19
TECARTUS	brexucabtagene autoleucel	July 2020	CD19
BREYANZI	lisocabtagene maraleucel	February 2021	CD19
ABECMA	idecabtagene vicleucel	March 2021	BCMA
CARVYKTI	ciltacabtagene autoleucel	February 2022	BCMA

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8. https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/carvykti

NOTABLE VISITORS

Mr. S. Vaitheeswaran, Vice Chairman and Managing Director, MEMG visited on 1st February 2024 and had tour of MCBR and its labs. They praised MCBR for its efforts in adhering to its mission and vision while delivering great research outcomes.

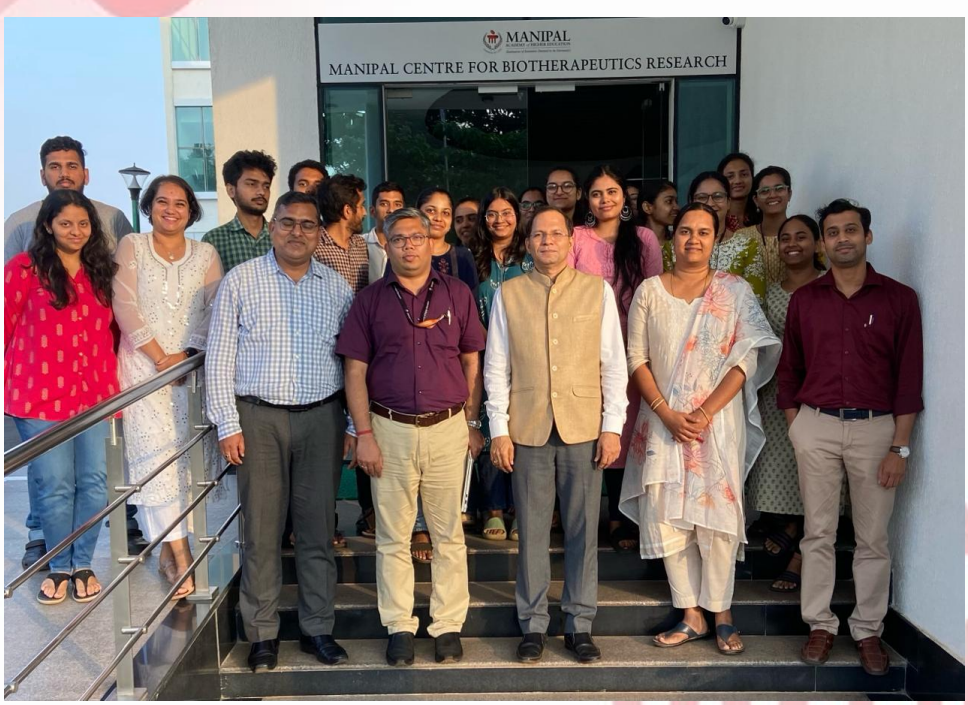
Dr. Madhusudan V. Peshwa, a Chief Technology Officer (CTO), Cell Therapy from Tessera Therapeutics, Cambridge, MA, USA visited MCBR, MAHE on 7th February 2024, interacted with MCBR faculty, and praised the MCBR for its vision and mission.

A team from the Global Center for Siddha Medicine and Research (GCSMR), North Carolina, USA - **Dr. Janakiaraman** (Cardiologist) and **Dr. Selva shunmugam** (Senior doctor), **Mr. Sivasailam**, **Mrs. Mallika Janakiraman**, and **Mrs. Senthamarai** (Software engineers) visited MCBR, MAHE and its laboratory setup on 6th March 2024 and lauded the vision, mission, infrastructure, and progress of the MCBR.

Mr. Ravikant Rajan - an executive officer at the International Relations Office of IIT Roorkee visited MCBR, MAHE on 15th March 2024 and shared his thoughts about international collaborations, international funding, and opportunities.

Celebration of Women's Day

On 8th March 2024, we celebrated Women's Day at MCBR, MAHE, Manipal. Gifts and games were arranged for all high achieving women of our department.



FUN MOMENTS

We had great **NEW YEAR CELEBRATION** and enjoyed gifts from our secret Santa on 1st January 2024.

On 1st January 2024, we also enjoyed **POTLUCK LUNCH** and lots of delicious dishes.

FUN MOMENTS

We celebrated **SCIENCE DAY** on 24th and 28th January 2024 with students from various schools.

FUN MOMENTS

BIRTHDAY Celebrations..!!

HOLI Celebrations..!!

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

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