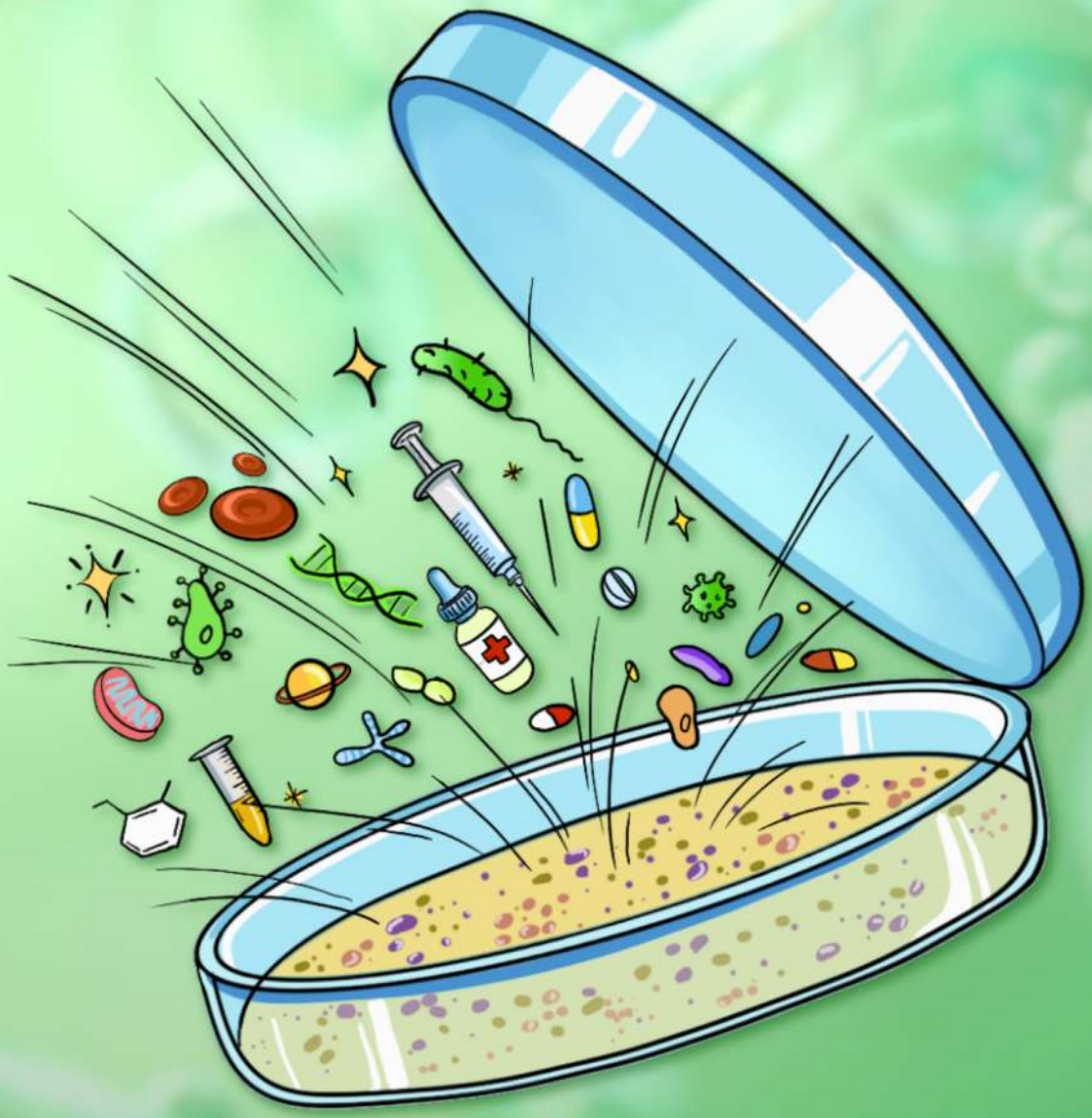
St. Xavier's College (Autonomous), Kolkata
POSTGRADUATE AND RESEARCH DEPARTMENT OF BIOTECHNOLOGY

CHIASMA 2025

A CROSSOVER OF MINDS

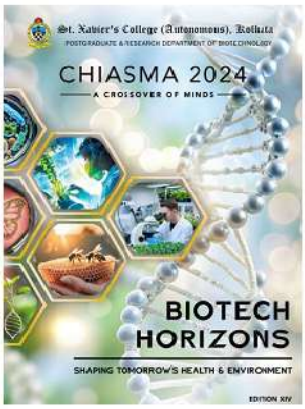
FROM PETRI TO PLANET

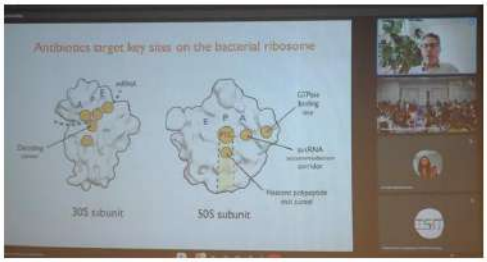
MOLECULAR ORIGINS TO SYNTHETIC BIOLOGY



EDITION XV

Some Glimpses of our Departmental Activities





B M B T

St. Xavier's College (Autonomous), Kolkata

POSTGRADUATE & RESEARCH DEPARTMENT OF BIOTECHNOLOGY

CHIASMA 2025

A CROSSOVER OF MINDS

DISCLAIMER

CHIASMA is published annually by the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata, 30 Mother Teresa Sarani, Kolkata - 700016, West Bengal, India.

All articles, artworks and photographs published in this magazine represent the views, interpretations and findings of their respective authors. They do not reflect the views of the college or the department in any manner.

Although every effort has been made to ensure the accuracy of the material published in this magazine, the college and department accept no responsibility for the veracity of claims or the accuracy of the information provided by the contributor/contributors.

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EDITORIAL BOARD

Messages

MESSAGE FROM
THE RECTOR

It gives me immense joy to witness the publication of the fifteenth edition of "Chiasma 2025 – A Crossover of Minds", the departmental magazine of the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata.

This year's theme, "From Petri to Planet: Molecular Origins to Synthetic Biology", beautifully encapsulates the vast journey of biotechnology, from the simplest explorations within a petri dish to innovations that can transform the planet. It reflects how molecular discoveries at the microscopic scale continue to shape global advancements in health, environment, and sustainability. The emergence of synthetic biology has opened new frontiers in understanding life and designing systems that can address the world's most pressing challenges.

I am delighted that Chiasma 2025 has embraced this forward-looking perspective, exploring the interconnectedness of molecular science and its planetary impact. The magazine not only celebrates scientific inquiry but testifies to the creative spirit and intellectual enthusiasm of our students and faculty.

I commend the Department of Biotechnology for nurturing a vibrant culture of research and innovation. This magazine stands as a testament to their dedication, teamwork, and passion for science. I am confident that Chiasma 2025 will enlighten, inspire, and ignite curiosity among its readers.

My heartfelt best wishes to all the students and faculty members of the Department of Biotechnology. May your collective efforts continue to lead you to greater discoveries and deeper understanding of the world we live in.

Rev. Fr. Jeyaraj Veluswamy, SJ
Rector
St. Xavier's College (Autonomous), Kolkata

MESSAGE FROM
THE PRINCIPAL

It gives me immense pleasure that the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata, is launching the fifteenth edition of its departmental magazine, "Chiasma 2025 - A Crossover of Minds". This year's theme is "From Petri to Planet: Molecular Origins to Synthetic Biology" which aptly encapsulates the expanding frontiers of biotechnology from the fundamental understanding of life at the molecular level to the innovative design of synthetic systems that can contribute to human well-being. The applications of biotechnology play a crucial role in the current global scenario by improving human lives and human health, enhancing food availability, promoting sustainable development and environmental conservation.

This magazine is a fruit of months of tireless effort on the part of the students and faculty members of the Postgraduate and Research Department of Biotechnology. This annual magazine provides a platform for the young aspiring biologists to express their innovative and critical ideas on the aforementioned theme. The department is productively engaged high end research which is reflected in the broad areas covered in this edition of the magazine on the part of the faculty members and students of the department.

Since its inception in 2006, the Department has continually strived toward excellence in teaching and research, fostering an environment that encourages inquiry, collaboration and innovation. The recognition earned by its members at national and international levels stands as a testament to their dedication and competence.

I extend my warm congratulations to the faculty members, research scholars and students of the Postgraduate and Research Department of Biotechnology for their hard work and collective effort in bringing out this edition of Chiasma 2025. May this spirit of academic pursuit and innovation continue to inspire greater accomplishments in the years ahead.

God bless you all. Nihil Ultra!

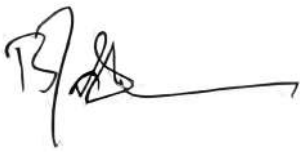
Rev. Dr. Dominic Savio, SJ
Principal
St. Xavier's College (Autonomous), Kolkata

Message From
THE VICE-PRINCIPAL (ARTS AND SCIENCE)

Chiasma, the annual publication of the Postgraduate Department of Biotechnology, is now in its fifteenth year. This continuity stands as a remarkable testament to the department's unwavering commitment to academic excellence, advanced research, and the dissemination of knowledge.

This year's theme, "From Petri to Planet: Molecular Origins to Synthetic Biology", reflects the expansive journey of biotechnology — from understanding life at the molecular scale to designing synthetic systems capable of addressing global challenges in health, environment, and sustainability. The magazine provides an engaging platform for students and research scholars to showcase their scientific insights, creativity, and intellectual curiosity. Beyond its scholarly focus, it also serves as a niche for literary and artistic expression, encouraging a holistic growth that nurtures both analytical and creative minds.

Congratulations to the Department of Biotechnology on this outstanding achievement. May Chiasma 2025 ignite a lasting spirit of discovery, creativity, and achievement in every learner and researcher.



Prof. Bertram Da'Silva

Vice - Principal (Arts and Science)

St. Xavier's College (Autonomous), Kolkata

Message From
THE DEAN OF SCIENCE

It gives me immense pleasure to extend my warmest congratulations to the Department of Biotechnology on the release of the fifteenth edition of their annual magazine, Chiasma 2025.

Over the years, Chiasma has evolved into an exemplary platform that not only celebrates scientific inquiry but also fosters collaboration and intellectual growth within our academic community. This year's theme, "From Petri to Planet: Molecular Origins to Synthetic Biology," aptly captures the transformative journey of biotechnology — from understanding life at the molecular scale to engineering synthetic systems capable of addressing some of the world's most pressing challenges.

The diverse range of articles featured in this edition reflects the department's unwavering commitment to interdisciplinary research, creativity, and scholarly excellence. I extend my heartfelt appreciation to the editorial team and all contributors of Chiasma 2025 for their dedication and effort in bringing this edition to life.

I am confident that this publication will continue to inspire students, researchers, and readers alike while further strengthening the Department's significant contributions to the ever-evolving field of biotechnology.

Dr. Indranath Chaudhuri

Dean of Science

St. Xavier's College (Autonomous), Kolkata

Message From
THE DEAN OF ARTS

Chiasma – A Crossover of Minds, with the theme for the 2025 issue, "From Petri to Planet: Molecular Origins to Synthetic Biology", captures the remarkable journey of biotechnology — from understanding life at the molecular level to designing innovative systems with the potential to impact our planet. This theme reminds us of the profound connection between scientific discovery and its broader implications for society, health, and the environment. As we explore these frontiers, we recognize that advances in biotechnology not only deepen our understanding of life, but also empower us to address global challenges responsibly and creatively. This shared pursuit of knowledge encourages collaboration, innovation, and thoughtful action, fostering a generation of scholars who are prepared to contribute meaningfully to the world around them. I congratulate the Department of Biotechnology, all contributors, editors, and readers for their dedication and commitment to this endeavour.

Farhat Bano

Dr. Farhat Bano
Dean of Arts
St. Xavier's College (Autonomous), Kolkata

Message From
THE HEAD OF THE DEPARTMENT

It is with great pleasure that I herald the unveiling of the 15th edition of our departmental periodical, 'Chiasma'. This magazine continues to serve as a vibrant platform for scholarly and creative expression, featuring contributions from our students, research scholars, and faculty, encompassing a wide range of themes—from the realm of biology to subjects of general interest.

I am deeply grateful to Rev. Dr. Dominic Savio, SJ, our respected Principal, for his constant encouragement, guidance, and steadfast support. My heartfelt thanks also go to Prof. Bertram Da' Silva, Vice Principal; Dr. Indranath Chaudhuri, Dean of Science; and Dr. Farhat Bano, Dean of Arts, for their invaluable and unwavering support.

I wish like to express my deepest appreciation and gratitude to Dr. Aniruddha Banerji and Dr. Priyanka De, whose tireless commitment and insightful guidance have been instrumental in bringing this edition to life. I commend the remarkable dedication of our dynamic editorial board, whose sustained efforts over the past several months have upheld this decade-long tradition of excellence in the Postgraduate and Research Department of Biotechnology.

I extend my sincere thanks to our entire departmental faculty, research scholars and students for their valuable contributions and enthusiastic support. This collective effort has enabled us to continue our journey with pride. May our spirit of collaboration and discovery endure. Nihil Ultra!

Dr. Jhimli Dasgupta
Associate Professor and Head of the Department
Postgraduate & Research Department of Biotechnology
St. Xavier's College (Autonomous), Kolkata

FROM THE EDITOR'S DESK

With every passing year, CHIASMA continues to evolve, much like the science it celebrates. It fills us with immense joy to present the 15th edition of CHIASMA, the annual departmental magazine of the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata.

This year, under the theme "From Petri to Planet: Molecular Origins to Synthetic Biology," we explore how life's simplest molecular beginnings have paved the way for extraordinary biotechnological innovations that now reach across ecosystems and even beyond our planet. From the flicker of cellular life in a petri dish to the vast potential of synthetic biology, this journey captures the essence of human curiosity and creation, the ever-growing desire to understand, design and sustain life.

CHIASMA 2025 seeks to reflect that spirit of exploration, connecting ideas, discoveries, and creative thought that move us from microscopic insight to macroscopic impact. Within these pages, readers will find contributions that span scientific rigour and artistic imagination, showcasing the vibrant minds of our department.

We express our heartfelt gratitude to Rev. Dr. Dominic Savio, SJ, our Principal, for his continuous encouragement, guidance and constant support. We also wish to thank, Rev. Fr. Jeyaraj Veluswamy, SJ, our Rector; Prof. Bertram Da Silva, our Vice Principal; Dr. Indranath Chaudhuri, our Dean of Science and Dr. Farhat Bano, our Dean of Arts, for their constant encouragement. We take this this opportunity to thank Dr. Jhimli Dasgupta, our Head of Department and all faculty members and support staff of the Department for their constant cooperation and support in this journey.

A special note of thanks to eminent scientists and all our contributors, whose insights and creativity breathe life into this magazine. Last but not the least, a special word of appreciation for our Chief Editors, Co-Editors, Editorial Committees, Design & Layout Team and Photography & Artwork Team for their relentless hard work for the past few months, without which this magazine would not have been possible.

As we turn each page of CHIASMA 2025, may it remind us that from the petri dish to the planet itself, science continues to unite imagination with impact. Nihil Ultra!

Dr. Aniruddha Banerji
Associate Professor,
Postgraduate & Research Department of Biotechnology
St. Xavier's College (Autonomous), Kolkata

Dr. Priyanka De
Assistant Professor,
Postgraduate & Research Department of Biotechnology
St. Xavier's College (Autonomous), Kolkata

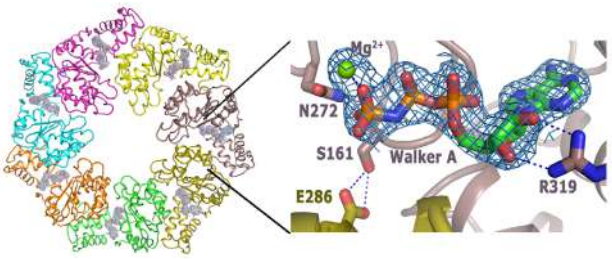
Faculty Profiles

Dr. Jhimli Dasgupta

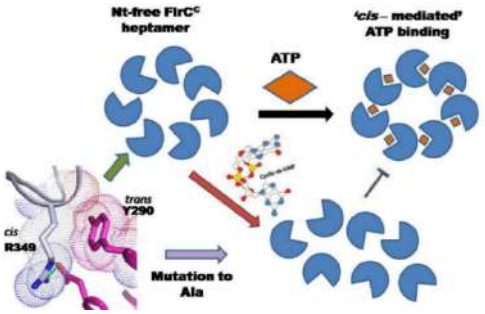
M. Sc., Ph. D

RESEARCH INTERESTS AND THE PROJECTS RUNNING IN THE LAB

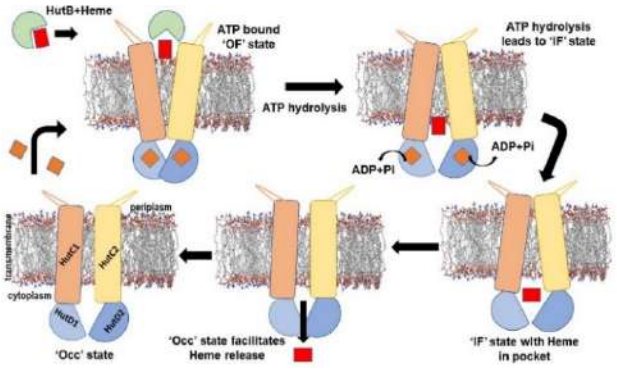
1. Structural and functional insights of the molecular motors such as σ^{54} dependent transcription activators, involved in flagellar gene transcription:
   - Structural and functional aspects of the AAA+ ATPase FlrC that control flagellar synthesis and biofilm formation in motile bacteria.
   - FlrA, the master transcription regulator of flagellar synthesis in motile bacteria: Structural insights, oligomerisation, functional implications, and regulation by the second messenger c-di-GMP.
2. Revelation of the sensory signal and mechanism of FlrB, a unique cytosolic sensor Histidine kinase playing a pivotal role in flagellar synthesis and motility of *V. cholerae*.
3. Understanding the mechanism of nutrient uptake by pathogenic bacteria using ABC.



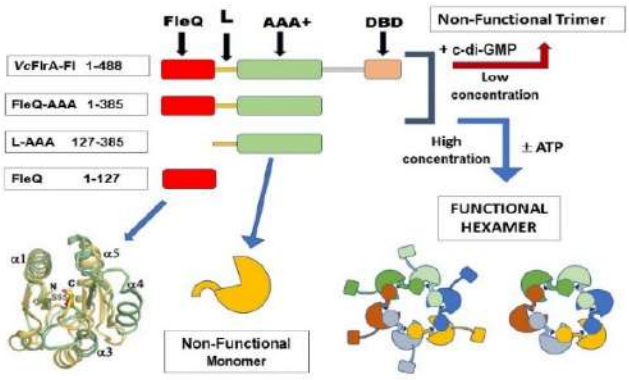
ATP binding to bEBP, FlrC



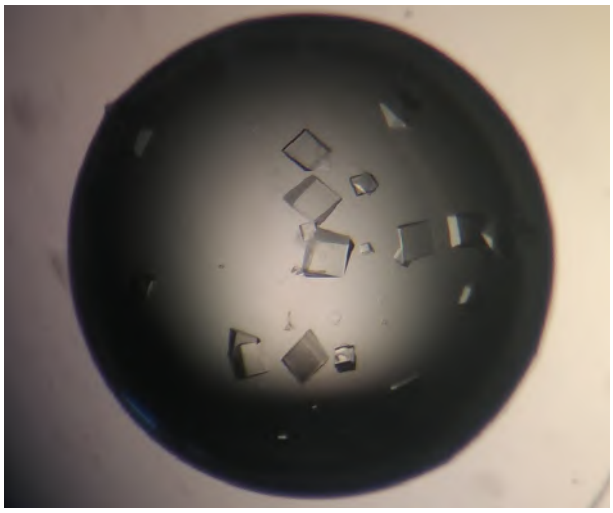
Modulation of bEBP, FlrC by ATP and c-di-GMP

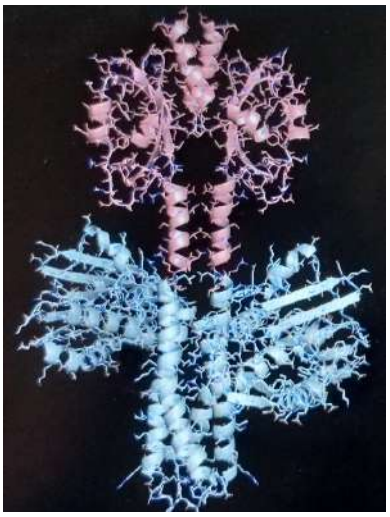


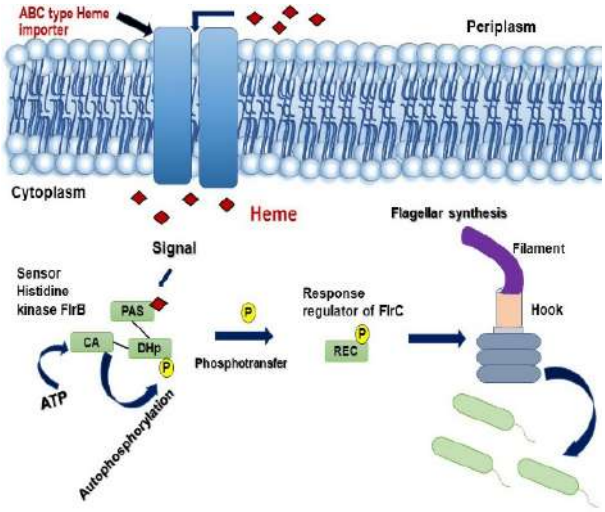
Heme transportation through ABC importer HutCD



c-di-GMP mediated regulation of FlrA







Sensor histidine kinase FlrB involved in flagellar synthesis, binds heme as sensory signal

PUBLICATIONS (2023-25)

1. Peeali Mukherjee, Wrick Chakraborty, Subhayu Chowdhury, Sayak Ganguli, **Jhimli Dasgupta**. Bioinformatic and genomic analyses on FlrB–FlrC-type TCS orthologs involved in flagellar synthesis of monotrichous Gram-negative bacteria. Journal of Proteins and Proteomics, 18 March 2025, 161 – 176.

2. Indrila Saha, Biplab Ghosh, **Jhimli Dasgupta**. Structural insights in to the atypical type-I ABC Glucose-6-phosphate importer VCA0625-27 of *Vibrio cholerae*. Biochem Biophys Res Commun. 2024 Jul 5;716:150030. doi: 10.1016/j.bbrc.2024.150030. Epub 2024 May 1.

3. Peeali Mukherjee, Shubhangi Agarwal, Sritapa Basu Mallick, **Jhimli Dasgupta**. PAS domain of flagellar histidine kinase FlrB has a unique architecture and binds heme as a sensory ligand in an unconventional fashion. Structure. 2024 Feb 1;32(2):200-216.e5. doi: 10.1016/j.str.2023.11.014. Epub 2023 Dec 28. (COVER ARTICLE of February 2024 issue)

4. Shrestha Chakraborty, Shubhangi Agarwal, Arindam Bakshi, Sanjay Dey, Maitree Biswas, Biplab Ghosh, **Jhimli Dasgupta**. The N-terminal FleQ domain of the *Vibrio cholerae* flagellar master regulator FlrA plays pivotal structural roles in stabilizing its active state. FEBS Lett. 2023 Sep;597(17):2161-2177. doi: 10.1002/1873-3468.14693. Epub 2023 Jul 10.

Dr. Uma Siddhanta

M. Sc., Ph. D

FIELDS OF RESEARCH EXPERIENCE	OTHER FIELDS OF INTEREST
• Enzymology • Protein Structure-Function • Cell Signaling	• Immunology • Virology

Dr. Sudipa Saha

M. Sc., Ph. D

AREA OF RESEARCH

Structure function studies of proteins

PUBLICATIONS (2023-25)

1. Aparajita Chakraborty, Sayak Ganguli, Priyanka De and **Sudipa Saha**. "An insight into the structural analysis of α-crystallin of habitat specific fish: a computational approach". Journal of Proteins and Proteomics, 2023. https://doi.org/10.1007/s42485-023-00107-7
2. Aparajita Chakraborty, Sushmita Nandy, **Sudipa Saha** and Priyanka De. "An Insight on α-crystallin Interactions with Various Proteins in Systemic Disorders" (Review). Journal of Stress Physiology & Biochemistry, Vol. 19, No. 3, (2023), 35-46. ISSN 1997-0838.
3. Aparajita Chakraborty, Priyanka De and **Sudipa Saha**. "Elucidating the mechanism of anti-apoptotic activity of α-crystallin and its therapeutic potential" (Review). Journal of Stress Physiology & Biochemistry, Vol. 21, No. 1, (2025), 182-189. ISSN 1997-0838.
4. Sutrisha Kundu, Vivek Raychaudhuri and **Sudipa Saha**. "GroEL/GroES Mechanism of Action and Formation of Complexes During Reaction Cycle: A Matter of Debate" (Review). Journal of Stress Physiology & Biochemistry, Vol. 21, No. 3, (2025), 143 - 160. ISSN 1997-0838.

Dr. Aniruddha Banerji

M. Sc., Ph. D

PRIMARY AREA OF RESEARCH INTEREST

Cancer biology

ADDITIONAL AREAS OF RESEARCH INTEREST

Wildlife biology, Evolutionary biology, Environmental biology, Ecology and Epidemiology

RESEARCH ACTIVITIES

PUBLICATIONS (2023-25)

JOURNALS

1. P. Ghoshal, **A. Banerji**. Looking at COVID-19 Pandemic Through the Lens of Epidemiological Transition Theory. Science and Culture (2023) vol. 89(1-2) pp. 27-32. ISSN: 0036-8156.
2. S. Sen, A. Biswas, **A. Banerji**. Analysis of Avian Diversity at Chintamoni Kar Bird Sanctuary: An Urban Forest Perspective. Uttar Pradesh Journal of Zoology (2023) vol. 44(12) pp. 7-15; ISSN: 0256-971X.
3. I. Chakraborty, A. Roy, **A. Banerji**. The Role of All-trans Retinoic Acid (ATRA) As A Potential Downregulator of Integrin α5β1 Mediated Signalling in Melanomas. South Asian Journal of Experimental Biology (2024) vol. 14(6) pp. 282-293. ISSN:2230-9799.
4. A. Roy, **A. Banerji**. Comparative Study of Curcumin, All-Trans Retinoic Acid and Resveratrol: Therapeutic Targeting of Breast Cancer Signalling. Annual Research & Review in Biology (2025) vol. 40 (4) pp. 154-164. ISSN: 2347-565X.

BOOK CHAPTERS

1. P. Ghoshal, **A. Banerji**. Forest Cover and Its Management: A Study in Indian Perspective. Novel Perspectives of Geography, Environment and Earth Sciences Vol. 9, Ed. H.L. Shrestha, Pub: Book Publisher International (2023) pp. 28-43. Print ISBN: 978-81-19491-52-0.
2. A. Roy, **A. Banerji**. Endogenous Regulators of Matrix Metalloproteinase Expression and Activity in Breast Cancers. Novel Research Aspects in Medicine and Medical Science Vol. 5, Ed. R.W. Sawadago, Pub: Book Publisher International (2023) pp. 37-49. Print ISBN: 978-81-19761-32-6.
3. I. Chakraborty, **A. Banerji**. Signalling Cascades in Melanoma: Understanding the Potential of Phytochemicals as Inhibitors. Research Perspectives of Microbiology and Biotechnology Vol. 1, Ed. E. Magiorkinis, Pub: Book Publisher International (2024) pp. 19-31. Print ISBN: 978-81-971580-1-8.
4. A. Roy, **A. Banerji**. Natural Compounds as Promising Modulators of Breast Cancer Signalling: The Significant Role of Tea Polyphenols. Medical Science: Trends and Innovations Vol. 5. Ed. M. Refaat, Pub: Book Publisher International (2025) pp. 88-103. Print ISBN: 978-93-49238-11-4.

PLENARY LECTURE (2023-25)

A. Banerji. "Exploring the potential of some natural phytochemicals for targeting epidermal growth factor receptor (EGFR) in breast cancers" Plenary lecture at International Conference on Chemistry for Human Development (ICCHD-2025) organized by University of Calcutta, Biswa Bangla Biswabidyalay, Professor Asima Chatterjee Foundation Kolkata and Luminescent Organic Consortium of India, Jan 2025.

SELECTED PRESENTATIONS / ACHIEVEMENTS FROM AB LAB (2023-25)

POSTER PRESENTATIONS

1. A. Roy, **A. Banerji**. "Targeting EGFR-Mediated MMP-2 and MMP-9 Expression in Metastatic Breast Cancer Cells by Curcumin and ATRA" at 42nd Annual Conference of Indian Association for Cancer Research (IACR-2023) (International Conference) organized by Advanced Centre for Treatment, Research and Education in Cancer, Mumbai, Jan 2023.

2. I. Chakraborty, **A. Banerji**. "All-trans Retinoic Acid (ATRA) as an Inhibitor of Integrin α5β1 Mediated Signalling in the Murine Melanoma Cell Line B16F10" at 42nd Annual Conference of Indian Association for Cancer Research (IACR-2023) (International Conference) organized by Advanced Centre for Treatment, Research and Education in Cancer, Mumbai, Jan 2023.

3. A. Roy, **A. Banerji**. "Curcumin and All-trans Retinoic Acid (ATRA) As Inhibitors of Matrix Metalloproteinase Expression and Activity in Breast Cancer Cells" at Bio Colloq: One Day Conference on Inter-Disciplinary Biological Sciences (National Conference) organized by Ramakrishna Mission Vivekananda Centenary College (Autonomous), Rahara & Academy of Biodiversity Conservation, Jan 2024. Awarded 1st prize for poster presentation.

4. I. Chakraborty, **A. Banerji**. "Potential of All-trans Retinoic Acid (ATRA) For Inhibiting Cellular Signalling Pathways in Melanoma Cells" at Bio Colloq: One Day Conference on Inter-Disciplinary Biological Sciences (National Conference) organized by Ramakrishna Mission Vivekananda Centenary College (Autonomous), Rahara & Academy of Biodiversity Conservation, Jan 2024.

5. I. Chakraborty, **A. Banerji**. "The Role of All-trans Retinoic Acid (ATRA) as a Potential Inhibitor of Signalling Pathways in Cervical Cancers" at 8th World Cancer Congress-2024 (International Conference) organized at JNU Convention Centre, New Delhi, March 2024.

ORAL PRESENTATIONS

1. A. Roy, **A. Banerji**. "Synergistic Treatment with Curcumin and All-trans Retinoic Acid: Effects on Matrix Metalloproteinases (MMPs) in Metastatic Breast Cancer Cells" at 8th World Cancer Congress-2024 (International Conference) organized at JNU Convention Centre, New Delhi, March 2024.

2. I. Chakraborty, **A. Banerji**. "Targeting Signalling Pathways in Cervical Cancers by All-trans Retinoic Acid (ATRA)" at 7th Regional Science & Technology Congress, West Bengal, 2024-25 organized by Presidency University, Kolkata & Department of Science and Technology and Biotechnology, Government of West Bengal, Jan 2025.

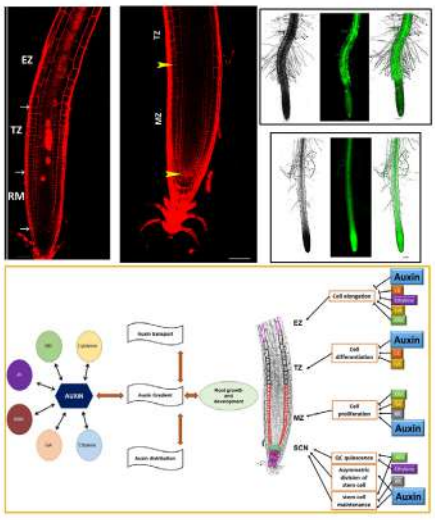
Dr. Ronita Nag Chaudhuri

M. Sc., Ph. D

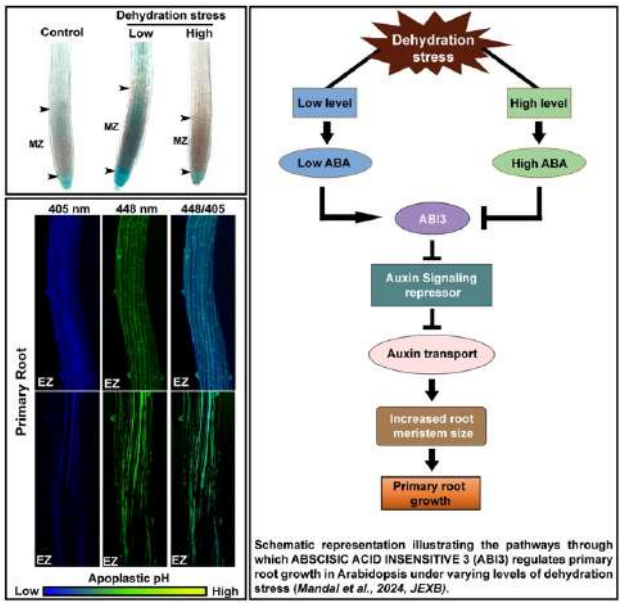
RESEARCH INTEREST

Investigating the genetic and epigenetic regulatory mechanisms involved in developmental and environmental signaling

- Cross talk between hormone signaling pathways in modulation of rootsystem architechture.
- Genetic and epigenetic regulation of root system architecture and its modulation in response to developmental and abiotic stress signals.
- Transgenic approach to improve quality traits in crop plants for better adaptaion to stress conditions.



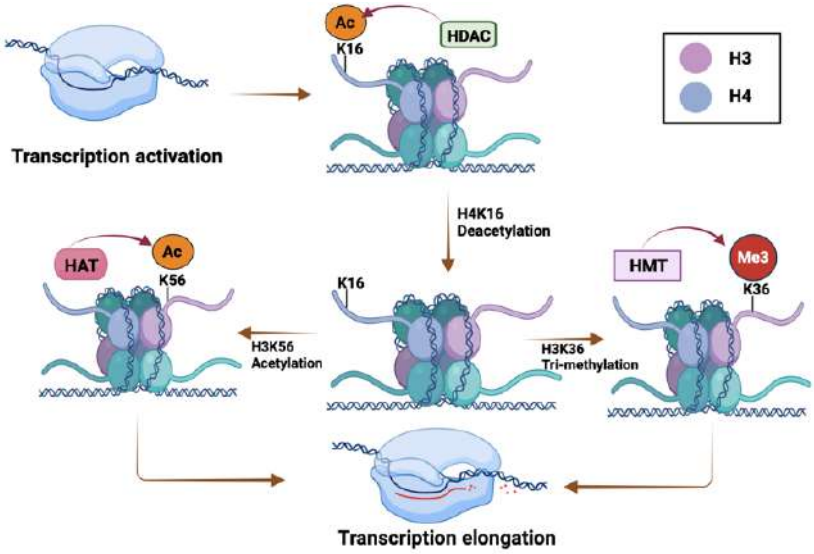
Cell signalling during modulation of Root System Architecture



Schematic representation illustrating the pathways through which ABSCISIC ACID INSENSITIVE 3 (ABI3) regulates primary root growth in Arabidopsis under varying levels of dehydration stress (*Mandal et al., 2024, JEXB*).

Investigating chromatin modifications during transcriptional regulation and DNA damage repair pathway

- Decoding the crosstalk between acetylation of histone residues during DNA templated processes including transcription and DNA damage repair.
- Understanding the correlation between histone methylation and acetylation during transcription regulation and gene looping.



AWARDS AND HONOURS

- Elected Fellow of West Bengal Academy of Science and Technology (FAScT) (Year of Election: 2024)
- Associate Editor, International Peer-reviewed Journal "The Nucleus" - Springer Nature Publication.

PUBLICATIONS (2023-25)

1. To grow or not to grow: the enigma of plant root growth dynamism. Drishti Mandal, Saptarshi Datta, Sicon Mitra, Swarnavo Chakraborty and **Ronita Nag Chaudhuri***. Plant Molecular Biology (2025) doi.org/10.1007/s11103-025-01631-4
2. ABI3 regulates ABI1 function to control cell length in primary root elongation zone. Saptarshi Datta, Drishti Mandal, Sicon Mitra, Swarnavo Chakraborty and **Ronita Nag Chaudhuri***. The Plant Journal (2024) DOI: 10.1111/tpj.17121.
3. ABI3 promotes auxin signaling by regulating SHY2 expression to control primary root growth in response to dehydration stress. Drishti Mandal, Saptarshi Datta, Sicon Mitra and **Ronita Nag Chaudhuri***. Journal of Experimental Botany (2024) doi: 10.1093/jxb/erae237
4. RNA Polymerase II dependent crosstalk between H4K16 deacetylation and H3K56 acetylation promotes transcription of constitutively expressed gene. Preeti Khan, Priyabrata Singha and **Ronita Nag Chaudhuri***. Molecular and Cellular Biology (2023) doi: 10.1080/10985549.2023.2270912
5. RAV1 mediates cytokinin signalling for regulating primary root growth in Arabidopsis. Drishti Mandal, Saptarshi Datta, Giridhar Raveendar, Pranab Kumar Mondal and **Ronita Nag Chaudhuri***. The Plant Journal (2023) doi: 10.1111/tpj.16039

Dr. Priyanka De

M. Sc., Ph. D

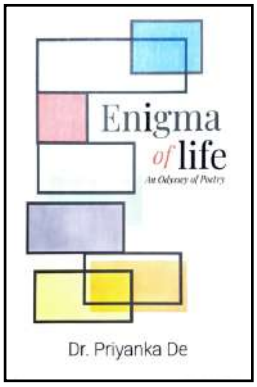
AREA OF EXPERTISE

Physiology, Animal Biology, Metabolism, Ecology, Ethology

PUBLICATIONS (2023-25)

BOOK PUBLICATION

Book entitled 'Enigma of life: An Odyssey of Poetry' (ISBN: 978-93-94035-83-6). January 2024.



JOURNAL PUBLICATION

1. Structure–function relationship of α-crystallin in the context of vertebrate lens evolution and its role in eye disorders. Chakraborty A, **De P**, Saha S. Journal of Proteins and Proteomics [eISSN 2524-4663], 14, 25-41, 2023.
2. An Insight into the Structural Analysis of α-crystallin of Habitat- specific – A Computational Approach. Chakraborty A, Ganguli S, **De P**, Saha S. Journal of Proteins and Proteomics [eISSN 2524-4663], 14, 111–127, 2023.
3. An Insight on α-crystallin Interactions with Various Proteins in Systemic Disorders. Chakraborty A, Nandy S, Saha S, **De P**. Journal of Stress Physiology & Biochemistry [ISSN 1997-0838], 19(3), 35-46, 2023.
4. Elucidating the mechanism of anti-apoptotic activity of α-crystallin and its therapeutic potential. Chakraborty A, **De P**, & Saha S. Journal of Stress Physiology & Biochemistry [ISSN 1997-0838], 21(1), 182-189, 2025.
5. Fentanyl abuse and its implication on health and society. **De P**, Mondal A, Bhattacharya A, Pal N. Journal of Mental Health Issues and Behavior [ISSN: 2799-1261], 5(1), 12-22, 2025.

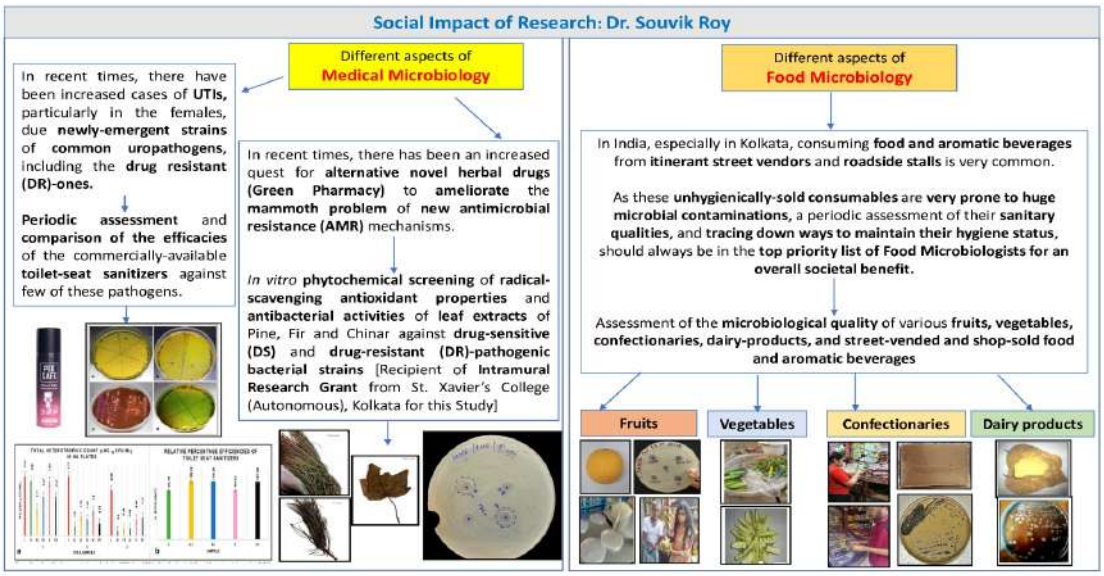
Dr. Souvik Roy

M. Sc., M. Phil., Ph. D

AWARDS & RECOGNITIONS

- B. Sc. [1st Class 1st; Gold-Medalist]
- M. Sc. [1st Class 1st; Gold-Medalist]
- 'Microbiologist Society Best Teacher' & 'Bharat Jyoti Puraskar' Awardee [National-Level Awards]

RESEARCH PROFILE AND ITS SOCIAL IMPACT



AWARDS & OUTREACH ACTIVITIES

PUBLICATIONS (2023-25)

PAPERS IN UGC-CARE APPROVED JOURNALS

1. Sarkar, S., **Roy, S**. & Choudhury, L (2025). Arbuscular mycorrhiza symbiosis—from molecular dialogues to biotechnological applications. Mycological Progress. 24:67. [ISSN (Online): 1861-8952; Impact Factor = 3.0].

2. **Roy, S**., Sarkar, S., and Choudhury, L. (2025). Microbial Compounds in Cosmetic Formulations: A Comprehensive Review. International Journal of Biology, Pharmacy and Allied Sciences. [ISSN (Online): 2277-4998; Impact Factor = 2.659].

3. **Roy, S**., Banerjee, D., Banerjee, A. and Choudhury, L. (2025). Sex hormones and gender differences in immune responses and anticancer immunity: A comprehensive review. Biologia Futura. (In Press). [ISSN (Print): 2676-8615; ISSN (Online): 2676-8607; Impact Factor = 1.8].

4. **Roy, S**., Sarkar, S., Paul, U., Biswas, A., Bera, A. and Choudhury, L. (2025). Quinones and their pharmaco-physiological roles in Prokaryotes and Eukaryotes: A Comprehensive Review. Applied Biochemistry and Microbiology. [ISSN (Print): 0003-6838; ISSN (Online): 1608-3024; Impact Factor = 1.0].

5. **Roy, S**., Mukherjee, P., Kundu, S., Majumder, D. & Raychaudhuri, V. (2024). Microbial Infections in Burn Patients. Acute and Critical Care. 39(2): 214-225. [ISSN (Print): 2586-6052; ISSN (Online): 2586-6060; Impact Factor = 1.7].

6. Das, M., Chakraborty, M., Das, P., Santra, S., Mukherjee, A., Das, S., Banyai, K., **Roy, S**., Choudhury, L., Gupta, R., Dey, T., Das, D., Bose, A., Ganesh, B. & Banerjee, R. (2024). System biology approaches for systemic diseases: Emphasis on type II diabetes mellitus and allied metabolism. Biocatalysis and Agricultural Biotechnology (Elsevier). 58:103176. doi: 10.1016/j.bcab.2024.103176. [ISSN (Online): 1878-8181; Impact Factor = 4.0].

7. **Roy, S**., Ray, D., Laha, I., & Choudhury, L. (2024). Human Mycobiota and Its Role in Cancer Progression, Diagnostics and Therapeutics: A Link Lesser-Known. Cancer Investigation (Taylor & Francis). 1-19. doi: 10.1080/07357907.2024.2301733. [ISSN (Print): 0735-7907; ISSN (Online): 1532-4192; Impact Factor = 2.4].

8. Bhattacharjee, A., Naga, R., Saha, M., Karmakar, S., Pal, A. & **Roy, S**. (2023). Viral inhibitory potential of hyoscyamine in Japanese encephalitis virus-infected embryonated chicken eggs involving multiple signaling pathways. Archives of Virology (Springer). 168:264. doi: 10.1007/s00705-023-05883-7. [ISSN (Print): 0304-8608; ISSN (Online): 1432-8798; Impact Factor = 2.7].

9. **Roy, S**. (2023). Assessing Public Health and Sanitation Status To Promote Preventive Healthcare In India. International Journal of Biotechnology and Allied Fields. 11(10):105-116 [ISSN (Online): 2320-0774].

10. **Roy, S**., Majumder, S., Deb, A., & Choudhury, L. (2023). Microbial contamination of cosmetics and the pharmaceutical products, and their preservation strategies: A comprehensive review. Novel Research in Microbiology Journal. 7(5):2116-2137 [ISSN (Print): 2537-0286; ISSN (Online): 2537-0294; Impact Factor = 1.3].

11. **Roy, S**., Manna, S., Chowdhury, S., & Choudhury, L. (2023). Improvement of Large-Scale Production of Lignocellulosic Bioethanol through Synthetic Biology Approaches: A Comprehensive Review. World Journal of Biology Pharmacy and Health Sciences. 14:316-331 [ISSN (Online): 2582-5542].

12. **Roy, S**., Shaw, D., Sarkar, T., & Choudhury, L. (2023). Mycotoxins in fermented foods: A comprehensive review. Novel Research in Microbiology Journal. 7(2):1897-1917 [ISSN (Print): 2537-0286; ISSN (Online): 2537-0294; Impact Factor = 1.3].

13. **Roy, S**., Chakrabarty, S., Pal, R. and Choudhury, L. (2023) Combating SARS-CoV-2: A Comparison between mRNA Vaccines and Killed Whole Cell Vaccines. International Journal of Biology, Pharmacy and Allied Sciences. 12(4):1781-1798 [ISSN (Online): 2277-4998; Impact Factor = 1.892].

14. **Roy, S**., Mullick, S., Chakrabarty, S. and Choudhury, L. (2023) Pathogen-based Molecular Mimicry and Autoimmune Disorders: A Close Look. International Journal of Biology, Pharmacy and Allied Sciences. 12(4):1701-1716 [ISSN (Online): 2277- 4998; Impact Factor = 1.892].

15. **Roy, S**., Banerjee, S., Bhowmick, P. and Choudhury, L. (2023) Psychobiotics: Deciphering its role in neuropsychiatry. World Journal of Biology Pharmacy and Health Sciences. 13(01):457–464 [ISSN (Online): 2582-5542].

BOOK CHAPTERS

1. **Roy, S**., Chakraborty, B., and Choudhury, L. (2025) Gut Microbiota in Regulation of Neuromuscular Coordination. Advancing Science and Innovation in Healthcare Research. Academic Press, Elsevier (Eds. Bhattacharya Debasmita, Das Prabir Kumar & Das Biswas Samapika). Edn 1. [ISBN: 978-0-443-33351-4].

2. **Roy, S**., Banerjee, D., Banerjee, A., and Choudhury, L. (2025) Genetics of bacterial biofilm-associated infections in livestock. Biofilm Associated Livestock Diseases and their Management. Springer (Eds. Lahiri Dibyajit, Nag Moupriya, Bhattacharya Debasmita & Ray Rina Rani). Edn 1. [ISBN (Print): 978-981-96-1884-2;].

3. **Roy, S**., Sarkar, S., and Choudhury, L. (2024) "Bacteria & Cosmetics – the 'Industry' connect!" Current Advances in Microbiology. Vijaygarh Jyotish Ray College (in association with the Microbiologists Society of India) (Ed. Saha Kesh Gargi). Pp 136-149 [ISBN (Print): 978-81-969267-6-2].

4. **Roy, S**., Manna, S., Chowdhury, S., and Choudhury, L. (2024) Ways of Improvement: A step ahead towards improved cellulosic ethanol production. Biofuels: Scientific Explorations and Technologies for a Sustainable Environment. CRC Press, Taylor & Francis (Ed. Banik Samudra Prosad & Bagchi Debasis). Edn 1. [ISBN 9781003350606].

5. **Roy, S**., Bhowmick, P., Banerjee, S., Choudhury, L. and Mukherjee, A. (2024) Neuropsychiatric applications of psychobiotics. Developments in Applied Microbiology and Biotechnology, Microbial Essentialism. Academic Press, Elsevier (Ed. Sarsan Sreedevi) Pages 301-315 [ISBN 9780443139321].

Dr. Sayak Ganguli

M. Sc., Ph. D

ACADEMIC INTERESTS

I am a biologist, trained in plant biology with specializations spanning Plant Tissue Culture, Cytogenetics, Bioinformatics; Community Genomics along with environmental microbiology and IPR.

CURRENT RESEARCH FOCUS

GENOMICS FOR A SUSTAINABLE PLANET

1. Livelihood Generation and Climate Change Mitigation Awareness Programs as part of the "Wipro Earthian Sustainability Education Programme, 2024" in collaboration with Paribesh Unnayan Parishad (PUPA) in Sagar Island of Indian Sundarbans
2. Nutritional Assessment Studies in different Tribal Settlements in Collaboration with the B.R. Ambedkar Chair, Department of Anthropology, University of Calcutta

United Nations SUSTAINABLE DEVELOPMENT GOALS

National Action Plan on Climate Change (NAPCC) introduced by Government of India – focusing on National Mission for a Green India; National Mission for Sustainable Agriculture; and National Mission on Strategic Knowledge for Climate Change

1. Sundarban Metagenomics: Our team explores the genomic diversity of ecosystems, particularly the unique flora and fauna in regions like the Indian Sundarbans. We study the rhizospheric and endophytic microflora to support habitat restoration efforts and understand the intricate relationships between plants and microbes.
2. Tribal Gut Microbiome: We investigate the gut microbiome of indigenous tribes in West Bengal to gain insights into their dietary habits and nutritional status. This research helps identify beneficial gut bacteria and enables us to provide insights into the gut bacteriome – metabolome axis; providing a better understanding of how such information can be used to benefit mankind.
3. Antimicrobial Resistance in Wastewater and COPD microbiomes: We are involved in development of methods for pathogen surveillance in urban and rural wastewater and nasal microbiome of COPD patients. This work is crucial for predicting future pandemics and monitoring public health.
4. Genomics Guided Drug Discovery: Our lab employs in-silico approaches to analyze the pangenome of different bacterial strains, aiming to identify therapeutic targets in COPD phenotypes

COLLABORATIONS

University of Calcutta (Department of Biotechnology); PUPA; Kolkata;
National University of Singapore (NUS);
Laboratório de Bioinformática e Química Medicinal - LABIOQUIM
Centro de Estudos de Biomoléculas Aplicadas à Saúde - CEBio

MEMBERSHIPS

JAPANESE SOCIETY OF MICROBIAL ECOLOGY
AICGG, INDIA
SOCIETY OF BIOLOGICAL CHEMIST, India
INDIAN SCIENCE CONGRESS ASSOCIATION

PUBLICATIONS

Scan to access Google Scholar

DATABASE ACCESSION

Scan to access NCBI Webpage

RESEARCH TEAM

1. Dr. Meesha Singh awarded in 2023 [Wastewater Surveillance and AMR]
2. Dr. Sarmishta Mukhopadhyay awarded in 2024 [Comparative Genomics and Drug Discovery]
3. Dr. Souradip Basu awarded in 2024 [Tribal Gut Microbiome Project]
4. Ms. Rupsha Karmakar – Research Fellow in Wastewater Surveillance
5. Mr. Wrick Chakraborty – IPCR Fellow in COPD Microbiome
6. Mr. Debava Chaudhuri – UGC – JRF – Sundarban Metagenome Project

LAB MOTTO

"IF YOU WANT TO WALK FAST WALK ALONE; IF YOU WANT TO WALK FURTHER, WALK TOGETHER"

HOBBIES

Collecting Folk Songs; Playing/Watching Cricket and Football, NGO Activities

CONTACT

Email: sayakganguli@sxccal.edu
sayakganguli2@gmail.com

LinkedIn

VIDWAN

Dr. Arindam Bakshi

M. Sc., Ph. D

RESEARCH EXPERIENCE

1. Postdoctoral Research Fellow in National Centre for Biological Sciences, Bangalore (May 2019-July 2019)
2. Postdoctoral Research Fellow in Iowa State University, USA (March 2020-Oct 2021)

PRIMARY AREA OF RESEARCH INTEREST

1. Structure-function relationship of plant viral proteins and domains in viral replication, genome encapsidation and cell to cell movement.
2. Functional characterization of plant viral RNA dependent RNA polymerase (RdRp) in vitro and in vivo
3. Use of proteomic approaches to identify interaction partners of viral RdRp and novel host factors in viral replication.

ADDITIONAL AREA OF RESEARCH INTEREST

1. Structural studies of Plant viral RdRp and its complexes using X-ray crystallography and cryo-electron microscopy
2. Engineering of plant viral coat proteins as nano particles (VNPs) or virus like particles (VLPs) for intracellular delivery of therapeutic antibodies
3. Subcellular localization of antibody tagged VNPs/VLPs inside mammalian cells and elucidation of biochemical pathways involved in antibody delivery.

COURSES TAUGHT

1. **UG level:** Molecular Biology, Cell Biology, Biophysical methods, Bioanalytical Tools, Microbial physiology, Bioprocess Technology, General Microbiology, Cell and Molecular Biology techniques
2. **PG level:** Advanced Plant Biology, Microbial Biotechnology, Plant Biotechnology, Plant Genetic Engineering.

PUBLICATIONS (2023-25)

1. Chakraborty S, Agarwal S, **Bakshi A**, Dey S, Biswas M, Ghosh B, Dasgupta J. (2023). The N- terminal FleQ domain of the Vibrio cholerae flagellar master regulator FlrA plays pivotal structural roles in stabilizing its active state. FEBS Lett. doi: 10.1002/1873-3468.14693. Epub ahead of print. PMID: 37402215.
2. Dev, B., **Bakshi, A.**, Kar, S. et al. (2023). Evaluation of potent marine ligninolytic bacteria and its efficiency in seawater-based delignification.Biomass Conv. Bioref. https://doi.org/10.1007/s13399-023-04731-7.

Dr. Ditipriya Hazra

M. Tech., Ph. D

AREAS OF RESEARCH

1. Investigating the role of epitranscriptomic modulators in methylation dependent RNA degradation using X-ray crystallography
2. Structure guided drug designing and deciphering protein-drug interaction by molecular dynamics simulation

PUBLICATIONS (2023-25)

1. Manna, S., Samal, P., Basak, R., Mitra, A., Roy, A.K., Kundu, R., Ahir, A., Roychowdhury, A. and **Hazra, D.**, 2023. Amentoflavone and methyl hesperidin, novel lead molecules targeting epitranscriptomic modulator in acute myeloid leukemia: in silico drug screening and molecular dynamics simulation approach. Journal of Molecular Modeling, 29(1), p.9.
2. Mitra, A., Manna, S., Kundu, R., **Hazra, D.** and Roychowdhury, A., 2023. Brute force virtual drug screening with molecular dynamics simulation and MM/PBSA to find potent inhibitors of METTL16. IEEE/ACM transactions on computational biology and bioinformatics, 20(3), pp.2356-2361.
3. Gupta, R., Ganguly, M., Jana, P., Roychowdhury, A. and **Hazra, D.**, 2025. Two Birds with One Stone: Targeting Wild Type and Drug Resistant Mutant ALK Using Brute Force Screening, MD Simulation and NCI. IEEE Transactions on Computational Biology and Bioinformatics.
4. Ganguly, M., Gupta, R., Roychowdhury, A. and **Hazra, D.**, 2025. De novo drug designing coupled with brute force screening and structure guided lead optimization gives highly specific inhibitor of METTL3: a potential cure for Acute Myeloid Leukaemia. Journal of Biomolecular Structure and Dynamics, 43(2), pp.1038-1051.
5. Bhattacharya, D., Chakraborty, S., **Hazra, D.**, Roychowdhury, A., Karmakar, A. and Chattopadhyay, S., 2025. Molecular-level analysis of alkyl chain dependent voltage-induced microfluidic alcohol droplet actuation on Teflon/Pt/glass substrate: Revealing the unconventional directional movement. Journal of Molecular Liquids, 417, p.126576.
6. Rahman, S., Bhattacharya, A., Jana, P., Ganguly, M., Das, A.K., **Hazra, D.** and Roychowdhury, A., 2025. Subtractive proteomics unravel the potency of D-Alanine-D-Alanine Ligase as the drug target for Burkholderia pseudomallei. International Journal of Biological Macromolecules, p.144106.
7. **Hazra, D.**, Rahman, S., Ganguly, M., Das, A.K. and Roychowdhury, A., 2025. Molecular dynamics simulation shows enhanced stability in scaffold-based macromolecule, designed by protein engineering: a novel methodology adapted for converting Mtb Ag85A to a multi-epitope vaccine. Journal of Molecular Modeling, 31(3), p.84.

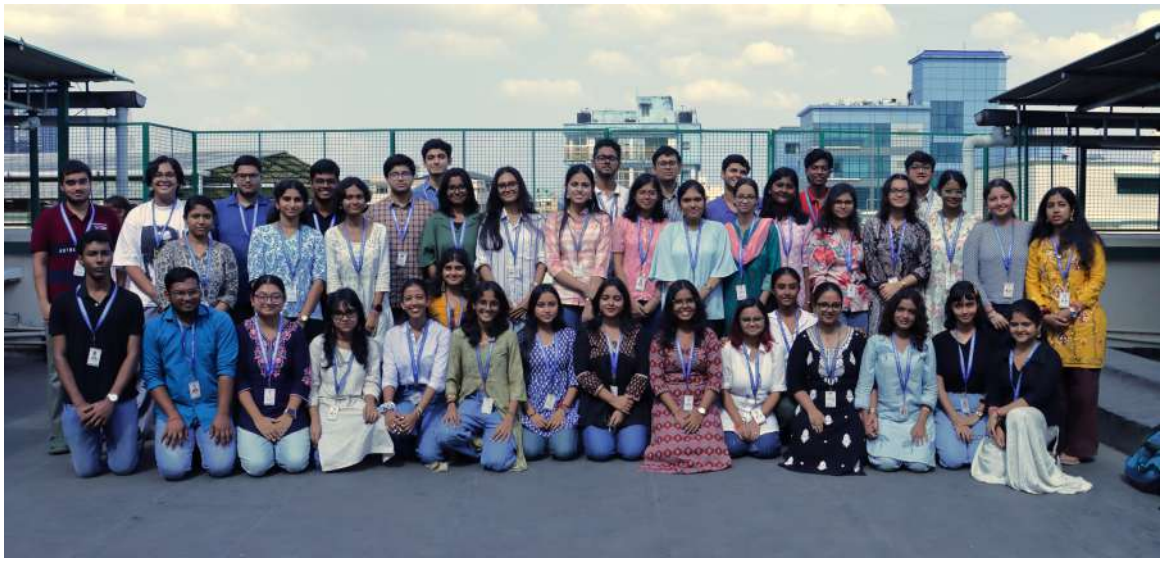
Departmental Diaries

TEACHING FACULTY

SUPPORT STAFF

CHIASMA 2025 COMMITTEE

FIRST YEAR
(Batch of 2025 - 2030)



SECOND YEAR
(Batch of 2024 - 2029)

THIRD YEAR
(Batch of 2023 - 2028)

FOURTH YEAR
(Batch of 2022 - 2027)

FIFTH YEAR
(Batch of 2021 - 2026)

RESEARCH SCHOLARS

Ruchira Das
PI: Dr. Jhimli Dasgupta

Arnab Pal
PI: Dr. Jhimli Dasgupta

Ankita Nanda
PI: Dr. Jhimli Dasgupta

Sushmita Nandy
PI: Dr. Sudipa Saha
Co - PI: Dr. Priyanka De

Aparajita Chakraborty
PI: Dr. Sudipa Saha
Co - PI: Dr. Priyanka De

Anirban Roy
PI: Dr. Aniruddha Banerji

Indira Chakraborty
PI: Dr. Aniruddha Banerji

Drishti Mandal
PI: Dr. Ronita Nag Chaudhuri

Saptarshi Datta
PI: Dr. Ronita Nag Chaudhuri

RESEARCH SCHOLARS

Priyabrata Singha
PI: Dr. Ronita Nag Chaudhuri

Sicon Mitra
PI: Dr. Ronita Nag Chaudhuri

Swarnavo Chakraborty
PI: Dr. Ronita Nag Chaudhuri

Adrija Chakraborty
PI: Dr. Ronita Nag Chaudhuri

Rupsha Karmakar
Joint PI: Dr. Sayak Ganguli,
Dr. Mahashweta Mitra Ghosh
[Thesis Submitted]

Wrick Chakraborty
PI: Dr. Sayak Ganguli
Co-PI: Dr. Partha Sarathi Bhattacharya

Debava Chaudhuri
PI: Dr. Sayak Ganguli

Sanchayita Roy
PI: Dr. Ditipriya Hazra

RESEARCH SCHOLARS - Ph.D AWARDED

(2023 - 2025)

Dr. Shrestha Chakraborty
PI: Dr. Jhimli Dasgupta
Ph. D Awarded: 2023

Dr. Indrila Saha
PI: Dr. Jhimli Dasgupta
Ph. D Awarded: 2024

Dr. Peeali Mukherjee
PI: Dr. Jhimli Dasgupta
Ph. D Awarded: 2025

Dr. Preeti Khan
PI: Dr. Ronita Nag Chaudhuri
Ph. D Awarded: 2024

Dr. Meesha Singh
PI: Dr. Mahashweta Mitra Ghosh
Co-PI: Dr. Sayak Ganguli
Ph. D Awarded: 2023

Dr. Souradip Basu
Joint PI: Dr. Sayak Ganguli,
Dr. Mahashweta Mitra Ghosh
Ph. D Awarded: 2024

Dr. Sarmishta Mukhopadhyay
PI: Dr. Sayak Ganguli
Co-PI: Dr. Santanu Chakrabarti
Ph. D Awarded: 2024

International Symposium on Biotechnology 2024

Convener: Dr. Sayak Ganguli
Co-convener: Dr. Arindam Bakshi & Dr. Ditipriya Hazra

The **International Symposium on Biotechnology (ISBT**) came to fruition for the second time on *12th & 13th of November, 2024,* convening an assembly of brilliant minds at the Postgraduate and Research Department of Biotechnology, St. Xavier's College (Autonomous), Kolkata. The first day officially commenced with an elegant Inaugural Session reverberating with inaugural song followed by Watering of Plants, where the presence of esteemed dignitaries, including respected Father Principal, **Rev. Dr. Dominic Savio, SJ**, & Rector, **Rev. Fr. Jeyaraj Veluswamy, SJ** underscored the institution's commitment to academic excellence.

Launch of Proceedings & Chiasma 2024

A major highlight of the ceremony was the ceremonial **launch of the Conference Proceedings & Chiasma 2024,** marking the start of a deep academic dive.

The intellectual momentum immediately accelerated with the first academic session. The **Keynote Address** by **Dr. Arindam Maitra** , Associate Director and Professor at the National Institute of Biomedical Genomics, Kalyani, deliberated on: **"Unravelling the Cellular Polyphony in the Tumour Ecosystem of Oral Cancers and Oral Submucous Fibrosis: Novel Insights and New Horizons".** This was seamlessly followed by a **Plenary Lecture**, where **Dr. Rupa Mukhopadhyay**, Senior Professor at the School of Biological Sciences, Indian Association for the Cultivation of Science, Kolkata, introduced attendees to the diagnostic frontier with her presentation on **"PCR-independent Nucleic Acid Sensing using Smart XNAS"**.

Glimpses of the inaugural session

A lively **Concurrent Poster Session** during the lunch interval allowed young researchers to showcase their work. Post Lunch session was handled by the associate sponsor **"Prescience Insilico"** who demonstrated the utility of their **PRinS³** software. The post lunch **Plenary Lecture**; titled **"A New Look at Ribosome - Targeting Antibiotics"** was delivered by **Dr. Axel Innis,** Research Director at ARNA Laboratory, INSERM, University of Bordeaux, France,. The day concluded with a vibrant **Cultural Program,** successfully blending rigorous scientific discourse with social engagement.

The second day of the symposium began with an insightful **Plenary Lecture** by **Dr. Shamik Choudhury,** from the School of Environmental Science and Engineering, Indian Institute of Technology, Kharagpur on **"Biotechnology Revolution: Innovations Shaping the Future of Health and Sustainability". Dr. Vinod Scaria,** credited with playing a crucial role in the early whole genome sequencing population genomics projects including the Indian, Sri Lankan and Malaysian genome projects deftly followed with his **Keynote Address** titled, **"Genomes – From Personal to Populations and Back"**. Oral presentations by research scholars, added a provided a different flavour to the proceedings. The last **Plenary Lecture** of the day was by **Dr. Helena Freitas**, Professor at the Department of Life Sciences, University of Coimbra, Portugal, and UNESCO Chair in Biodiversity, titled **"The Importance of Ecological Science in the Twenty – First Century".** The two-day conference ended with a dynamic and exhilarating valedictory session, where prizes were awarded to the oral and poster presenters, along with critical appreciation to all the committee members and support staff. The chief guest of the valedictory session was Mr. Atul Agarwal, Professor of Practice of the department.

Keynote Addresses and Plenary Lectures of ISBT 2024

Cultural Program of ISBT 2024

Field Visit to a Tribal Settlement for Assessment of Livelihood Practices and Dietary Subsistence Patterns as Part of NEP Internship Program

Semester 2

Professors in charge

Dr. Sayak Ganguli & Dr. Arindam Bakshi

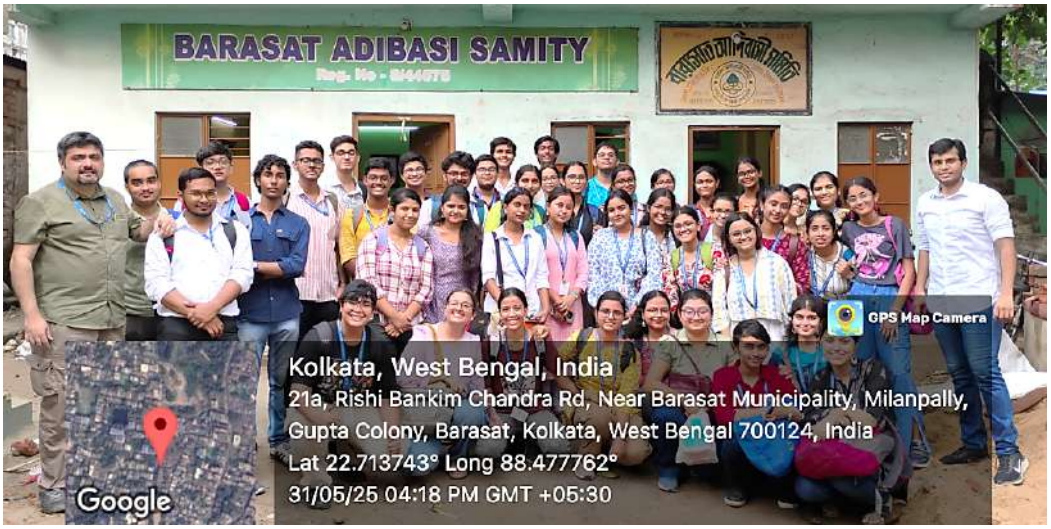
The Oraon, also known as Kurukh, are a Dravidian-speaking tribal group in India, primarily inhabiting the Chhotanagpur Plateau and surrounding areas. Historically, they relied on agriculture and the forest for their livelihoods and rituals.

Today, they are mostly settled agriculturalists. However, climate change associated habitat loss or general migration for better livelihood has forced several members of these tribes to urban settlements, where mostly they work as daily wage workers. This has prompted them to shift from their regular dietary patterns to more urbanized diets. Consequences such as nutritional imbalance and childhood malnutrition have been noted in some studies conducted on this tribe; however, there are no specific reports on the impact of urbanization towards the dietary patterns of this community.

To address this lack of data, the group of semester II students accompanied by Dr. Arindam Bakshi, Dr. Sayak Ganguli and a few research scholars; visited an urban Oraon settlement in Barasat on the 31st of May 2025 to conduct a survey with the objective of studying their health and subsistence parameters.

Key Outcomes of the field activity

1. Students learned to interact with ethnic populations and obtain information about their livelihood and dietary patterns thus enabling them to get an insight on the marginalised people of the country and state, thereby enabling them to identify key issues in science for society.
2. Students learnt exploratory data collection and sampling and were exposed to techniques in anthropometric assessments as well as Bioimpedance analyses which are widely used in the fields of human genetics, sports medicine and other epidemiological studies.
3. Once back from the field the students analysed the data using various statistical tests and submitted a field report.



Field Visit to Vivekananda Institute of Biotechnology, Nimpith, West Bengal

Semester 7

Professors in charge

Dr. Sayak Ganguli & Dr. Arindam Bakshi

The educational trip is a scheduled curriculum program. Students of semester 7 of the department assembled on the 13th of August 2025 at the College premises at 8:30 AM and boarded a chartered bus. They were accompanied by Dr. Arindam Bakshi and Dr. Sayak Ganguli, Professors involved with the MBTCR7152T/P Paper on Advanced Plant Biology. The trip from the college to the institute took around 3 hours and we reached Vivekananda Institute of Biotechnology (VIB) at around 11:30 AM.

Following this, the students were taken to the institutes museum which houses the different working models of the various research and technology transfer programs that the researchers of the institute is engaged in over the years. They were introduced to the different programs by the coordinator, who took them on a tour of the following facilities:

1. Mushroom cultivation and rearing centre
2. Apiculture and Honey Manufacturing Unit
3. Biopesticide Unit
4. Biofertilizer Unit
5. Soil Chemistry and Analyses Unit

In every unit, the researchers in charge explained the nuances of the background science and methods that were being used for the development of the products which were then provided to the farmers and village folks for selling. At around 1:30 PM the students were served lunch, following which the students also got a glimpse of the training and skill development programs that were being conducted in the research facilities where young entrepreneurs were being counseled into starting small sustainable manufacturing and production units of mushroom and biofertilizers.

The return journey was initiated at 4 PM from VIB and the students were dropped off at specific vantage locations while some of the students returned to college along with their professors and dispersed to their respective destinations. Overall the trip was extremely satisfying and the students enjoyed the rural backdrop and understood the real meaning of translational science and science for society by experiencing the excellent endeavours of the institute. They shall be submitting a field report on this visit as part of their curriculum requirement and assessment.

Field Trip to the Indian Museum, Kolkata

Semester 9

Professors in charge
Dr. Aniruddha Banerji & Dr. Priyanka De

On November 1, 2025, we, the students of Semester 9, went on an educational field trip to the Indian Museum, Kolkata as a part of our curriculum for Animal Biotechnology Practical. The professors in charge of the field trip were Dr. Aniruddha Banerji and Dr. Priyanka De. Founded by the Asiatic Society in Kolkata in 1814, this museum is the largest by size of collection in all of Asia. This trip exposed us to a wide range of sections and displays related to zoology, anthropology, evolution, ecology and biotechnology, providing an enriching experience that connected classroom learning with real specimens and historical artefacts.

We explored several galleries and gained a plethora of knowledge. The Reptile and Bird Gallery housed many preserved specimens which provided insights into the diversity of the animal kingdom and their natural habitats. The Fish Gallery contained preserved fishes and other aquatic creatures, giving us a glimpse of underwater biodiversity. The Mammal Gallery had an impressive array of mammal skeletons and taxidermy specimens, preserved to show their features and adaptations. One of the most interesting exhibits was the skeletal parts of a blue whale, the largest animal on Earth.

The Textile Gallery displayed clothes, utensils, and everyday objects from past centuries, shedding light on the culture, traditions and lifestyle of earlier civilizations. The Egypt Gallery featured a mummy, figurines and statuettes offering a fascinating glimpse into the grandeur of ancient Egyptian civilisation and the art of pyramidology.

The Ecological Gallery highlighted various ecosystems, biogeographic zones and hotspots, emphasising the urgent need for conservation of biodiversity. The Botanical Gallery illustrated the multifaceted use of plants in medicines, perfumes, food, oils and textiles, while the Invertebrate Fossil Gallery traced the evolution of life in its many forms. Particularly fascinating was a stromatolite fossil from 3200 million years ago which is the earliest record of life found in India.

Overall, this educational field trip enriched our understanding of science, history and the environment, helping us appreciate the vast ecological and biological diversity around us while reinforcing the significance of preserving it for the future.

Student Achievements

Semester 3

1. **Janhabi Acharya:** 2nd runner-up in Xavotsav Eastern Solo Dance Competition (Jhaankar) '25
2. **Ayushi Singh:**
   - 1st position in Inter District Senior Throwball Championship
   - Represented Kolkata 1st position in Throwball, Xcceleration '25
   - 2nd position in Throwball, Xavier's Premier League
3. **Tusaradri Bhattacherjee:**
   - 1st position in 4x100m Relay
   - 2nd position in 100m SW singles
   - 2nd position in Kho Kho, Khel 8, the flagship sports event of NCC
4. **Rupayan Mukhopadhyay:**
   - Represented St. Xavier's College in India College Chess Championship '25
   - 1st position in the tournament at division 28

Semester 5

1. **Ritoja Paria:**
   - Zonal Topper in Mimamsa '25, IISER Pune
   - 1st position in Eureka: Model making competition, SIGMA 2025
   - Publication in the Compendium of The National Youth Climate Conference, VICHAR '25
   - Publication in Pebbles (Ed. 17), '25
   - Finalists in Bandits of Callisto, Astrovaganza 2025 & Qudos, SIGMA '25
2. **Prapti Gargari:** 1st position in Eureka: Model making competition, SIGMA '25
3. **Rimisha Dhabal:**
   - Participant in MIMAMSA 2025, IISER Pune
   - 1st position in Eureka: Model-making competition, SIGMA'25
   - Publication in Pebbles'25
4. **Archisman Ghosh:**
   - Zonal Topper in Mimamsa 2025, IISER Pune
   - 1st position in Eureka-Model Making SIGMA'25;
   - Goonj'24 Dwita Finalist
   - Publication in Pebbles '25 (17th Edition)
   - Finalists in Bandits of Callisto, Astrovaganza '25
5. **Labony Sahani:** Publication in Pebbles magazine '25
6. **Sreya Kar:** 1st position in Interdepartment SXC Aquatics Meet '25
7. **Ritisha Chakraborty:**
   - Publication in Pebbles '25
   - Finalist in Event Tarana, Goonj '24
8. **Meghna Chatterjee:** Photograph published in Pebbles magazine '25
9. **Shreshtha Biswas:**
   - 1st position in Table Tennis Women in Shaurya '25
   - 1st position in Event Tarana in Goonj '24
   - 2nd position in Xavrang '25
10. **Debanwita Sinha:**
    - 1st position in Carrom
    - 2nd in Blackout Poetry in Cofradia '25
11. **Liza Augustina Tirkey:** 1st position in tug of war in Cofradia '25
12. **Rittika Dhar:**
    - Finalist in Event Tarana in Goonj '24
    - Participant in Mimamsa '25 (IISER Pune)
    - Publication of scientific article and photograph in Pebbles Magazine '25 (Ed. 17)
13. **Poulami Sinha:** 1st position in Eureka: Model-making competition, SIGMA '25

Semester 7

1. **Srabonti Chattopadhyay:**
   - Editor of Pebbles '25
   - Achieved 3rd Position in 'Fictionary' at Sigma '25, organized by The Science Association, St. Xavier's College (Autonomous), Kolkata
2. **Saksham Arya Deo:** 1st in Tug of War, Khel-8 '25
3. **Shreyan Ghosh:**
   - Finalist in Ibso Facto Quiz '25
   - 3rd position in Enquesta Quiz '25
   - 1st position in MTIM Biology Quiz '25
4. **Tiyasha Nandi:** 1st position in Carousel Concertos-Inter-College Instrumental Competition, ECSTACY '25 - NRS Medical College
5. **Aishani Bhattacharya:** Awarded the IASc-INSA-NASI SRF '25
6. **Sukanya Banerjee:** Awarded with the IASc-INSA-NASI SRF '25
7. **Madhushree Pramanik:** Awarded IASc-INSA-NASI SRF '25
8. **Lajbarna Mandal:** Selected for Students Undergraduate Research Graduate Excellence (SURGE) Programme 2025 conducted by IIT, Kanpur

Semester 9

1. **Heeya Gupta, Subham Sarkar and Dyutishmita Bhattacharjee:** Received the 3rd prize for the poster titled "Isolation and Characterization of Notorious Food-Borne Bacterial & Fungal Pathogens from Chocolates of Three Popular Brands of India: A Novel Look Through" in the Poster Presentation Event of the International Conference on 'Emerging Trends in Bio-engineering and Food Technology' organized by the Food Technology Department of Guru Nanak Institute of Technology and held on 18-19 March, 2025
2. **Urjashi Chatterjee:**
   - Qualified GATE XL 2025 with All India Rank 163
   - Oral Presentation at the 24th International Conference on Bioinformatics (InCoB 2025) organised at Bose Institute, Kolkata titled "ASOBASE - a curated database of antisense oligonucleotide (ASOs).
3. **Baibhab Chakraborty:**
   - Oral presentation at the 24th International Conference on Bioinformatics (InCoB 2025), organised at Bose Institute, Kolkata, India, titled "ASOBASE: a curated database of antisense oligonucleotides (ASOs)"
   - Awarded 1st runner up prize for Poster Presentation at the International Symposium on Biotechnology, 2024 (ISBT 2024) organised by the Postgraduate and Research Department of Biotechnology of St. Xavier's College (Autonomous), Kolkata titled "Quest for improving Gut Health – A Probiotic consortium formulated from gut microbes identified from tribes of West Bengal, India"
4. **Roopkatha Sen:** Awarded the IASc-INSA-NASI SRF '25
5. **Sruty Dey:** Summer Research Fellowship Program 2025, Indian Academy of Sciences

Guest Articles

An Overview of Biosensing: From Fundamental Mechanisms to Multidisciplinary Applications

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Abstract

A biosensor combines a biological recognition element with a physicochemical transducer to create a platform for the rapid, sensitive, and selective detection of a wide range of analytes. In recent decades, advancements in nanotechnology, microfabrication, and bioengineering have transformed biosensor design, significantly improving their analytical performance and clinical applications. This review provides an overview of biosensor development, focusing on their classification, transduction mechanisms, and various applications. The integration of nanotechnology, artificial intelligence, and the Internet of Things (IoT) is shaping the next generation of biosensing platforms, enabling autonomous, connected, and predictive diagnostics. These interdisciplinary innovations are set to redefine global healthcare, environmental management, and food security. Overall, biosensors have emerged as transformative analytical tools at the intersection of biology and engineering, paving the way for an intelligent and sustainable monitoring systems for the 21st century.

Introduction

The convergence of biotechnology, materials science, and nanotechnology has positioned biosensing as a crucial element of modern diagnostic approaches. A biosensor integrates a biological recognition element, such as an enzyme or antibody, with a physicochemical transducer to convert biological responses into measurable signals. Since Leland C. Clark introduced the first enzyme-based glucose electrode in 1962, biosensors have evolved into sophisticated tools that can detect a wide range of analytes with high precision. The incorporation of nanomaterials, such as graphene and carbon nanotubes, has enhanced sensitivity, miniaturisation, and signal efficiency, leading to the development of portable and cost-effective detection systems. These advancements have improved clinical diagnostics and broadened biosensor applications to areas such as environmental monitoring and food safety. As demand for decentralised healthcare and point-of-care testing grows, biosensors are increasingly seen as essential for personalised and preventive medicine. This review highlights recent advancements in biosensor technology, focusing on design principles, classifications and their future potential in global healthcare.

Biosensing Principles

A biosensor is a device that measures biological or chemical reactions by generating signals that are proportional to the concentration of an analyte, which is the substance of interest that needs to be detected. A typical biosensor consists of four key components: a bioreceptor, a transducer, a signal processing unit, and a display unit. The bioreceptor interacts selectively with the analyte and may consist of enzymes, whole cells, aptamers, or antibodies, depending on the nature of the analyte being detected. The interaction between the bioreceptor and the analyte generates a signal in a process referred to as bio-recognition. The transducer then converts the bio-recognition event into a measurable signal, a process known as signalisation. Most transducers produce either optical or electrical signals that correspond to the

level of interaction between the analyte and the bioreceptor. The signal processing unit consists of complex electronic circuitry that performs tasks such as signal conditioning, amplification, and converting the signals from analogue to digital form. Once processed, the signals are quantified by the display unit. This display combines hardware and software to present the results in a user-friendly format. Depending on the user's requirements, the output can be shown as numeric values, graphs, tables, or images (Ahmed et al. 2025).

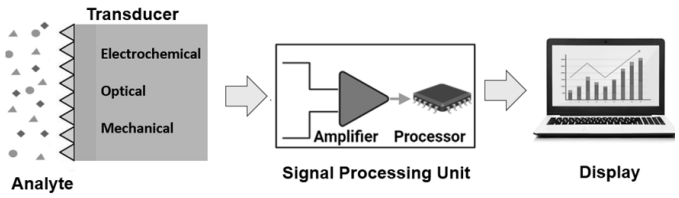

Figure 1: Principle for biosensor operation

The performance of a biosensor is determined by several key attributes: selectivity, reproducibility, stability, sensitivity, and linearity. Optimizing these properties is central to the design and development of biosensors. Selectivity refers to the ability of a bioreceptor to detect a specific analyte in a sample that contains other substances and contaminants. A classic example of selectivity is the interaction between an antigen and an antibody. In many biosensors, antibodies serve as bioreceptors and are immobilized on the surface of the transducer. Reproducibility involves the precision and accuracy of the transducer and electronics in a biosensor. Precision is the sensor's ability to provide consistent results each time a sample is measured, while accuracy indicates how close the mean value of multiple measurements is to the true value of the sample. Stability is the susceptibility of the sensing setup to external disturbances that can cause drift in the output signals of the biosensor during measurement, potentially affecting precision and accuracy. For instance, the responses of transducers and electronics may be sensitive to temperature changes, which can influence the overall stability of the biosensor. Additionally, factors such as the affinity of the analyte for the bioreceptor and the longevity of the bioreceptor over time can also impact stability. Sensitivity, or the limit of detection (LOD), is defined as the smallest amount of analyte that a biosensor can detect. It is desirable for a biosensor to detect trace amounts of analytes in a sample. Linearity describes how accurately the measured response correlates with various concentrations of the analyte. It indicates the resolution of the biosensor and the range of analyte concentrations being tested. Resolution measures the smallest change in analyte concentration that induces a measurable change in the biosensor's response. A high resolution is preferred, as many applications require not only the detection of analytes but also the measurement of their concentrations across a broad working range.

Classification of biosensors

Biosensors may be classified based on the bio-recognition elements used or according to the transducer groups. The most widely used biorecognition elements include antibodies, enzymes, nucleic acids (DNA/RNA), aptamers, nanobodies, whole cells, and bacteriophages, each offering distinct advantages depending on the sensing application and detection mechanism employed (Table 1) (Bhalla et al. 2016).

Table 1: Features and Detection Mechanisms of Biological Elements of Biosensors

Biological Element	Features	Mechanism of Detection
Antibodies	High sensitivity; strong bond (high affinity); high selectivity.	Electrochemical (e.g., impedance, amperometric); Optical (e.g., fluorescence, surface plasmon resonance); Piezoelectric (mass-sensitive).
Enzymes	Binds to the sample of interest; high selectivity; catalytic activity; fast response.	Electrochemical (amperometric, potentiometric); Optical (colorimetric, fluorescence); Thermal (calorimetric).
Nanomaterial	Small size; stable; can be used instead of antibodies; high affinity; suitable for structural analysis of proteins.	Electrochemical (impedimetric); Optical (surface plasmon resonance, fluorescence); Quartz Crystal Microbalance (QCM).
RNA – DNA	Establishes strong bonds; cost-effective; enables early diagnosis of diseases at the molecular level through sequence recognition or hybridization.	Electrochemical (DNA hybridization sensors); Optical (fluorescence, FRET-based); Piezoelectric (QCM).
Aptamers	Synthetic oligonucleotides or peptides that bind specifically to targets (proteins, ions, cells); high stability; easy to synthesize and modify; reusable.	Electrochemical (voltammetry, impedance); Optical (colorimetric, fluorescence, SPR); Mass-sensitive (QCM, SAW).
Cells	Low cost; flexible; requires fewer facilities; portable; does not require expert technicians; can detect biological and environmental changes.	Electrochemical (cell metabolism measurement); Optical (bioluminescence, fluorescence imaging); Mechanical (microcantilever).
Bacteriophage	High sensitivity; high selectivity; low cost; often used in the diagnosis of plant and bacterial diseases; strong host recognition ability.	Electrochemical (impedimetric); Optical (plasmonic, fluorescence); Piezoelectric (mass-sensitive detection).

Biosensors can also be systematically classified by transducer type, which determines how the biological recognition event is converted into a measurable signal. The primary transducer categories follow electrochemical, optical, piezoelectric/acoustic, thermal, and nanomechanical modalities. Electrochemical biosensors rely on the measurement of electrical parameters such as current, potential, or conductivity generated during biochemical reactions at an electrode surface. They are categorised into amperometric (quantifying current resulting from redox reactions), potentiometric (measuring potential differences between electrodes) and conductometric (monitoring variations in electrical conductivity due to changes in ionic concentration) biosensors (Bhatnagar et al. 2024). Optical biosensors, in turn, detect biomolecular interactions in terms of light-based phenomena. For example, Surface Plasmon Resonance (SPR) sensors utilize changes in refractive index upon binding; fluorescence-based sensors detect emitted light after fluorophore excitation while photonic biosensors use waveguides or photonic crystals for label-free detection (Chalklen et al. 2020) (Dincer et al. 2019). Piezoelectric biosensor platform converts mechanical stress or mass changes into electrical signals. When biomolecules bind to a piezoelectric crystal, such as quartz, the resulting mass variation alters its oscillation frequency. Common devices include Quartz Crystal Microbalance (QCM) and Surface Acoustic Wave (SAW) sensors (Erickson et al. 2008). Thermal or calorimetric biosensors detect temperature changes caused by exothermic or endothermic biochemical reactions. These are advantageous for enzyme-based detection systems but require high thermal stability and isolation from environmental variations (Chalklen et al. 2020). Nanomechanical biosensors, including microcantilever and nanoelectromechanical systems (NEMS), detect biomolecular interactions through mechanical deflection, surface stress, or resonance frequency shifts. These systems enable ultra-sensitive detection often down to the single-molecule level—and are increasingly used for early disease diagnosis and biomarker discovery (Haleem et al. 2021) (Hassanpour et al. 2018) (Mahmood et al. 2024).

Multifarious Applications of Biosensors

Biosensors have become essential analytical tools in various sectors, providing rapid, sensitive, and selective detection of biological and chemical substances. Their versatility, potential for miniaturization, and capability for real-time analysis have driven their use in medical diagnostics, environmental monitoring, food safety, and wearable health technologies. The medical field is the largest beneficiary of biosensor advancements, especially in disease diagnosis and therapeutic monitoring. Biosensors are commonly used to detect biomarkers linked to chronic and infectious diseases. For instance, glucose monitoring is a well-known application (Munawar et al. 2019). Additionally, these sensors allow for the rapid identification of cardiac biomarkers, such as troponin and myoglobin, significantly reducing diagnostic time for myocardial infarction (Pang et al. 2012). Similar technologies have also been adapted for the early detection of cancer markers, improving treatment outcomes through timely interventions. Furthermore, biosensors that can detect viral and bacterial pathogens, including HIV, SARS-CoV-2 and Mycobacterium tuberculosis, facilitate point-of-care diagnostics with high specificity and minimal sample volume (Sharma et al. 2021).

Biosensors play a crucial role in environmental protection and pollution control, enabling real-time detection of toxic compounds such as pesticides, heavy metals, and industrial effluents. Enzyme-based, microbial, and DNA biosensors have been developed for monitoring air and water quality, supporting environmental sustainability efforts (Sobhan et al. 2025). Food safety is a major global concern, and biosensors have emerged as vital tools for detecting microbial contamination, toxins, allergens, and chemical residues in agricultural and processed foods. Electrochemical and optical biosensors, including surface plasmon resonance (SPR) and fluorescence-based systems, have been successfully utilized for detecting *Salmonella*, *E. coli*,

and mycotoxins such as aflatoxin B1 in food matrices (Tamayo et al. 2013). Recent advances in IoT-enabled biosensors have introduced intelligent packaging systems that continuously monitor food freshness, detect spoilage gases, and alert consumers in real time (Thévenot et al. 1999). Such innovations bridge biotechnology and smart logistics, ensuring safer supply chains and extended product shelf life. Last but not the least the advent of wearable biosensors has transformed personal healthcare by enabling continuous, non-invasive monitoring of physiological and biochemical parameters. Flexible, skin-integrated devices can measure metabolites such as glucose, lactate, cortisol, and electrolytes from sweat, saliva, or interstitial fluid (Wang et al. 2025). Notably, recent smart textile biosensors have been designed for long-term monitoring of athletes and patients with chronic conditions, offering both diagnostic and preventive healthcare solutions (Yao et al. 2022).

Conclusion

The rapid evolution of biosensor technologies has sparked a paradigm shift across many sectors. From early disease detection and personalized medicine to real-time environmental monitoring and food safety, biosensors showcase the intersection of biology, engineering, and data science. Emerging trends highlight the merging of nanotechnology, artificial intelligence (AI), and the Internet of Things (IoT),leading to the development of autonomous biosensing networks with predictive and adaptive features. These integrated biosensing systems aim to transform healthcare, environmental sustainability and food security in the future. However, despite their potential, several major challenges remain in advancing and widely adopting biosensor technologies. These include issues with stability and reproducibility of bioreceptors, manufacturing scalability and costs, and signal interference in complex biological or environmental samples. Additionally, integrating biosensors with digital platforms raises concerns about data accuracy, security, and regulatory compliance. Overcoming these obstacles is crucial to turning laboratory innovations into reliable, real-world solutions that support global health, environmental goals, and food security.

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Collective Strategies: Response of Social Fish to a Changing Climate!

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Introduction

Freshwater ecosystems—rivers, lakes, ponds, and streams—cover less than one percent of Earth's surface, yet they support nearly **half of all fish species** on the planet. These habitats are biodiversity hotspots, nurturing species that have evolved in remarkable ways to thrive in dynamic environments. Aquatic habitats can be dynamically challenging for living organisms, as individuals need to assess changing environmental conditions and respond to these situations. The long-term survival of species is dependent on their ability to adapt and respond to their surroundings. Freshwater fish are known to show a diversity of behavioural, morphological, and physiological adaptations because of selection pressures over evolutionary timescales. These species occupy diverse niches from high altitude cold/harsh environments, to warm estuarine habitats and even subterranean dark caves! In their natural habitats, factors such as predation pressure, food availability, shelter, and water chemistry play a crucial role in their long-term survival.

In recent times, our freshwater habitats are threatened by major climatic and anthropogenic activities leading to unprecedented changes to the habitats of these fish communities. Major threats include rising water temperatures, industrial pollution, dams and hydroelectric projects, along with microplastic/other harmful pollutants and invasive species. Sensitivity of species to these changes may vary, with some resilient species being able to cope with these challenges, while others (more sensitive ones) are likely to be impacted, leading to their population declines or even extinction. In the face of such environmental upheaval, survival often depends not just on physiology or genetics, but on **behaviour** - how animals interact with one another and respond to change. Among these behavioral adaptations, **group living** (from loose shoals to tightly coordinated schools) plays a pivotal role. For many freshwater fish, living in groups may be the key to enduring a warming, increasingly unpredictable world.

Life in the Freshwater World

Unlike the vast, relatively stable oceans, freshwater habitats are **patchy, fluctuating, and vulnerable** to human activities. Rivers experience seasonal floods and droughts, lakes stratify and deoxygenate as temperatures rise, streams can turn turbid and warm within days. Fish in these systems have evolved extraordinary flexibility to survive such variability.

Species like **zebrafish** ***(Danio rerio)***, **guppies** ***(Poecilia reticulata)***, **and minnows** ***(Cyprinidae)***, which are often used as models in behavioural ecology, show intricate social behaviours that help them cope with uncertainty. Risk of predation is a crucial driver for adaptive responses among prey species. Predation pressures in aquatic environments can be through aquatic (other carnivorous aquatic species) as well as aerial (e.g. birds) predators. Fish species have developed a range of adaptive mechanisms to avoid predation and improve survival chances. For example, species like smaller barbs often have dull coloration and adjust their foraging activities to avoid being visible to aerial as well as underwater predators. Often smaller fish species are known to occupy underwater foliage and other refuge environments to avoid being spotted. Several

species of cyprinids are known to forage and swim in groups called schools as these are known to improve survival changes. It is interesting to note that these fish schools most often consist of individuals that match in looks as well as body size, making it difficult for predators to focus their attention to any single prey. Group living is believed to have evolved as a direct response to predation pressure as it provides critical benefits to individuals by providing greater vigilance, promoting confusion and dilution effects.

There can be several other advantages to group-living. Group-living, once viewed mainly as an anti-predator tactic, is now recognized as a complex adaptive strategy shaped by both ecological pressures and social dynamics.

Why Shoal?

A **shoal** refers to any group of fish that remain together for social reasons, while a **school** is a more tightly coordinated group moving in synchrony. Shoaling offers several well-documented benefits. For example, group living offers '**Safety in numbers**'- when predators find it harder to target individual fish in large, moving groups. This "confusion effect" and "dilution effect" can reduce an individual's risk of being eaten. Living in shoals also allows efficiency in **foraging**. Groups of individuals can locate food patches faster and exploit them more effectively. Fish often copy successful feeders or follow chemical cues from conspecifics. Swimming together also offers **hydrodynamic advantages** in terms of reduction in drag and energy expenditure, especially in flowing waters. Other benefits include **social learning**, where young or naïve individuals learn about safe habitats, predators, or novel food sources by observing others.

However, group living is not without costs. Competition for food, risk of disease transmission, and the need for coordination can make social living energetically demanding. The balance between these costs and benefits shifts under changing environmental conditions-especially in the context of **climate change.**

Climate driven stressors in the environment

Freshwater systems are among the most **sensitive indicators of climate change.** Warming water reduces dissolved oxygen levels, alters flow regimes, and increases the likelihood of algal blooms. Extreme events (such as heatwaves, floods, and droughts) disrupt ecological stability and push species beyond their physiological limits. In these rapidly changing systems, group behaviour can profoundly influence survival. For example,

- **Thermal stress:** Fish in groups can benefit from behavioural thermoregulation. In shallow streams, individuals may collectively move to shaded or deeper refuges when temperatures spike, guided by social cues from early movers.
- **Hypoxia (low oxygen):** Groups may coordinate movements to areas with better oxygen availability, aided by collective sensing.
- **Turbidity and altered visibility**: In murkier waters, visual communication weakens, challenging the ability to maintain coordinated schools. Some fish compensate by relying more on chemical or lateral line cues to stay together.

These behavioural adjustments reveal how **social plasticity,** i.e., the ability to modify group behaviour based on context, could buffer species against climate-driven stress. Research on species like **zebrafish**, native to South Asian streams, offers key insights into how environmental change reshapes social structure. In clear, oxygen-rich water, zebrafish maintain tight, visually guided shoals. When turbidity increases (conditions common in disturbed or sediment-laden rivers) these groups become looser and less coordinated. Yet, this loosening isn't simply a breakdown of sociality. Rather, it reflects **behavioural flexibility.** Individuals may prioritize exploration over cohesion, balancing the need to find resources in degraded environments with the protection offered by groups. Such trade-offs underscore that "group living" is not a fixed trait but a **context-dependent strategy**.

Such flexibility has been observed in other species

too. **Guppies** from high-predation streams form larger, more cohesive shoals than those from low-predation areas. But under warmer or hypoxic conditions, even these tight groups may fragment to reduce competition for oxygen or food. Unfortunately, even as the **ecological context determines the social structure,** climate change is rewriting that context at unprecedented speed.

Group Decisions Under Pressure

Group living also entails **collective decision-making**-how fish choose where to move, when to feed, or when to flee. In stable environments, social hierarchies or consensus rules can ensure efficient decisions. But as conditions fluctuate, leadership and coordination become more dynamic.

Recent studies have shown that **increased temperature** can heighten metabolic rates and aggression, altering dominance relationships within groups. Additionally, **variable flow regimes** can also make following leaders more difficult, disrupting coordinated swimming. Water bodies often becoming dumping ground for industries and agricultural waters. Such **pollutants or endocrine disruptors** can interfere with sensory cues, impairing the ability to form or maintain shoals.

Despite these challenges, collective behaviour often enhances resilience. Groups can integrate information from multiple individuals to make more accurate navigational or foraging choices under uncertainty. This decentralized decision-making could be especially valuable as environmental predictability declines.

Social Plasticity: A Hidden Form of Resilience

Behavioural ecologists increasingly recognize **social plasticity**, i.e., the ability to adjust group behaviour to changing conditions, as a critical yet understudied dimension of climate resilience. Unlike physiological adaptation, which can take generations, social and behavioural adjustments can occur **within hours or days.**

For example, fish may

a. alter group size or spacing depending on water clarity and temperature,
b. switch between visual and chemical communication, or
c. reassign leadership roles based on experience or stress tolerance.

These rapid adjustments can buy populations valuable time to survive until genetic or ecological adaptation catches up. However, there are limits. If environmental change outpaces behavioural flexibility, even the most socially adept species may struggle.

From Streams to Science: Why It Matters and the Future of Freshwater Environments

Understanding how species respond to environmental stress has far-reaching implications to their immediate and long-term survival. **Conservation and management planning** needs to have an understanding of how social structure affects population survival. This can inform reintroduction or captive breeding programs that can be species specific. Fish raised in isolation, for instance, often show impaired social skills when released. Group behaviour can also influence nutrient cycling, predator-prey dynamics, and even water clarity through collective movement. Incorporating social behaviour into ecological and climate models can improve predictions of species persistence under different warming scenarios.

Moreover, studying group living in fish provides broader insights into the **evolution of cooperation,** applicable across taxa—from birds to mammals to humans. The same principles that help fish shoals navigate murky waters can inform how other social species (including us) cope with uncertainty.

The coming decades will test the resilience of freshwater biodiversity like never before. Habitat connectivity, water quality, and flow regimes will determine not just where fish can live, but **how they live together.**

To safeguard these ecosystems, scientists emphasize the importance of:

- **Protecting habitat mosaics:** shaded pools, vegetated banks, and refuge zones that support group refuge during stress events.
- **Maintaining water quality and flow variability** that sustain natural behavioural patterns.
- **Integrating behavioural monitoring** into conservation programs to detect early warning signs of ecological stress.

As we continue to alter freshwater landscapes, we must remember that fish are not passive victims of change. They are active, social beings - communicating, coordinating, and adapting in ways that often surprise us. Understanding and protecting these social dynamics could be as crucial as conserving the physical habitat itself. By swimming together, sharing information, sensing danger, and making collective choices, freshwater fish demonstrate that cooperation is not merely a social behaviour but a profound evolutionary tool for resilience. A lesson we can learn as a society is, survival often flows strongest when we move together!

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Faculty Corner

Demographic Transition Phase: The Current Scenario of India

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Introduction

India, like many other countries, has come a long way from the initial days of evolution when mortality was considerably high due to conditions like natural calamities, epidemiologic transitions and war and when relatively high levels of fertility was essential for human survival. Over the years, as countries have become better equipped in dealing with diseases and vagaries of nature, they have witnessed a significant increase in life expectancy along with a steep fall in mortality. Confronted with Malthusian growth, changing social mores and spurred by government interventions, populations have responded by taking steps to reduce fertility. The continued increase in number of women in reproductive age has however, ensured high number of births each year. In the current scenario, India appears set to witness a sharp slowdown in population growth over the next couple of decades.

Although India as a whole will enjoy the "demographic dividend" phase (the economic growth potential which occurs when the proportion of a country's working-age population is larger than its non-working-age population, i.e. the children and the elderly population), some states will start transitioning to an ageing society by the 2030s. The population in the 0-19 age bracket has already peaked due to sharp declines in total fertility rates (TFR) across the country. Population growth in India has been slowing in recent decades from an annual growth rate of 2.5% during 1971-81 to an estimated 1.3% as of 2011-16.

This article highlights some of the key convergences between the actual occurrences with the theoretical biological perspectives in the area of population growth with reference to India.

Populations, Demography and Age Structures

Considering N_t as the population size after time t and N_{t+1} as the population size after time t+1, changes in the population size between the times t and t+1 are represented as:

$$\Delta N = N_{t+1} - N_t$$

$$N_{t+1} = N_t + B + I - D - E$$

where B = number of births, D = number of deaths, I = number of individuals added by immigration and E = number of individuals lost by emigration.

Demography, the study of population dynamics, seeks to quantify changes in populations over periods of time with relation to natality, mortality, immigrations and emigrations. Demographic data can be represented by the use of life tables, survivorship curves and population pyramids. Growth of populations can be represented by the following equations:

$$\Delta N/\Delta t = rN$$

(equation of geometrical increase)

$$\Delta N/\Delta t = rN\ (K-N)/K$$

(logistic equation where environment acts in a limiting way)

where r refers to the biotic potential and K refers to the carrying capacity.

The former equation represents a growth curve which is typically J shaped while the latter equation represents a growth curve which is S shaped. The biotic (reproductive) potential, natality (birth rate), mortality (death rate) and survivorship all play vital roles in population growth and are related to the age structure of populations.

Data related to age structures of populations is often represented in the form of population pyramids. These are effectively two bar graphs running vertically with males to the right and females to the left of a central line. Populations are divided into pre-reproductive, reproductive and post-reproductive groups for the purpose of analysis. Rapidly expanding populations have high natality giving rise to a population pyramid which is pyramidal in shape. For populations which are stable, pre-reproductive and reproductive age groups are of similar size and the population pyramid is somewhat bell shaped. When a population is in decline, mortality is high and natality low and the population pyramid has a shape like an inverted urn with a lower number of pre-reproductive and reproductive individuals. Studying the age structure of populations is an important part of demographic studies.

The Demographic Transition Theory: The Indian Perspective

The demographic transition theory seeks to explain why all developed nations have passed through approximately the same three stages of modern population history. In the early periods of economic growth (Stage 1), countries had stable or slowly growing populations exhibiting a combination of high birth rates (natality) and almost equally high death rates (mortality). Stage 2 was characterized by modernization, higher incomes, better public health and more nutritious diets which all combined to cause a marked decline in mortality leading to a rise in life expectancy from around 40 years to over 60 years. As the decline in mortality was not associated with a commensurate decline in fertility, this caused a sharp increase in population growth. Stage 2 marked the beginning of the demographic transition (from stable, slowly increasing populations to populations which are rapidly increasing). Stage 3 occurred under the forces and influences of modernization and development which led to a significant decline in fertility and declines in both natality and mortality, leading to a situation where there is little or no population growth.

The occurrence of the COVID-19 pandemic had posed challenges to the demographic transition theory, leading to the necessity of revisiting this theory along with the necessity of forecasting population trends both for the developed countries and for the developing countries. The current phase of demographic transition occurring in India is in compliance with the above-mentioned theory as it has been argued that India has entered into the Stage 3 of demographic transition. The substantial loss of individuals from certain cohorts along with the demographic shifts can lead to a loss of human capital if not adequately replenished. In this current scenario, the three key demographic transitions which are evident in India are as follows:

1. An appreciable increase in the proportion of ageing populations with the percentage of people over the age of 65 years expected to double to 14% by 2050. Around 30% of the elderly population live below the poverty line and over 62% of those who need palliative care are currently not receiving it.
2. With fast urbanization, the concerned urban populations are expected to double by 2050. However, high levels of urban poverty and a very low insurance coverage remain critical challenges for India to overcome in order to reach universal health coverage.
3. One third of India's population is currently in the 10-24 years age group and the working age population is expected to grow at a rate of approximately 9.7 million per year during the period 2021-31. India's youth face an increasing burden of noncommunicable diseases (NCDs), including mental health disorders.

Thus, India is facing a future with an ageing population which would have a grave implication on the human capital formation capability of the country. The term "human capital" is used to refer to skills, knowledge, attitudes, aptitudes, and other acquired traits all of which contribute to production. Human capital formation is thus one of major backbones for growth of a country. Accumulation of human capital principally occurs in three ways:

formal schooling, on-the-job training and off-the-job training. Strong complementary effects have been observed between early ability (acquired or innate) and the skills acquired through formal education or via training on the job. In fact, the earnings of individuals are dependent on the stock of human capital.

The following graph represents the change in the birth rates and death rates of the Indian subcontinent over the past decades which helps us to visualize the demographic transition as discussed above.

Table 1: State wise birth rate and death rate of India
Source: Office of the Registrar General of India, Ministry of Home Affairs

States/UTs	Birth rate		Death rate	
	2010	2020	2010	2020
(1)	(2)	(3)	(4)	(5)
Andhra Pradesh	17.9	15.7	7.6	6.3
Assam	23.2	20.8	8.2	6.2
Bihar	28.1	25.5	6.8	5.4
Chhattisgarh	25.3	22.0	8.0	7.9
NCT of Delhi	17.8	14.2	4.2	3.6
Gujarat	21.8	19.3	6.7	5.6
Haryana	22.3	19.9	6.6	6.1
Jammu & Kashmir	18.3	14.6	5.7	4.6
Jharkhand	25.3	22.0	7.0	5.2
Karnataka	19.2	16.5	7.1	6.2
Kerala	14.8	13.2	7.0	7.0
Madhya Pradesh	27.3	24.1	8.3	6.5
Maharashtra	17.1	15.0	6.5	5.5
Odisha	20.5	17.7	8.6	7.3
Punjab	16.6	14.3	7.0	7.2
Rajasthan	26.7	23.5	6.7	5.6
Tamil Nadu	15.9	13.8	7.6	6.1
Telangana		16.4		6.0
Uttar Pradesh	28.3	25.1	8.1	6.5
Uttarakhand	19.3	16.6	6.3	6.3
West Bengal	16.8	14.6	6.0	5.5
Arunachal Pradesh	20.5	17.3	5.9	5.7
Goa	13.2	12.1	6.6	5.9
Himachal Pradesh	16.9	15.3	6.9	6.8
Manipur	14.9	13.3	4.2	4.3
Meghalaya	24.5	22.9	7.9	5.3
Mizoram	17.1	14.4	4.5	4.2
Nagaland	16.8	12.5	3.6	3.7
Sikkim	17.8	15.6	5.6	4.1
Tripura	14.9	12.6	5.0	5.7
Andaman & Nicobar Islands	15.6	10.8	4.3	5.8
Chandigarh	15.6	12.9	3.9	3.9
Dadra & Nagar Haveli	26.6	20.3	4.7	3.7
Daman & Diu	18.8		4.9	
Lakshadweep	14.3	14.6	6.4	6.5
Ladakh		14.3		5.0
Puducherry	16.7	13.1	7.4	5.4
India	**22.1**	**19.5**	**7.2**	**6.0**

Conclusion

As demography and human capital are issues which are country specific, the government needs to take special care to minimise the adverse impacts in both these areas at the time of policy making to facilitate human capital formation and maintain the Productivity Of Various Sectors In India.

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When the Taps Run Dry: Kolkata's Climate Reckoning

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Understanding Day Zero

The phrase Day Zero first rattled the world in 2018, when Cape Town nearly became the first major city to shut off its taps. It marked the point where municipal water reserves were so low that supply to households and businesses would cease, leaving people dependent on rationed tanker deliveries. The very phrase has since become a symbol of urban fragility in the age of climate change. Kolkata, the sprawling city on the banks of the Hooghly, may face its own Day Zero by 2050. Government reports from the **Central Ground Water Board (CGWB)** and the **National Water Mission** have repeatedly sounded the alarm about over-extraction, shrinking aquifers, and saline intrusion in the Ganges delta. The warnings are stark: Without decisive action, the City of Joy could wake up one day to dry taps and broken promises.

Kolkata @ 2050

Imagine a June morning in 2050. The monsoon is late again, the temperature has been hovering above 45°C, and the government declares what once seemed unthinkable: Kolkata has reached Day Zero. Tankers line up outside hospitals. Long queues of residents, carrying plastic buckets and steel cans, snake through narrow lanes. Fights break out as tempers flare under the sweltering sun. The privileged have private borewells or can pay for water delivered to gated apartments, **but the majority stand waiting, ration cards in hand.** The seeds of this disaster were sown decades earlier. The **NITI Aayog Composite Water Index** already listed West Bengal among states at "high risk" of severe water stress. The **IPCC** warned of Himalayan glacial retreat reducing flows to the Ganges basin. Add unchecked borewell drilling, unplanned construction, and toxic industrial effluents, the outcome is almost inevitable.

From Wetlands to Wastelands: The Ecological Fallout

The **East Kolkata Wetlands (EKW)** have long been the city's secret ally. This sprawling Ramsar site recycles nearly 750 million liters of sewage every day, transforming waste into fertile fishponds and farmland. It is a rare example of a city in symbiosis with its wetlands. But by 2050, with freshwater inflows dwindling, the EKW would collapse. Without replenishment, the ponds would stagnate into toxic cesspools. Fish harvests — once a lifeline for **100,000 people** — would plummet. The reeds and water hyacinths that acted as natural biofilters would rot in chemical sludge. Migratory birds, once abundant, would stop visiting altogether. The transformation from wetlands to wastelands would not just devastate ecology — it would disrupt livelihoods, traditions, and an entire urban ecosystem that sustained Kolkata for centuries.

The Drying of a Delta: Rivers, Aquifers and Biodiversity at Risk

Kolkata's fate has always been tied to the Hooghly River, a distributary of the Ganges. But the river's future is precarious. Climate models project reduced summer flows, as Himalayan glaciers retreat and rainfall patterns falter. Meanwhile, rising seas push saline water further upstream, turning the river brackish. The aquifers, already overdrawn, risk becoming dry or worse —poisoned by arsenic, a problem already endemic to West Bengal's groundwater. With no reliable backup, the entire city becomes vulnerable. The ecological fallout is

immense. Fish produce staples of Bengali cuisine could vanish from local markets. Riparian forests that stabilize banks would wither, worsening erosion and flooding. Birds and reptiles dependent on the delta's rich food chain would lose their habitats.

"Science Does Not Run on Electricity Alone."

Water scarcity doesn't just cripple households — it strangles science. Research Laboratories, depending on high-quality purified water for PCR amplification, DNA sequencing, protein crystallization, and cell culture would also bear the brunt. On Day Zero, when even municipal pipelines run dry, these labs would grind to a halt. Purification plants cannot operate without reliable inflows. Kolkata's intellectual capital will continue and amplify its current trend of talent migration. The crisis would thus rob not only today's citizens of water but also future generations of discoveries.

A Warning the World Can't Ignore: Socialand Human Impacts

Day Zero would ripple through every corner of society. In the city's sprawling slums, women and children would wait for hours in water lines, missing school and work. Public health would collapse under outbreaks of diarrhea, cholera, and skin infections as sanitation crumbles. Hospitals would cancel surgeries for lack of sterile water. The city's economy would bleed. Textile factories, leather tanneries, and IT parks alike would struggle. Real estate markets would crash, while migration patterns would reverse, with thousands fleeing Kolkata in search of water.

Insights from Government and Scientific Reports

- **Groundwater dynamics in Kolkata:** Recent studies up to 2024 show that urbanisation (built-up area expansion) strongly correlates with falling groundwater levels in Kolkata. Approximately 52% of Kolkata's population depends on groundwater. Time-series analyses forecast a further decline unless interventions are adopted.
- **National projections:** The India study "Assessing Groundwater Dynamics…" suggests India may transition from "water-stress" to "water-scarce" status in many areas by 2050 if rates

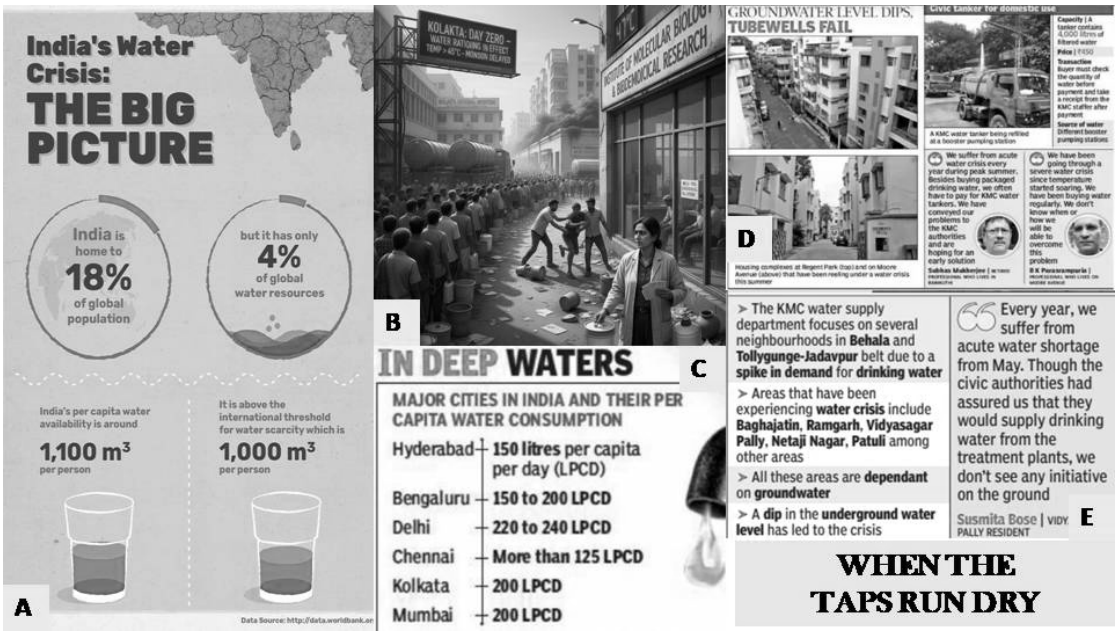

Figure 1: A collection of images depicting the scenario of water crisis. A- World bank infographics on the prevalent water crisis in India; B – An AI generated image in line with the article depicting the futuristic scenario; C – Per Capita Water Consumption in major cities across India; D – A 2019 Times News Network coverage on water scarcity in South Kolkata; E – A 2024 Times News Network coverage on the same issue during summer.

of extraction, population growth, and climate change continue.

- **Government programs and warnings:** The Atal Bhujal Yojana (launched in 2019) is designed to manage groundwater depletion, particularly in water-stressed districts. The "Addressing Groundwater Depletion" report (2024) also warns that rates of depletion may triple by 2080 unless urgent corrective measures are taken.

These reports give credence to the possibility that Kolkata could face Day Zero by mid-century if current trends continue, especially given its high population, heavy dependency on groundwater in many wards, and shrinking recharge due to urban sprawl.

Fighting Back: Climate Action, SDGs and Mitigation Pathways

Yet, even on the brink, hope remains — if action is urgent and collective. Avoiding or delaying Day Zero will require nothing short of a water revolution:

- **Recharge and Replenish:** Build widespread rainwater harvesting and artificial recharge systems.
- **Protect the Wetlands:** Strictly enforce conservation laws for East Kolkata Wetlands.
- **Recycle Wastewater:** Treat and reuse wastewater for agriculture and industry.
- **Diversify Sources:** Invest in desalination and alternative supply options.
- **Govern Smartly:** Regulate borewell drilling, effluents, and unplanned construction.
- **Engage Citizens:** Mobilize communities for conservation, awareness, and audits.

These measures align with the **Kolkata Climate Action Plan** and resonate strongly with global frameworks like the **Sustainable Development Goals (SDGs):**

- **SDG 6** (Clean Water and Sanitation)
- **SDG 11** (Sustainable Cities and Communities)
- **SDG 13** (Climate Action)
- **SDG 15** (Life on Land)

Taken together, these goals form a lifeline for Kolkata. They remind us that Day Zero is not destiny but a warning. The time to act is not 2050 — it is now.

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Symphony of Microcosm and Macrocosm

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Within the humble cell's embrace,
An entire universe begins to trace —
Nuclei shimmer bright as gem,
With sentient organelles hard to tame.

Membranes ripple like cosmic seas,
Chromatin spiralling code-galaxies,
Laws of life stay ready to scroll,
Cytoskeletal array framing us all.

Each vesicle drifts, a planet in its arc,
Golgi constellations embossing the dark.
Ribosomes craft, while proteins adorn,
Peroxisomes cleansing like stars reborn.

ATP comets aid mitochondria glow,
DNA nebulae designing life-flow,
Electrons of galaxies dance and spin,
Chloroplasts shaping the world of green.

Each neuron sparks with cosmic aim,
Each heartbeat echoing stellar claim,
Macrocosm creates vast living room,
Microcosm preserving its usual bloom.

Scientific Articles

Age is Just a Number (of DNA Methylations): Exploring the Epigenetics Basis of Ageing and Longevity

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Keywords: Heterochromatin, DNA methylation, epigenetic clock, age, histone

Introduction

Ageing is a universally experienced physiological deterioration of the body and the myriad of processes occurring in it. It comprises a steady decline in the functions of the tissue as well as cell, with an elevated risk of various cardiovascular, muscular, immune system and neurodegenerative diseases. Current research on this biological phenomenon is focused upon but not restricted to the gradual instability of the genome, modifications in the epigenetic atlas, the increased senescence of cells and decreased levels of proteostasis as a result of exogenous and endogenous stresses (Guo et al., 2022). Of these, studies with respect to epigenetic alterations are particularly important because these directly influence the progression and define the timeline during which ageing sets in. Epigenetic changes, being regulators of ageing and its related processes are thus also potential targets for attenuation of the same, resulting in a longer and healthier lifespan (Wang et al., 2022). This article focuses on two concepts based on such changes.

The Heterochromatin Loss Model of Ageing

The higher order chromatin in eukaryotes can be divided into euchromatin and heterochromatin. Euchromatin is a decondensed region of the chromatin, open to active transcription. Heterochromatin, formed and regulated initially during the process of embryogenesis, is a condensed, compact structure with a transcription status that is inactive and can be subdivided into facultative and constitutive heterochromatin. This very chromatin organisation, on facing age-related dysregulation can cause malfunctions in cellular processes and accelerate the process of ageing. One of the earliest models proposing this was the 'heterchromatin loss model of ageing'. This model explains that the heterochromatin domains initiated when embryogenesis takes place are eventually lost during ageing, resulting in architectural changes in the nuclear landscape globally and causing aberrant expression patterns of genes. In H3 histone for example, the ninth lysine undergoes trimethylation (H3K9me3), due to which the DNA binds more tightly to the histone complex via Heterochromatin Protein 1 (HP1) and forms heterochromatin. This particular modification and hence the heterochromatinised region is lost during ageing. Several facultative heterochromatin domains, known as senescence associated heterochromatin foci (SAHF) are seen to increase in number in senescent cells. This is a primary reason for global heterochromatin loss in the concerned organism. Certain cellular models in this context also exhibit enlarged nuclei, a clear sign of loss of heterochromatin and nuclear DNA decondensation. There have been numerous experiments carried out in various organisms which are evident of the fact that transcriptional silencing is disrupted due to the relationship between ageing and heterochromatin loss (Lee et al., 2020).

Premature ageing and related diseases are also influenced by major epigenetic modulations. Hutchinson-Gilford Progeria Syndrome (HGP), caused when Lamina Associated

Polypeptide 1 (LMNA) gene undergoes germline mutations, results in a sharp drop in H3K9me3 levels. In Werner Syndrome (WS), the mutations occur in the DNA repair gene, the levels of Suppressor of Variegation 3-9 Homolog 1 (SUV39H1), a histone methyltransferase, is lowered. When mesenchymal stem cells from mice as well as normally ageing humans were treated with a knock-in of this methyltransferase gene that was catalytically inactive, cellular senescence characteristics in both cases were accelerated (Lee et al., 2020; Wasserzug-Pash et al., 2022).

Since heterochromatin loss often coincides with widespread alterations in DNA methylation, researchers began exploring whether these methylation changes could quantitatively mirror biological ageing itself — a concept that gave rise to the idea of the 'epigenetic clock'.

The Epigenetic Clock

The concept that DNA methylations could lead to a calculation of the biological age of an organism has been in debate since a long time. The methylation of the 5th position of carbon in the cytosine ring in DNA followed by oxidation, changes the base to 5- Hydroxymethylcytosine, which can function as an epigenetic marker. When compared to actively proliferating or quiescent cells, senescent cells have been observed to carry lower numbers of the aforementioned modification. The heterochromatin faces a dearth of DNA methylation modifications during ageing, whereas a distinctive increase in hypermethylation is noted in the promoters of CpG islands (Guo et al., 2022). The accumulation of such DNA methylation changes with age is defined as 'epigenetic drift' and the predictable or measurable component of this drift is the 'epigenetic clock'. The description of the first 'epigenetic clock' was given by Steve Horvath. His laboratory reported the development of a human multi-tissue age predictor that made use of methylation signatures across the body and was based on 353 CpG sites. The predictor was made from 8000 samples from 51 healthy cells and tissues and 82 Illumina DNA Methylation array data sets. Four properties of DNA Methylation age were proposed: it is by magnitude very close to zero for induced pleuripotent stem cells as well as embryonic cells, it can be associated with cell passage number, it is capable of a heritable age acceleration measure and this principle can also be used for chimpanzee tissues (Horvath, 2013). This has since been actively used as a biomarker of ageing and has laid the groundwork for the development of various other epigenetic clocks such as GrimAge, GrimAge2 and DNAm PhenoAge. A distinctive feature of the Horvath clock or DNAm age is that it ticks after conception until old age. Inspite of the substantial differences in proliferation histories of various tissues in the body, it is able to give proper results with precision that was previously unprecedented. This becomes critical in determining early onset ageing due to diseases such as Werner Syndrome (Gems et al., 2024; Horvath & Raj, 2018). The mechanism of the working of these clocks is still a question under research and from the little that is known, stem cells have been found as primary contributors to these clocks in various parts of the body. They are also responsible for maintaining tissue homeostasis as slow changes occur with age (Raj & Horvath, 2020).

Conclusion

The discovery and establishment of epigenetic changes as markers of ageing in a body are also indicative of the fact that these very changes, if reversed, could lead to a longer lifespan. On partially reprogramming the Yamanaka factor in progeriod mice, metabolic dysfunction and ageing characteristics improved (Zhang et al., 2023). Ageing interventions in present times is largely dependent on Calorie Restriction (CR) and the use of epigenetic clocks to achieve a healthier life could be groundbreaking. The present generation of clocks even though robust have several limitations. The accuracy of these tests are prone to decline as epigenetic drift increases with age. Despite all these shortcomings, innovative research and valuable resources at our disposal hint at the fact that achieving all of this might be possible after all.

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A Molecular Shield Against Heat – Unravelling TCF19's Role in Genome Protection

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Keywords: DNA damage response, TCF19, heat stress, chromatin regulation, ROS

Introduction

DNA, the molecular blueprint of life, is constantly exposed to a wide range of DNA damaging agents from both endogenous sources, such as reactive oxygen species (ROS) and exogenous factors, like ultraviolet radiation or toxins. Unrepaired DNA lesions can result in mutations, genomic instability, and cause diseases, including cancer and neurodegeneration.

To maintain the genome integrity, cells use a highly coordinated DNA Damage Response (DDR) system that detects the lesions, signals, and repairs them. The recruitment of the repair machinery depends on various DDR markers. One of the most important marks is the phosphorylation of histone H2AX to γH2A.X, which helps recruit repair proteins like 53BP1 and BRCA1. Chromatin architecture and epigenetic modifications such as DNA methylation and histone modifications regulate chromatin accessibility and thereby regulate DDR efficiency.

DDR is further regulated by transcription factors with chromatin-reading domains by influencing repair gene transcription and chromatin remodelling.

Transcription Factor 19: An Epigenetic Reader and Transcriptional Regulator

Transcription factor 19 (TCF19) is characterized by two conserved domains: a plant homeodomain domain, or a PHD finger, which recognizes trimethylated histone H3 lysine 4 (H3K4me3), and a Forkhead association, or FHA domain, which bonds to phosphorylated moieties. Through the 2 domains, TCF19 functions as both an epigenetic reader and a transcriptional activator, positioning it to integrate chromatin cues into transcriptional responses.

Functional experiments have shown that TCF19 enhances the transcriptional activation of genes associated with cell cycle progression, proliferation, and the response to DNA damage. For instance, removing its PHD or FHA domains weakens its capacity to boost proliferation in liver and β cells, whereas its excessive expression in pancreatic β cells directly increases DDR and inflammatory gene activity. Consequently, TCF19 functions beyond simple chromatin attachment—acting as an active transcriptional modulator coordinating genes vital for cellular development, persistence, and stress response.

Moreover, its expression is sensitive to metabolic perturbations such as high-glucose exposure, indicating its involvement in adaptive cellular mechanisms. Despite its established role in metabolic stress, its contribution to environmental stress responses, particularly heat-induced genotoxicity, remained unexplored

Heat Stress and Genotoxicity

Heat stress induces widespread protein misfolding, lipid peroxidation, and oxidative DNA damage through elevated ROS production. The resulting lesions—oxidized bases, single-strand breaks (SSBs), and DSBs—can overwhelm repair systems if unmitigated. Cells respond by activating the heat shock response (HSR) and DDR pathways, producing molecular chaperones (e.g., HSP70, HSP90) and initiating repair cascades. However, prolonged or severe thermal stress disrupts genomic stability, leading to apoptosis or senescence.

Role of TCF19 in heat induced genotoxicity

Given the role of TCF19 in transcriptional regulation and chromatin-mediated gene control, understanding the role of TCF19 in maintaining genomic integrity during heat-induced DNA damage by modulating DDR and oxidative stress responses was of prime importance.

To study its role in heat induced genotoxicity, the following experiments were performed.

- HepG2 human hepatocellular carcinoma cells were used to study the function of Transcription Factor 19 (TCF19) in the cellular response to thermal stress. The protein was knocked down in the cells using short hairpin RNA (shRNA) constructs introduced via lipid-based transfection to study its function.
- Both control and TCF19-deficient cells were exposed to 41°C heat stress for 30 minutes, followed by a recovery period at 37°C. Genomic damage and oxidative stress were then assessed using established assays.
- DNA damage was visualized through immunofluorescence staining with an antibody against phosphorylated histone H2A.X (γH2A.X), a marker of double-strand breaks. Nuclei were counterstained with DAPI, and fluorescence microscopy was used to quantify the extent of DNA damage.
- Reactive oxygen species (ROS) levels were determined using a DCFDA-based fluorescence assay, which measures intracellular oxidative stress. Fluorescence intensity readings were compared across control and TCF19 knockdown groups under both normal and heat-stressed conditions.

Discussion

Knockdown of TCF19 resulted in a noticeable increase in γH2A.X foci, indicating elevated basal DNA damage even without heat stress. This suggests that TCF19 is important for maintaining genome stability under normal conditions.

Upon exposure to acute heat stress, control HepG2 cells displayed an expected rise in γH2A.X signal intensity, reflecting activation of the DNA damage response. However, this effect was significantly amplified in TCF19-deficient cells, which exhibited extensive foci formation. The combined impact of heat stress and TCF19 depletion thus revealed a synergistic increase in DNA double-strand breaks, confirming that TCF19 has a protective role during genotoxic stress.

Consistent with this, ROS quantification showed substantially higher oxidative stress levels in cells lacking TCF19, particularly under heat-stressed conditions. These observations imply that TCF19 contributes to cellular antioxidant defence, possibly through transcriptional regulation of stress-response genes.

Conclusion

Collectively these findings suggested that TCF19 acts as a protective factor during heat-induced DNA damage by regulating both the oxidative environment and DNA repair mechanisms. Its depletion leads to higher ROS levels and accumulation of DNA double-strand breaks, emphasizing its role in maintaining genomic stability. Further studies focusing on TCF19's transcriptional targets may provide insight into new strategies for enhancing stress resilience and genome protection.

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Microbial Cell Factories: The Living Factories Powering Tomorrow

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Keywords: Microbial cell factories, Biology, Metabolic engineering, Microorganisms

Introduction

As the world wrestles with climate change and the slow exhaustion of fossil fuels, a silent revolution emerges not in machines, but in microbes. In this race against depletion, Microbial cell factories [MCFs] are emerging as microscopic heroes, having the capabilities of producing valuable compounds such as vitamins, biofuels, and bioplastics representing a cornerstone of this bio-based transition. These factories convert renewable feedstocks like agricultural waste, glycerol, or CO_2 into industrially important chemicals under mild and sustainable conditions, by exploiting various advantages from microbial metabolism. The convergence of synthetic and systemic biology with metabolic engineering has enabled the logical design of microorganisms that perform complex biosynthetic tasks more efficiently than ever before.

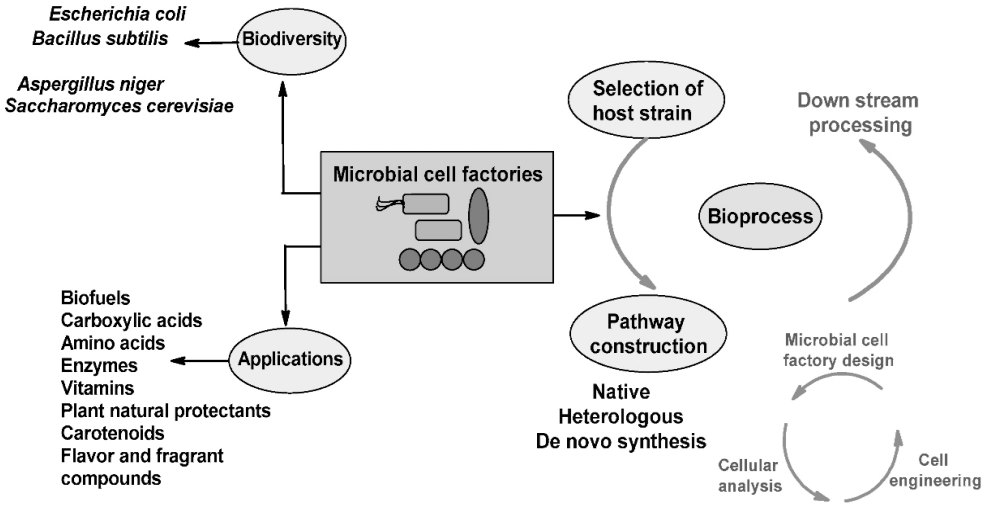

Figure 1: Overall summary of Microbial Cell Factories: industrial processes, applications, and biodiversity
Source: Chaudhary et al., 2024; https://doi.org/10.3390/microbiolres15010018

Microbial Biodiversity the Cornerstone of Microbial Cell Factories

The success of modern biotechnological procedures is based on microbial biodiversity. Among the estimated millions of microbial species on Earth, only a small fraction has been cultured or genomically characterized, yet even this subset offers immense potential for metabolic innovation.

Natural Producers and their Potential

Classical industrial microorganisms such as *Saccharomyces cerevisiae, Escherichia coli,* and *Corynebacterium glutamicum* remains the most widely used production hosts due to their well-understood genetics and robust fermentation performance. However, non-conventional yeasts like *Yarrowia lipolytica* and *Pichia pastoris,* and filamentous fungi like *Aspergillus niger*, are

increasingly utilized for lipid, enzyme, and acid production because of their ability to metabolize diverse substrates and secrete complex proteins.

Furthermore, photosynthetic bacteria and cyanobacteria are being engineered as autotrophic platforms capable of fixing CO_2 directly into biofuels and bioplastics, enabling carbon-neutral or even carbon-negative production.

Genome Mining and Novel Pathways

Metagenomics and genome mining tools such as antiSMASH and MIBiG have expanded access to uncultured microbial diversity. Through the application of these databases, researchers identify biosynthetic gene clusters which encode pigments, terpenoids, and antibiotics, unlocking previously untapped metabolic potential.

Pathway Engineering: Redirecting Metabolism for Value Creation

The core of microbial cell factory design lies in influencing metabolic flux toward target compounds through pathway engineering. Three major strategies—native, heterologous, and de novo synthetic pathway, define this framework.

- Native Pathways- Native pathways exploit the host species' preexisting metabolic networks. For example, *C. glutamicum* naturally overproduces amino acids such as glutamate and lysine, which are enhanced for industrial production through promoter engineering and feedback-resistant enzymes. Similarly, Mannheimia succiniciproducens efficiently converts CO_2 to succinic acid, an important platform chemical, through metabolic rerouting and redox balancing.
- Heterologous Pathways- Heterologous pathway construction involves introducing genes from other species to reconstitute entire biosynthetic routes. A significant achievement demonstrating the economic viability of this method was made when yeast was altered to generate artemisinic acid, the precursor of the antimalarial medication artemisinin. Similarly, *E. coli* expressing nitrile hydratase from *Rhodococcus rhodochrous* can synthesize high yields of niacin (vitamin B_3). In recent years, machine learning-based retrosynthetic tools have accelerated the design of cross-species pathway combinations, minimizing trial-and-error experimentation while improving productivity and efficiency.
- De Novo Synthetic Pathways – De novo pathway construction facilitates the generation of artificial pathways from scratch in circumstances when there is not a natural metabolic pathway. This strategy leverages enzyme promiscuity and computational pathway prediction. For instance, *E. coli* was redesigned to produce 1,5-pentanediol, a polyester precursor, through synthetic pathways combining enzymes from multiple species. Such examples highlight the creative potential of synthetic biology to transform microbes into programmable chemical factories.

Systems Biology and Systems Metabolic Engineering

The integration of systems biology with metabolic engineering has evolved design of MCFs from trial-based manipulation to data-driven optimization.

- Omics-Guided Optimization- Systems-level omics like genomics, transcriptomics, proteomics, metabolomics, and fluxomics, provides a comprehensive insight into cellular networks. These data sets help identify rate-limiting steps, redox imbalances, and metabolic bottlenecks. For example, transcriptomic analysis of *Salvia miltiorrhiza* revealed cytochrome P450s are crucial for tanshinone synthesis, which were successfully expressed in yeast.Similarly, metabolomic studies in vitamin-producing strains have identified key intermediates in thiamine and riboflavin pathways, enabling targeted improvements in vitamin yields.
- Adaptive and Computational Approaches- Adaptive laboratory evolution (ALE) and CRISPR-based multiplexed editing enable rapid strain adaptation to industrial stresses. The

emerging field of systems metabolic engineering combining systems analysis, machine learning, and synthetic control circuits has yielded robust strains those which are capable of withstanding high substrate concentrations, temperature fluctuations, and oxidative stresComputational models now simulate entire metabolic networks to predict genetic perturbations that maximize yield or minimize by-product formation, greatly enhancing process predictability.

- Microbial Consortia and Division of Labor-Complex pathways often overload single cells. Synthetic consortia that are co-cultures of specialized microbes dividing metabolic labour have emerged as efficient solutions. For example, co-cultures of *E. coli* and *Pseudomonas putida* have been used to convert lignin-derived aromatic compounds into biodegradable plastics. Such modular consortia improved utilization of carbon and reduction of metabolic burden, elaborating the concept of distributed biomanufacturing.

Industrial Applications and Sustainability

Microbial cell factories are now integral to the bio-based economy, driving innovation across diverse industries.

- Vitamins and Nutraceuticals: Microbial fermentation has replaced chemical synthesis in the large-scale production of riboflavin, vitamin B_{12}, and vitamin K_2 due to lower environmental impact and higher stereochemical purity.
- Biofuels: Engineered *Clostridium* and *Saccharomyces* species produce ethanol, butanol, and fatty acid-derived biodiesels, providing renewable alternatives to fossil fuels.
- Biopolymers and Plastics: *Cupriavidus necator* and *Pseudomonas putida* synthesize polyhydroxyalkanoates (PHAs) and polylactic acid precursors, offering biodegradable replacements for petrochemical plastics.
- High-Value Chemicals: MCFs produce organic acids (succinic, lactic, and citric acids), terpenoids, and aromatic flavor compounds that serve as eco-friendly replacements for chemical synthesis.

Microbial systems consistently exceed traditional petrochemical production in sustainability parameters like carbon efficiency, energy input, and waste reduction, highlighting the crucial role MCFs play in reaching global carbon neutrality targets.

Conclusion

Microbial cell factories stand at the nexus of nature's ingenuity and human innovation—a living testament to the harmony between biodiversity, engineering precision, and sustainability. From vitamin biosynthesis to bioplastic production, they are redefining industrial chemistry through biological design. The integration of systems biology, machine learning, and synthetic modularity continues to expand the capacity of microbes as programmable production systems. Future directions include the deployment of AI-assisted pathway optimization, synthetic microbial ecosystems, and bio foundry-based automation for rapid strain prototyping.

In this unfolding bio-industrial renaissance, microbial cell factories emerge not merely as instruments of production but as symbols of a sustainable future—where life itself becomes the engineer, and renewable resources are transformed into the essential molecules that sustain and inspire modern civilization.

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Exploring Chirality: From Homochirality to the Rise of Mirror Life and its Biosafety Implications

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Keywords: Homochirality, Synthetic Biology, Spiegelmers, Biosecurity, Immune Evasion

Introduction

Life on Earth operates under a strict molecular rule known as homochirality. Although most biological molecules can exist in two mirror-image forms (enantiomers), life relies on only one orientation: left-handed (L-) amino acids for proteins and right-handed (D-) sugars for DNA and RNA. This preference for a single "handedness" remains one of biology's enduring mysteries, first recognized by Louis Pasteur in 1848. Recent progress in synthetic chemistry and genetic engineering has brought scientists closer to creating "mirror life", a hypothetical form of life built from molecular components that are the mirror images of those found in all known organisms. This article discusses the breakthroughs that have made this idea scientifically feasible, the potential applications, and, most importantly, the serious ecological and health risks that demand immediate and global precaution.

Molecular Chirality

Most biological molecules are chiral, meaning they cannot be superimposed on their mirror image. These mirror-image molecules (enantiomers) are produced equally in standard chemical reactions, forming a racemic mixture. Even though enantiomers share the same chemical structure, they rotate light differently and often have notably distinct biological effects. DNA, RNA, sugars and amino acids are all chiral. Earth's life exclusively uses right-handed nucleic acids and left-handed amino acids. Natural organisms and mirror molecules fail to interact when their chirality is mismatched, which means receptors on immune cells, for example, cannot recognize a mirror bacterium. The unique properties of these mirror components have wide applications in medicine, agriculture, and manufacturing, but creating an entire mirror organism remains an extreme technical challenge.

Reversing Life's Handedness

Mirror proteins and genetic material could be created by substituting natural left-handed amino acids and right-handed nucleic acids with their opposite enantiomers, creating mirror versions of lifeforms. To address the chirality of cell membranes, geneticist George Church proposed employing achiral fatty acids instead of mirror phospholipids. Recent developments in synthetic biology, such as the creation of synthetic bacteria (2010) and viruses (2002), indicate that the possibility of creating complete mirror cells is growing. Notably, in 2016 scientists were able to successfully synthesize mirror-image proteins such as polymerase.

Synthetic Breakthroughs: Mirroring the Central Dogma

There are two suggested approaches to construct mirror life: a top-down approach involving the chiral inversion of a living bacterial cell's components, or a bottom-up approach focusing on synthesizing and assembling all mirror-image molecules from scratch. Important discoveries have focused on the core dogma machinery, specifically DNA polymerase, the enzyme necessary for genetic material copying. A high-fidelity mirror-image Pfu polymerase capable of storing stable information in L-DNA was developed after the initial work successfully synthesized the mirror-image polymerase from the African swine fever virus. Recently, scientists reported a two-fold increase in the synthesis yield of the mirror-image

DNA polymerase Dpo4, which helped to overcome a significant bottleneck—the difficulty of synthesizing large, complex mirror proteins. The persistent challenge of building complex mirror structures has made the ribosome the central pursuit of "mirror life" research. This technical leap made the synthesis of the most complex component, the mirror ribosome (a structure of three RNAs and more than 50 proteins), more feasible by employing a "one-pot multi-segment condensation strategy" to produce larger mirror-image proteins more effectively.

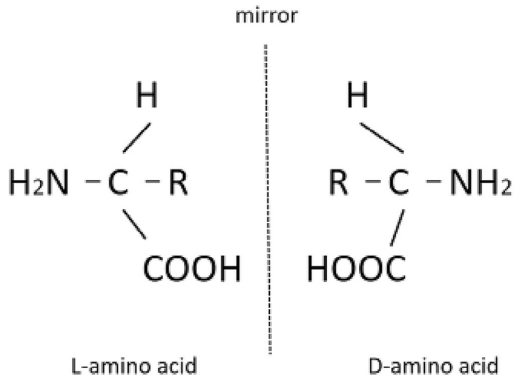

Figure 1: Concept of Molecular Chirality. The L- and D-forms of amino acids are mirror images that cannot be superimposed on one another, known as enantiomers. In all known forms of life on Earth, proteins are composed solely of L-amino acid

Pharmacological and Industrial Applications

The primary motivation for creating mirror life lies in its potential pharmacological and industrial applications that exploit homochiral immunity. Mirror molecules exhibit a profound resistance to biological degradation because they are less susceptible to the body's natural enzymes and immune systems, resulting in low immunogenicity and a longer half-life for drugs. Spiegelmers, or L-aptamers, are mirror-image nucleic acid ligands that provide the best example of this. Spiegelmers have a substantially longer therapeutic half-life in the bloodstream than natural D-aptamers because they are nuclease-resistant. For instance, the L-RNA Spiegelmer Emapticap pegol has demonstrated safety and efficacy in Phase II clinical trials for diabetic nephropathy. Mirror microbes, which are naturally resistant to infection by any natural-chirality pathogens, could be employed in bioreactors to generate these valuable mirror-image biomolecules on an industrial scale.

Biosafety Challenge: Immune Evasion and Ecological Collapse

The creation of mirror life represents the greatest biosecurity challenge, with a broad scientific coalition warning it poses "unprecedented and irreversible harm". The risk arises from the fact that mirror organisms are fundamentally foreign, necessitating a complete re-evaluation of safety protocols. Immune evasion is the main threat to human health. Chiral-dependent binding is the only way our bodies, which are composed of D-sugars and L-amino acids, can identify dangers. The opposite chirality would make a mirror bacterium molecularly invisible, like attempting to fit a left hand into a right-handed glove. Due to this mismatch, infections could spread unchecked and possibly become fatal in humans, animals, and plants since immune receptors and antibodies would not be able to recognize them. This threat is amplified by pervasive antibiotic resistance. Since most of our existing antibiotics are themselves chiral, they rely on specific "handedness" to target bacterial mechanisms. Mirror bacteria would render these drugs useless, leaving only a handful of achiral alternatives and creating an Antimicrobial Resistance (AMR) threat of unprecedented magnitude. The effects on the environment are equally disastrous. Predators such as viruses (bacteriophages) and microscopic protists (amoebae) control bacterial populations in nature by limiting their growth. Mirror organisms would possess a homochiral immunity to these natural controls because predation relies on chiral-mediated interactions. Imagine an invasive species with no natural predators: that is what a mirror microbe would be. If left unchecked, it would quickly become an extremely successful invader that would disrupt the planet's nutrient cycles and destroy natural bacteria, resulting in the extinction of many species and complete ecological collapse. The biggest concern is that the displacement of fundamental soil and ocean microbes responsible for fixing nitrogen and carbon would catastrophically

dismantle the base of the global food web, threatening primary producers and eventually all higher life forms.

Conclusion

Taken together, advancements in synthetic biology have introduced the unprecedented possibility of reversing life's molecular chirality, yet this capability presents a fundamental conflict between scientific innovation and planetary biosafety. Although mirror enzymes have considerable potential for use in medicine by enabling stable, nuclease-resistant treatments like Spiegelmers, synthetic mirror life poses major biosafety challenges—and, if uncontrolled, could even become a planetary threat. The existential threats posed by self-replicating mirror organisms greatly exceed any potential benefits. Such organisms could evade immune detection, exhibit broad antibiotic resistance, and cause irreversible ecological damage, exceeding the capabilities of existing containment strategies. Therefore, the scientific community bears the responsibility of ensuring absolute safety since the limited prospective benefits cannot justify the creation or potential release of mirror life.

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Synthetic Blood Substitutes: Redifining Haematology?

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Keywords: Haemoglobin vesicles, Artificial blood, Emergency medicine, Oxygen carriers

Introduction

What if blood-body's most essential vascular fluid, could be engineered within a laboratory? This, once a speculative vision confined to the theory of biomedicine, is now a tangible reality as science advances toward creating synthetic blood substitutes capable of sustaining life without donors. This breakthrough addresses the critical challenges of donor shortages, blood -type incompatibility, limited shelf life and the risk of transfusion -transmitted infections, offering a universally compatible and safe alternative for therapeutic use.

In blood, the primary role of erythrocytes is the transport of oxygen mediated by haemoglobin via a tightly regulated mechanism. However, replicating this remarkable efficiency outside the human body has been a scientific challenge, taking into account the oxygen-carrying thermodynamics, stability, redox environment and minimizing irreversible MetHb formation. Despite these complexities, the demand for safe and universally compatible blood continues to exceed supply, underscoring the urgent need for blood substitutes. The shortage creates life-threatening situations during surgeries, trauma-induced hemorrhages, acute coagulopathies, battlefield conditions, and in remote locations where timely access to blood is crucial. Limited storage conditions, donor incompatibility, contamination risks and short shelf life further intensify the challenge. To address these limitations, scientists developed haemoglobin-based oxygen carriers (HBOCs) as semi-synthetic surrogates for blood.

What are haemoglobin vesicles (HbVs)?

Haemoglobin vesicles (HbVs) are a specialized form of cellular structured haemoglobin-based oxygen carriers. These vesicles encapsulate a purified, concentrated and chemically modified haemoglobin solution within a liposomal membrane. The membrane is composed of phospholipids, which shield the toxic effects of molecular haemoglobin. This lipid membrane of the vesicles somewhat resembles a biological membrane, enhancing stability. The inclusion of cholesterol to phospholipids stabilises the packaging of membrane and negatively charged lipids reduce lamellarity, leading to higher encapsulation efficiency. Haemoglobin vesicles (HbVs) typically have a diameter of about 250 nm, and contain a haemoglobin concentration of around 10g/dL, which is notably higher than that found in human red blood cells. These haemoglobin-based oxygen carriers mimic the function of natural red blood cells, offering efficient oxygen delivery, promising a great therapeutic alternative to conventional blood transfusion.

Preparation method of Haemoglobin vesicles

HbVs offer multiple advantages over conventional transfusions. They are synthesised using expired donor blood, older than 3 weeks and devoid of any blood type antigens. The Preparation process involves a series of complex and carefully regulated steps.

- The haemoglobin extracted from expired blood is first subjected to pasteurisation at 60°C and then purified by ultrafiltration, resulting in a sterile, virus- free solution.

- To stabilise and prevent further oxidation, this purified haemoglobin is converted to carbonyl-haemoglobin (HbCO) at a concentration of approx. 40g/dL. This conversion maintains haemoglobin in its ferrous (Fe^{2+}) state, thereby preventing the formation of methaemoglobin (MetHb).
- A lipid mixture is prepared using powdered lipids containing saturated and negatively charged phospholipids, cholesterol and PEG-conjugated lipids, enhancing membrane stability and encapsulation efficiency.
- The carbonyl-haemoglobin (HbCO) previously prepared is mixed with the powdered lipid using a rotation-revolution mixer for approximately 10 mins to form a uniform viscous paste, enhancing encapsulation efficiency several fold.
- The high viscosity of the Hb-lipid mixture induces frictional heat during kneading, raising the temperature and thereby enhancing lipid dispersion and vesicle formation encapsulating haemoglobin.
- These vesicles are stabilised by maintaining optimal temperature and pH conditions to prevent denaturation and leakage.

Handedness Advantages and limitations of HbVs

Haemoglobin vesicles are universally compatible as they are made from purified, antigen- free, expired donor blood, eliminating the risk for blood type matching, transmitting blood-borne infections like HIV or Hepatitis and transfusion reactions. Unlike donated blood, which expires within 42 days, this synthetic substitute can be stored up to two years at room temperature and five years refrigerated increasing the shelf-life upto 30 folds. Encapsulating the haemoglobin increases their circulation time up to 24h allowing sustained availability to cells, tissues and organs without systemic risk. These vesicles can be manufactured at a large scale in vitro, sterilised and stored as small volume units for a long period. They can be easily reconstituted and administered on demand in emergency situations, effectively mimicking the natural functions of blood to counter severe blood loss.

Despite these advantages, haemoglobin vesicles face notable limitations. The preparation process is quite complex and resource-intensive, hindering large-scale production and increasing manufacturing costs. Even though encapsulation extends haemoglobin's lifespan, the circulation time of HbVs (~24 hours) is still much shorter than that of native RBCs (~120 days). Rapid clearance of the vesicles by the reticuloendothelial system, especially the liver and spleen, further limit their sustained use. Ongoing studies are focused on addressing these challenges to enable the clinical application of hemoglobin vesicle (HbV) formulations and similar liposome-based hemoglobin delivery systems.

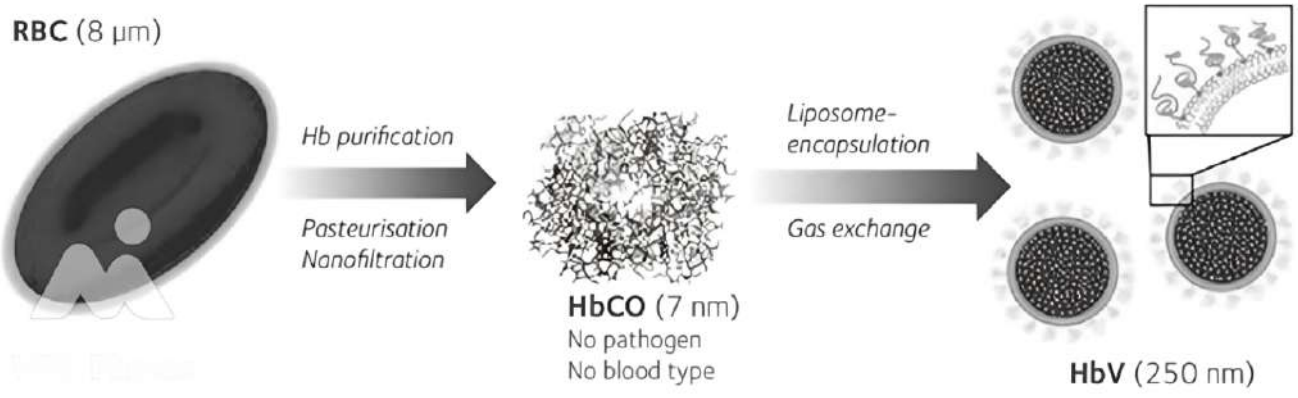

Figure 1: Schematic illustration of haemoglobin vesicles being prepared from expired haemoglobin through a process of purification followed by liposomal encapsulation (Sakai et al., 2022)

Conclusion and Future Prospects

Haemoglobin vesicles have successfully completed initial human trials in the year 2022, where 12 healthy individuals were administered a 100 ml dose of the synthetic vesicles, and notably, no serious side effects were observed. Encouraged by these results, researchers now plan to test for the efficacy and safety of larger doses, upto 400 ml. If the next phase is successful and fulfils the desired requirement of circulation and oxygen delivery, scientists aim to scale up production and enable practical clinical use by 2030, bridging the gap between supply and demand for safe blood substitutes. Some versions of this blood will include platelet substitutes for clotting, offering coagulation as an additional advantage. Further researches continue for newer HBOC designs as encapsulated Hb vesicles. With ongoing trials and experiments replicating this intricate system in vitro, will revolutionise emergency medicine, redefining the boundary between biology and technology. Soon, a world will emerge where every hospital, ambulance, and disaster zone has instant access to safe, ready-to-use blood, turning dream into reality.

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Protein Hitmen: The PROTAC Revolution in Drug Discovery

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Keywords: Targeted Protein Degradation, PROTACs, Polyubiquitination

Introduction

The application of small-molecule medications to inhibit active protein targets has revolutionised therapeutic approaches for numerous diseases over the past three decades. However, drug resistance has always posed a significant challenge for classical inhibitors. While small molecules have revolutionised treatment possibilities for numerous hard-to-treat ailments, varying levels of resistance to their mechanisms can develop over time, leading to the recurrence of disease symptoms. This often results from an increase in the expression of the protein through transcription and translation, which is why targeted protein degradation (TPD) is attracting significant attention due to its ability to therapeutically influence proteins that are challenging to target using conventional small molecules. Some of these proteins have proven difficult to inhibit because their active sites consist of wide, shallow pockets that are hard to target with small molecules; others have 'smooth' surfaces that present few opportunities for small molecule binding. Many of these protein targets play crucial roles in cancer and various other diseases, thus maintaining their importance in therapeutic contexts.A concerning statistic is the limited number of drug targets, which currently comprises only 20–25% of all protein targets under investigation for significant therapeutic potential. As a revolutionary and innovative technology, PROteolysis TArgeting Chimeras (PROTACs) have proved to be of significant interest from both academia and the industry.

Mode of Action

PROTACs consist of a heterobifunctional structure that includes three components: an E3 ubiquitin ligase ligand, a ligand for the protein of interest (POI), and a linker that connects the two ligands. The POI ligand specifically binds to the target protein, essentially 'hijacking' it and bringing it into contact with the attached E3 ligand. Subsequently, the E3 ligase ligand attracts an E3 ubiquitin ligase from the cytosol to the PROTAC complex that includes the protein of interest, with the linker region serving to link the POI and E3 ligase ligands. Thus, the protein of interest and the E3 ligase are artificially positioned near each other, enabling the polyubiquitination of the target protein, which leads to its degradation by the proteasome. PROTACs have the capability to degrade virtually any protein target, including those not typically subject to ubiquitination. Existing literature concludes that more than 50 different proteins can potentially be degraded using PROTAC technology. Current targets include protein kinases, nuclear receptors, and transcription factors, with numerous additional targets in various stages of development.

Why PROTACs?

The mechanism of action (MoA) and event-driven pharmacology characteristic of PROTACs set them apart from traditional inhibitors, which generally operate on a one-to-one basis with the protein of interest (POI) and whose pharmacological effects depend on stoichiometry and typically entail interactions with a catalytic site (occupancy-driven phenomenon). Once the target protein is eliminated,

PROTACs can separate and be reused for the degradation of another protein target. This means that the PROTAC not only endures the ubiquitination and destruction processes of the target protein but also remains effective, allowing it to participate in several additional rounds of target degradation. This enzymatic, event-driven mechanism of action reduces the requirement for administering a high dosage of the drug.

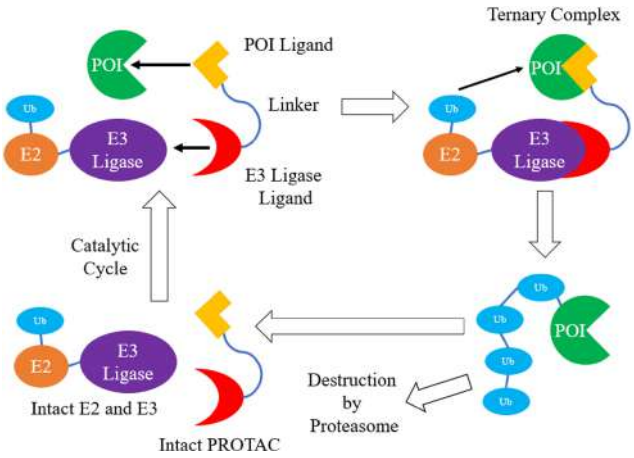

Figure 1: Structure and Mechanism of Action of PROTACS
Source: Graham, 2022

The target is exposed to the drug for a shorter period, just enough to recruit an E3 ligase and trigger the ubiquitin-proteasome system, which minimizes the chances of drug-resistant mutations emerging in the target compared to conventional small-molecule compounds.

A primary emphasis in drug development is the enhancement of drug specificity and selectivity. This is essential to avoid undesirable side effects caused by “off-target” interactions that frequently happen with traditional drugs administered at higher doses . Within the cell, there are numerous alternative binding partners for a drug apart from the intended target, including various proteins, DNA, lipids, sugars, metabolites, and other small molecules .Owing to the bifunctional nature of PROTACs, both the ligand for the protein of interest (POI) and the ligand for the E3 ligase can be fine-tuned to enhance target selectivity. For instance, this approach has led to the creation of a PROTAC that degrades cyclin-dependent kinase 9 (CDK9), which can be utilized for effectively treating cancers characterised by increased activity of this protein. Moreover, the CDK9 PROTAC was demonstrated to have no impact on other cellular functions that depend on the activity of various CDK isoforms. The generation of these highly selective and specific PROTACs is achievable through a comprehensive screening method, which involves iterative testing and adjustment when pairing different POI ligands with different E3 ligase ligands until a successful combination is identified.

Clinical aspect

In 2019, the first PROTAC molecules began clinical trials; by 2020, these trials offered the first clinical proof-of-concept for this approach against two well-known cancer targets: the oestrogen receptor (ER) and the androgen receptor (AR).

One of the first PROTACs to enter clinical trials is ARV-110, developed by Arvinas. This compound targets the androgen receptor (AR), a crucial factor in prostate cancer progression. ARV-110 is currently being assessed in individuals with metastatic castration-resistant prostate cancer (mCRPC), especially in those who have become resistant to conventional AR inhibitors. Early clinical data has indicated promising signs of safety and effectiveness, particularly in patients with specific AR mutations that render them less responsive to standard treatments. Another significant candidate is ARV-471, also created by Arvinas, which targets the oestrogen receptor (ER) in oestrogen receptor-positive (ER+) breast cancer. ARV-471 has demonstrated strong ER degradation in preclinical studies and is now undergoing Phase II clinical trials, showing encouraging results when used in combination with CDK4/6 inhibitors. This marks an important advancement in the treatment of hormone-driven cancers, especially in cases where resistance to endocrine therapy has developed.

Conclusion

PROTACs offer new hope for treating various challenging diseases. Given their clear advantages over traditional small molecule inhibitors as

discussed, these compounds could transform the approach to selectively eliminate even drug-resistant protein targets while significantly lowering side effects. Furthermore, PROTACs have the capacity to target previously considered 'undruggable' protein targets due to their innovative mechanism of action. Nevertheless, PROTACs still need significant development to refine their pharmacological attributes in vivo, making the forthcoming years an exhilarating period for PROTAC drug development.

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Biofabrication: Building Tomorrow's World with Living Materials

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Keywords: Biofabrication, Synthetic Biology, Living Materials, Sustainability, Biomaterials

Introduction

As science transcends from discovery to design, biology is no longer confined within Petri dishes—it is reshaping the foundations of our physical world. From clothing and furniture to buildings and machines, every aspect of human life depends on materials that often harm the environment. **Biofabrication**, an emerging discipline rooted in molecular biology and synthetic biotechnology, seeks to replace these materials with living, self-healing, and sustainable alternatives.

By integrating molecular design with engineering and environmental consciousness, biofabrication exemplifies the very spirit of modern biology—where the smallest molecular interactions can redefine the largest human structures. It represents a tangible step from the microscopic realm of cells to the macroscopic scale of planet-wide sustainability

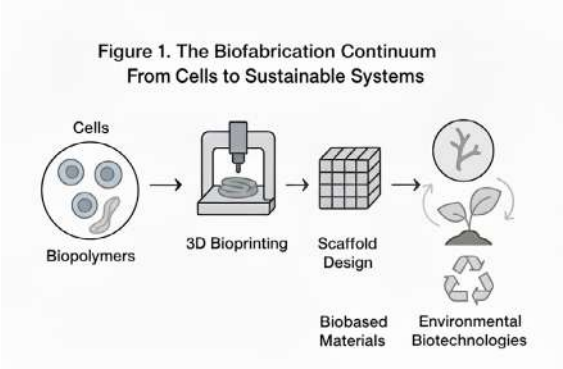

Figure 1: The Biofabrication continues from cells to sustainable systems

The Molecular Foundation of Biofabrication

The journey of biofabrication begins at the molecular level, where cells are treated as programmable factories. Advances in synthetic biology and genetic engineering now allow scientists to design microorganisms that synthesize biopolymers, pigments, and structural proteins.

For instance, bacterial cellulose, produced by *Komagataeibacter xylinus*, is being explored as a renewable alternative to leather and plastic. Similarly, mycelium, the root-like network of fungi, can be cultivated into lightweight, durable, and biodegradable building materials.

These biological systems are guided by DNA-level instructions—engineered through CRISPR editing, metabolic rewiring, and computational gene design—to produce materials that are not only strong and flexible but also capable of growing, repairing, and adapting.

Engineering with Life: The Concept of Living Materials

Traditional materials are static; once created, they degrade over time. In contrast, living materials retain the capacity to sense and respond to their environment. This paradigm shift merges architecture with biology, giving rise to structures that can heal cracks, absorb pollutants, or regulate humidity on their own.

A remarkable example is self-healing concrete, where spores of Bacillus subtilis are embedded within the matrix. When cracks appear, water triggers the spores to germinate and precipitate calcium carbonate, sealing the damage naturally. Likewise, genetically engineered bacteria can be integrated into textiles that change colour in response to toxins or pH changes.

These innovations blur the boundary between the

built and the biological, turning passive materials into living collaborators.

From Petri Dish to Planet: Sustainable Bioarchitecture

Biofabrication not only replaces synthetic materials but also redefines the sustainability of global industries. Conventional material production, such as cement, steel, and plastic, accounts for nearly 40% of global CO_2 emissions.

Biofabrication provides an eco-friendly alternative by utilizing renewable feedstocks and microbial cultures, rather than fossil fuels.

Startups like Ecovative grow mushroom mycelium to create biodegradable packaging and furniture. Modern Meadow uses engineered yeast to produce collagen-based bioleather, reducing animal slaughter and chemical waste. Even space agencies like NASA are exploring biofabricated habitats that can self-grow using Martian dust and engineered microbes.

Thus, what begins in a Petri dish can scale up to entire planetary systems, linking molecular design with environmental harmony.

The Technological Convergence Behind Biofabrication

Biofabrication thrives at the intersection of biology, computer science, and materials engineering.

- **3D Bioprinting:** allows precise layering of cells and biomolecules to produce tissues, prosthetics, and organ scaffolds.
- **Computational Modelling:** simulates cellular behaviour to predict mechanical strength, metabolic efficiency, and sustainability outcomes.
- **Synthetic Gene Networks:** enable custom biological "machines" that express desired properties—such as elasticity, fluorescence, or carbon capture.

These tools transform biofabrication into a truly interdisciplinary enterprise, where scientists, engineers, and designers co-create with nature.

Challenges, Ethics, and Future Prospects

Despite its promise, biofabrication faces challenges in scalability, cost, and public acceptance. Maintaining living systems in industrial settings requires stable bioreactors, controlled conditions, and biosafety protocols. Moreover, questions arise about ownership and ethics—if we build with life, who ensures its welfare and containment?

Yet, the potential far outweighs the limitations. The next frontier involves integrating artificial intelligence to optimize biological production, biosensors to monitor environmental adaptation, and synthetic ecosystems that self-balance and self-renew.

The ultimate vision is a world where buildings breathe, fabrics grow, and cities sustain themselves, a true merging of life and design.

Conclusion

Biofabrication represents the harmonious fusion of molecular biology, creativity, and sustainability. It exemplifies the evolution of biotechnology from experimental curiosity to planetary necessity. By constructing living materials from engineered cells, we are not merely creating substitutes—we are reimagining the material basis of civilization.

In the grand journey "from Petri to Planet," biofabrication stands as a symbol of responsible innovation—a testament to how molecular knowledge can heal, rather than harm, our shared home.

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EV-miRNA: Tiny Messengers Shaping the Future of Precision Medicine

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Keywords: Extracellular Vesicle (EV), microRNA, Therapeutic Delivery, Precision Medicine

Introduction

In the molecular symphony of life, small RNAs emerged as an ancient feature of cellular biology which is found in all three domains of life from bacteria to eukarya. It was found that these small RNAs were primarily evolved as a defense mechanism against foreign nucleic acids specially guiding the effector proteins to selected target nuclei acids via antisense-complementarity a phenomenon recognized as RNA-based interference (RNAi). This system consists of two components, a specific target sequence and effector protein that mediates downstream effects with varying outcomes (L, 2020).

Since the discovery of the first microRNA, lin-4, in 1993 by Ambros and Ruvkun groups, brought us to a new zone of thoughts about its potential constraints that is its instability and delivery challenges. The biogenesis and mechanism of action of miRNAs are extensively discussed in various publications and journals over the years. The focus of this topic lies on how we can target these miRNAs as a curative for specific human diseases caused due to aberrant gene expression.

What are EV miRNAs and Why they Matter?

Extracellular vesicles (EVs) are membrane bound, nanosized vesicles that carry cargo which includes DNA, RNA, Proteins. These vesicles are released from the cells as a form of intracellular communication. These EVs are broadly classified into four main types- micro vesicles (MVs), Exosomes, oncosomes and apoptotic bodies. Microvesicles bud directly from plasma membrane and ranges from 100-1000nm in diameter. Exosomes are formed by fusion of multivesicular bodies and ranges from 40-120nm in diameter. Membrane protrusions give rise to large EVs called Oncosomes which are primarily produced by malignant cells. Dying cells, however release large apoptotic bodies more abundant than MVs and exosomes under specific conditions. (MIKOŁAJ P. ZABOROWSKI, 2015)

RNA transported by EVs is predominantly shorter in size 100-200nts. The structural attributes of EVs plays a crucial role in stabilizing miRNAs during transport, protecting them from dynamic extracellular environment. The phospholipid bilayer acts as physical barrier by preventing it from degradation by RNases that threaten naked miRNAs in circulation. Simultaneously, sphingolipids, cholesterol, tetraspanins, protect miRNAs from oxidative stress and immune detection. Additionally, EV-associated proteins like Argonaut 2, Y box protein 1, selectively stabilize miRNAs. These notable properties make EVs as promising vehicle for miRNA-based therapies.

Biogenesis and Loading: How miRNAs Get Packaged into EVs

Cells have evolved specific mechanisms for selectively loading and targeting miRNA to specific cells via EVs. The endosomal sorting complex required for transport (ESCRT) pathways plays a vital role in processing, facilitating the formation of multivesicular bodies where miRNAs are loaded before released as EV-miRNAs. ESCRT-II forms filaments that promote membrane bending and sever the exosomal neck from membrane (W.M. Henne). There are ESCRT-independent pathways that sort based on motifs or associated proteins like Y box 1 binds to miRNAs for sorting, resulting in

EVs enriched in proteins that regulate cell sorting, biogenesis and targeting (Shurtleff MJ, 2016).

The Journey and Uptake: How EV miRNAs Reach Target Cells

Although some extracellular miRNAs are considered as by-products of cellular activities, like cell injury or cell death, there are increasing evidences suggests that release of these extracellular miRNAs is a regulated process. In neuroendocrine cells, miRNAs in large dense-core vesicles (LDCVs) are released by exocytosis through vesicle fusion, and this process is mediated by SNARE complex and accelerated by Ca^{2+} stimulus. The mechanisms of extracellular miRNA uptake are not well understood till date. It has been proposed that vesicle-associated extracellular miRNA may enter cells by endocytosis, phagocytosis, or direct fusion with the plasma membranes. Few studies have shown that miRNA enter recipient cells by endocytosis and micropinocytosis via clathrin dependent or caveolae dependent or lipid rafts dependent pathways (Wei F, 2017).

Therapeutic Potential: Tiny Vesicles, Big Potential

EVs can be sourced from a variety of cell populations, such as stem cells and their progeny, including MSCs, Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), each with distinctive regenerative and immunomodulatory potential. MiRNA-enriched EVs from stem cells offer promising results in regenerative medicine without risk of using whole cells, opening doors where traditional cell-based therapies faced limitations.

A diverse array of loading techniques is advancing for the use of EVs as vehicles for therapeutic miRNAs. Together with the advances in EV engineering, from optimized loading methods to parent-cell modifications, the therapeutic potential of EVs is expanding across various disease models. (Upadhya R)

Analytical and Technological Advances

A major bottleneck in EV miRNA research is the isolation and detection of EVs. Differential ultracentrifugation (UC) has become classical method for EV enrichment but due to its expensive protocol cannot be adopted to diagnostic purposes. A better approach is use of polyethylene glycol (PEG) for enrichment of EVs followed by Nanoparticle Tracking Analysis (NTA) (Zoraida Andreu, 2016).

There are some useful databases such as ‘miRbase’ from NCBI, and web-interfaces such as ‘EV-miRNA’ (Chun-Jie Liu 1, 2018) that gives a comprehensive investigation of miRNA expression profiles and sample information of EVs from different sources such as blood, breast milk etc. as wells as miRNA annotations including miRNA expression in EVs and TCGA cancer types.

Challenges and Future Directions

Although EV miRNAs hold great promise, several challenges and open questions must be addressed. The inherent heterogeneity of EV populations such as variations in size, molecular composition and functional properties can generate inconsistent therapeutic outcomes which demands for refined isolation and characterization of protocols.

As miRNA can influence the expression of numerous genes, these therapies carry the risk of off-target effects. To mitigate these effects researchers are exploring methods to engineer EVs with specific targeting receptors to direct them towards target cells or tissues (Vandergriff A, 2018).

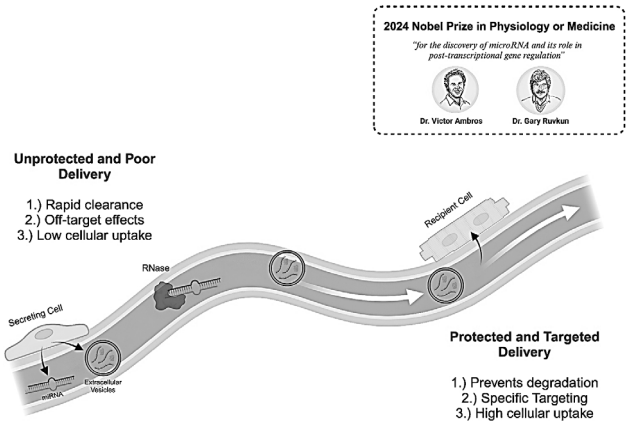

Figure 1: Encapsulating miRNA in Extracellular vesicles for therapeutics (Vanessa YiRan Li, 2025)

The complex nature of EVs presents significant regulatory challenges from agencies like FDA and EMA to classify EV-based miRNA therapies within

existing framework. Despite these hurdles, in 2019 FDA announces exosomes used in human disease treatment to be classified as 'drugs and biological products'.

Conclusion: From messengers to medicine

EV-based miRNA therapies offer a promising approach to advancing personalized medicine by customizing EVs to deliver miRNA profiles tailored to individual patients. While full potential of EV-miRNA as precision medicine is still being explored, this progress signals the emergence of a new era of individual therapies that are closely related to individual's unique biological profile.

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What are Species?

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Keywords: Phylogenetics, Evolution, Cloning, Sperm Parasitism

Introduction

One of the fundamental questions in biological thought has been how to define a species. This has shaped the very basis of our modern science. Darwin and Wallace thought of species in terms of their phenotype, now called the morphospecies concept [1]. Modern Evolutionary synthesis, particularly the pioneering works by Ernst Mayr in the 1940s, has led to the idea of biological species. According to this definition ,species are groups of actually or potentially interbreeding natural populations, which can potentially interbreed. Thus reproductive isolation is the defining feature for species [2]. In this study, the researchers found that one species of ant, *Messor ibericus* could clone males of a completely distinct species, Messor structor. This finding challenges our basic understanding of the species concept. Moreover, it also questions the modes of reproduction which we have known, opening the door for further research into the this fascinating mode of reproduction.

Methods

Researchers found that on the Island of Sicily , off the Italian Coast, in colonies of *M. ibericus* , two phenotypically different ant types were observed. To confirm if the colonies contained different species, a phylogenetic tree was constructed – it was concluded that both *M. ibericus* and *M. structor* are present in the *M. ibericus* colonies. This was very surprising , because *M. structor* wild populations are not found on the island of Sicily [3].

To analyse this bizarre geographical distribution of these ants, far away from their expected colonies, another phylogenetic analysis was performed, this time using the mitochondrial genome of *M. structor*. To identify the paternal species, a similar analysis was performed with the nuclear DNA. Moreover ,another phylogenetic analysis was performed on the mitochondrial and nuclear DNA of a wild type *M. structor* colony in it's native range away from Sicily.

Results

All hybrid workers showed mitochondrial DNA similar to *M. ibericus*, suggesting that *M. ibericus* passed on its mitochondria to these hybrid males. Thus, the hybrid workers in the colony shared the same mother [3]. All hybrid workers showed paternal DNA similar to *M. structor*, suggesting that it had inherited nuclear genes from the paternal lineage [3]. The nuclear and mitochondrial DNA sequences of wild type populations matched, unlike those individuals living in the *M. ibericus* colonies,where there was a mismatch between nuclear and mitochondrial genes [3].

Thus there were two distinct divisions of the nuclear phylogeny of *M. structor* - one subdivision corresponded to a clonal lineage, consisting exclusively of nearly identical *M. structor* males, all found within *M. ibericus* colonies and carrying *M. ibericus* mitochondria. Another was a 'wild-type' ,which was a lineage of *M. structor* in their own colonies [3]. These results implied that *M. ibericus* depends on hybridization for worker production. Here, *M. ibericus* queens strictly depend on males of *M. structor*, which is a different, non-sister species [3].

Discussion

These two species have diverged a long time back, around 5 million years ago. When the *M. structor* ants cloned by the Iberian harvester ants were put

into a regular *M. structor* colony, the insects were killed for being foreign invaders, though having phenotypic similarities. This was because, in the cloned ants, the pheromones present were similar to that of *M. ibericus* species rather than the wild type *M. structor* species [3].

Ants are organisms known for their novel reproductive systems. In some species of ants, sperm parasitism is prevalent, in which a queen mates with males of a different species to produce sterile worker offspring and with males of the same species to produce queens. Examples include some types of harvester ants (members of genus *Pogonomyrmex*) and fire ant (members of the genus *Solenopsis*) [4].

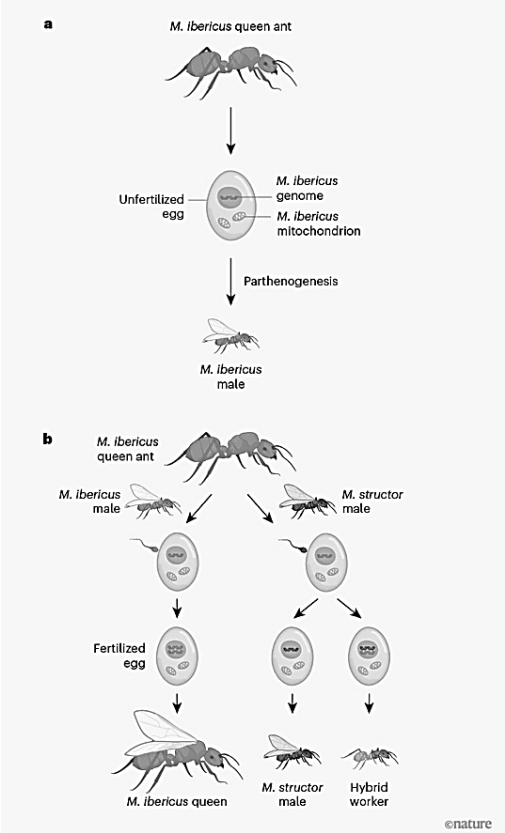

Figure 1: A summary of the Reproduction system of *M. ibericus*

Source: https://www.nature.com/articles/d41586-025-02524-8

The reproductive system in question might have started out the same way, with queens in *M. ibericus* colony mating with males of *M. structor* to produce worker ants. Eventually, the queens could now produce males with the *M. structor* genome directly using eggs fertilized with *M. structor* sperm. By mating with these males, *M. ibericus* queens could continue to produce *M. structor* males even without the presence of *M. structor* females, essentially 'domesticating' the *M. structor* genome [3].

Conclusion

This sort of reproduction is yet unknown in the natural world. Here, the domesticating species (*M. ibericus*) is directly cloning the domesticated one (*M. structor*) through the cytoplasm of its own eggs. Thus, a foreign genome is being replicated inside the own cytoplasm. This indeed reminds us of the endosymbiotic origin of the mitochondria [5]. The population of clonal males can thus be thought of as organelles, but at the level of organism [6].

This unique form of reproduction ,which challenges our basic understanding of the species concept, has been termed as 'Xenoparity' by the authors [5]. This name is completely new to science. It would be extremely interesting to know if there are more such examples of Xenoparous organisms hidden away in nature.

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Delving in through Darkness: Innovations Uncovering The Dark Genome

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Keywords: Dark genome, ECSFinder, OGM, SynHG

Introduction

The dark genome, which earns its name from dark matter in space, refers to the vast majority of genetic material in higher organisms, including humans, that does not encode for proteins. Despite making up roughly 98% of the human genome, for much of scientific history, these regions were disparagingly labelled as "junk DNA." Their function remained unexplored, and their importance was underestimated. Advances in sequencing technology have enabled scientists to analyse the "dark genome" with more clarity. In this article, some novel methods adopted for unravelling the dark genome shall be discussed with emphasis on SynHG- a synthetic-biology-based method.

What is Dark Genome?

The dark genome is primarily composed of repetitive elements, including long interspersed elements (LINEs), short interspersed elements (SINEs), human endogenous retroviruses (HERVs), and other non-coding DNA sequences. These are mobile genetic elements, sometimes referred to as "jumping genes," that can undergo duplication and repositioning within the genome, influencing the structure and potential function of chromosomes.

Modern genomic research has revealed that the dark genome plays essential regulatory roles in gene expression and cellular functioning. Most sequences within the dark genome are transcribed into various forms of non-coding RNA (ncRNA), including long non-coding RNAs and microRNAs. These RNAs can act as epigenetic regulators, orchestrating gene expression in response to environmental stimuli, stress, and developmental signals.

In disease states, especially in cancer, mutations and aberrant expression in dark genome regions can have harmful clinical outcomes, increase genomic instability, and promote tumour progression. Researchers have found that "dark genes", which include genes residing in poorly annotated or non-coding stretches, exhibit high mutation rates in certain cancers. The dark genome also preserves evolutionary relics such as transposons, which serve as a living fossil record of ancient genetic alterations.

Methods Adapted to Explore the Dark Genome

Recent research has outlined several ingenious methods to uncover the dark genome, with a strong focus on advanced sequencing technologies, artificial intelligence, and synthetic genomics. A prominent development in this field is brought about by the advent of artificial intelligence tools trained to detect conserved RNA structures masked within non-coding regions. For example, ECSFinder, developed by UNSW Sydney, has demonstrated significant promise by identifying evolutionarily conserved RNA secondary structures (ECSs) within the genome using multiple sequence alignments. This AI-powered pipeline, when used together with RNA sequencing, allows the detection of regulatory elements typically invisible to standard approaches. ECSFinder has been shown to outperform existing methodologies, providing a robust framework for the systematic study of the dark genome and potentially uncovering hundreds of thousands of previously hidden RNA structures in the process.

Additionally, optical genome mapping (OGM) has emerged as a highly sensitive technique, capable of inspecting large and repetitive regions of DNA which

are often refractory to conventional short-read sequencing. OGM utilises high molecular weight DNA fragments, fluorescent labelling, and nanofluidic imaging to produce long-range maps that can resolve previously inaccessible regions, thereby detecting clinically significant structural variations and clarifying ambiguous genetic alterations in diseases like cancer. This approach provides single-assay capabilities that surpass the limits of traditional cytogenetic tools, contributing greatly to the mapping of dark regions and uncovering pathogenic variants.

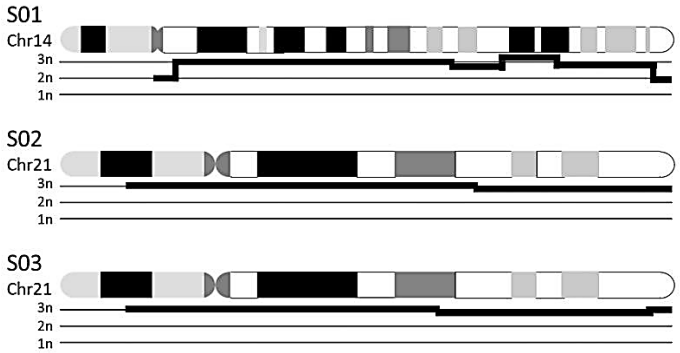

Figure 1: Schematic representation of Optical Genome Mapping (OGM) data to visualize trisomies
Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC8701374/

SynHG

A groundbreaking initiative in this field is the SynHG (Synthetic Human Genome) project, launched in 2025. The SynHG Project pioneers the programmable assembly and synthesis of human chromosomes, with the ultimate goal of synthesising the whole genome. With an initial funding of £10 million from Wellcome Trust, the SynHG Project brings together leading research communities from the Universities of Kent, Manchester, Cambridge, Oxford, and Imperial College London in the United Kingdom, under the leadership of Professor Jason Chin of the MRC Laboratory of Molecular Biology and the Generative Biology Institute at the Ellison Institute of Technology, Oxford. SynHG aims to move beyond traditional methods of genome editing, such as CRISPR, by enabling the programmable and complete synthesis of human chromosomes and eventually entire genomes. While editing brings about the modification of existing sequences, genome synthesis allows the construction of new chromosomal segments and entire chromosomes with enhanced control, accuracy, and density of genetic changes.

A rough outline of the procedure of the SynHG Project would be as follows:

1. Short DNA sequences, called oligonucleotides, are chemically synthesized in the laboratory. These short fragments serve as building blocks. These oligonucleotides are then assembled into longer strands through processes like Polymerase Cycling Assembly (PCA) and Gibson Assembly. These techniques stitch together overlapping fragments, allowing stepwise construction of genes or chromosomes.
2. Stepwise DNA assembly takes place both in vitro and in vivo to enable replicative assembly and error correction. In vitro assembly links oligonucleotides into longer DNA fragments under stringent conditions to minimize errors. In vivo assembly uses host cell machinery for replicating and assembling larger pieces of DNA naturally.
3. Synthetic DNA is prone to synthesis errors, so correction and validation become necessary. Error correction mechanisms include sequencing-based quality controls and computational tools to identify and fix mistakes in synthesised DNA.
4. The final synthetic chromosomes or genome segments are introduced into cellular systems to verify proper biological functions such as protein expression, gene-regulatory capacity and cellular replication, like in natural DNA.
5. The project integrates cutting-edge generative artificial intelligence and robotic assembly systems to automate and scale the synthesis and assembly processes.

The project's immediate aim is the creation of a fully synthetic human chromosome, which constitutes around 2% of our DNA, serving as a proof-of-concept

demonstration for synthesising the entire genome. SynHG builds upon recent breakthroughs, such as the creation of stable, single-copy Human Artificial Chromosomes (HACs) by the J Craig Venter Institute in 2024, overcoming previous difficulties with uncontrollable multimerisation that had hindered precise experimentation. In addition to technical advances, SynHG places strong emphasis on the establishment of reliable methods allowing small sequence changes without pronounced effects on chromosome function or protein production, thereby ensuring predictable and safe outcomes in experimental and therapeutic applications. By leveraging scalable genome design and synthesis, SynHG not only hopes to construct functional synthetic genomes but also to systematically test, modify, and annotate non-coding elements - the “dark” segments of the human genome. This ambitious, multi-institutional project aims to unlock fundamental insights into genome organisation and function, to accelerate the development of novel cell-based therapies, and to reveal the precise role of dark genome regions in human health and diseases. SynHG combines both cutting-edge genome synthesis technologies and a strong commitment to ethical and social considerations, with an embedded social science program exploring the societal implications of synthetic genomics.

Conclusion

The roles of dark genome have long remained unexplored . However, with AI-driven RNA structure prediction, advanced mapping technologies, and synthetic genomics projects like SynHG, the exploration of the dark genome is being reshaped. They are enabling researchers to move beyond the constraints of traditional sequencing, and potentially translate this new knowledge into innovative therapeutic strategies.

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The Rain Smell Mystery

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Keywords: Petrichor, Geosmin, Soil Ecology, Rainfall Chemistry, Soil-rain interactions

Introduction

The rich scent that wafts up from the ground when raindrops fall onto parched earth has fascinated humans for centuries, motivating poetry, folklore and science. The smell, or petrichor, was named in 1964 by Australian researchers Isabel Joy Bear and Richard G. Thomas. Petrichor is derived from the Greek term 'Petra', which signifies stone and 'ichor', which is a fluid that runs through the Gods' veins in Greek mythology. Petrichor may induce emotional memories because olfactory bulb is directly linked with the limbic system – specifically the amygdala and the hippocampus. The scent of rain might be relaxing and calming, reducing anxiety and tension. It can trigger the release of serotonin or dopamine. Apart from its sensory beauty, petrichor has ecological and biological importance. Petrichor is closely linked with microbial life-cycles commonly seen with sporulation and survival mechanisms. It is therefore more than a poetic metaphor for rain; it is also a reminder of the unseen conversations between soil, microbes, atmosphere and human perception.

Physical Mechanism Behind the Scent of Rain

To find out the physical process of how the scent of rain enters into air, research was done by Cullen Buie and Youngsoo Joung (Nature,2017) in which they recorded raindrops colliding with 28 surfaces: 12 man-made materials and 16 soil types; with high-speed cameras. They noticed that when a raindrop collides with a porous surface, it gets stuck with small air bubbles at the contact point, similar to those in champagne. These bubbles subsequently propel upwards and burst at the surface, expelling microscopic aerosols. This mechanism for generating aerosols can be held responsible for the emission of soil originated scents such as petrichor and air-borne transportation of soil microbes. Petrichor is formed from the oils secreted by some plants during droughts, which are absorbed by clay-type soil and stones. When it rains, these oils are emitted into air together with Geosmin, a chemical emitted by Actinobacteria as a byproduct of metabolism. Geosmin specifically adds to the distinct earthy smell. The olfactory receptors pick it up with very high sensitivity – down to 5 parts per trillion. If lightning goes with the rain, ozone can also be present, providing the smell a distinctive sharp, fresh touch. When there is a thunderstorm, lightning dissociates oxygen molecules into separate oxygen atoms, which reform into ozone. Ozone does not chemically interact with geosmin but contributes a fresh sharp component to petrichor. It increases detection and makes geosmin's earthy odor more dramatic. When raindrop impacts porous surfaces, the force of impact pushes air out of pores and creates small bubbles and when the bubbles are ruptured, they expel aerosols carrying the odor along with the bacteria. This process is termed Aerosolization or Splash Effect. Surprisingly light showers where raindrops strike the ground gradually result in higher aerosols that is why petrichor often becomes more pungent following light showers than heavy rainfall.

Geosmin - The Microbial Source of Earthy Aroma

Geosmin (Chemical formula: $C_{12}H_{22}O$) is a naturally occurring terpene that is formed predominantly by members of the Streptomyces group of bacteria which inhabit soil. It possesses a typical earthy odor. A few species such as *Streptomyces coelicolor*, *Streptomyces avermitilis* and *Streptomyces griseus* are found to form geosmin. It is formed

as a secondary metabolite. The enzyme geosmin synthase is coded by the geoA gene. Farnesyl phosphate is reduced to germacradienol and Germacrene D intermediates that get rearranged to yield geosmin. Production of geosmin is generally initiated under conditions of nutrient limiting or stress as a part of bacterial sporulation. Restricting major nutrients particularly phosphate and nitrate, augmented production of musty odour compounds such as geosmin. Vegetative growth is characterized by *Streptomyces* to utilize nutrients and develop filamentous hyphae. When nutrients are low, they retard growth, induce sporulation pathways and produce secondary metabolites such as antibiotics and Geosmin. Antibiotics repress rivals and Geosmin may serve as environmental signals to invite insects or invertebrates to facilitate the dissemination of spores. This can improve the survival or dissemination of spores in the wild. These actinobacteria produce spores during dry spells. The longer the dry spells, the more spores are typically found. Under nutrient stress, Streptomyces redirected metabolic activity from primary to secondary metabolism resulting in increased production of Volatile Organic Compounds (VOCs). Geosmin was produced mainly during the stationary phase that happened much earlier under nutrient stress. Low phosphate concentration induces expression of geoA and thus higher production of Geosmin. With increasing phosphate concentrations, geoA expression began to decline. Geosmin biosynthesis is developmentally regulated frequently coincident with sporulation which is under the control of PhoP.

Regulation of Geosmin Production in *Streptomyces*

PhoP is the response regulator of the PhoR – PhoP two-component system. *Streptomyces* PhoP orchestrates the initiation of secondary metabolism under phosphate restriction. The metabolic redirection induced upon PhoP activation (through phosphorylation by sensor kinase PhoR in low phosphate levels) tends towards downregulation of primary metabolic processes and upregulation of geoA, which enhances geosmin production. In an earlier research (Wang et.al 2014), the geoA gene and surrounding genes were investigated in a different Actinobacterium, Amycolatopis uranica. They discovered that the geoA is part of a transcriptional unit which has two genes for encoding cyclic nucleotide binding proteins (cnb proteins). CNB proteins are generally responsible for perceiving concentrations of cyclic nucleotides and signaling responses to changes in cellular energy or signal states. GeoA and CNB gene co-localization implies that Geosmin biosynthesis perhaps is regulated by cell signaling mechanisms that include cAMP or environmental signals. Petrichor research showcases how subtle natural processes can arise from intricate chemical and biological interactions.

Conclusion

It is what we encounter as earthy smell that is really the result of combined action of soil living microbes, plant products and raindrop striking. While, at times perceived as fragrant, it possesses deeper scientific significance in affecting soil ecosystem, microbial existence and even animal behavior. The study of petrichor illustrates how minor chemical activities in nature lead to broad ecological and cultural significations.

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Traditional v/s Reverse Vaccinology

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Keywords: Reverse, Traditional, Vaccinology, Fast-mutating viruses

Introduction

Traditional vaccinology relies on growing of pathogen followed by attenuation/killing of the whole pathogen and immunogenicity testing. Reverse vaccinology begins with computational analysis of the genomic sequence to predict all potential antigens. This overcomes the major limitation of traditional vaccinology: inability to identify rarely expressed or highly variable antigens. It has enabled researchers to develop effective vaccines against fast-mutating viruses like Influenza and HIV, hence, preparing for future pandemics.

Louis Pasteur rationalised and established the basic rule of vaccinology: ''isolate, inactivate and inject the microorganism that causes the disease" [1]. There were significant developments in vaccinology following this rule. Polio vaccine was developed by killing poliovirus with formaldehyde treatment (Jonas Salk). Its attenuation was carried out using in-vitro serial passage (Albert Sabin). Viral antigens were isolated from the plasma of chronically ill patients.

However, when Craig Venter first published the genome of a free-living organism, a technology to develop vaccines beyond Pasteur's rule emerged. It allowed vaccine development to start from computers, using information present in the genome, without growing the microorganism. This approach was called reverse vaccinology. This technique "combines genomics with proteomics and bioinformatics to identify potentially protective antigens" [2].

What exactly is reverse vaccinology?

The possibility of determining the whole sequence of a bacterial genome led to the idea of using the genomic information to discover novel antigens that were missed by conventional vaccinology. In-silico analysis of the microbial genome sequence is used to identify antigens as potential candidates for a vaccine, followed by cloning, expression and purification of these antigens and immunogenicity testing, as shown in Figure 1.

- **In-silico Analysis**

  Secreted or extracellular proteins are better vaccine candidates than intracellular proteins because they are more accessible to antibodies. Certain algorithms can identify such proteins from the data bank sequences. However, the cellular localization of proteins is often predicted wrong by such algorithms. It is later checked using immunoblot, Enzyme-Linked Immunosorbent Assay (ELISA) and Fluorescence-Activated Cell Sorter analysis (FACS) techniques. A combination of various algorithms and critical evaluation of the information generated are needed to make the correct selection of potential antigens.

- **Expression and Purification**

  Oligonucleotide primers are designed from the genomic sequences, containing additional sequences corresponding to appropriate restriction sites for cloning into prokaryotic expression vectors or recognition sites for recombinases where in vitro recombination is employed to cloned genes. The product of each PCR reaction is cloned and screened for expression in a heterologous system. Integral membrane proteins are particularly difficult to produce by recombinant techniques in

Escherichia coli. Histidine-tag and/or glutathione S-transferase is fused for purification of the recombinant proteins by simple affinity column chromatography.

- **Immunogenicity Testing**

  The recombinant proteins are used to immunize mice. The immune sera are tested using western blot analysis of the recombinant proteins, Outer Membrane Vesicles (OMVs) and total extracts of the bacterium. These three assays determine if the antibodies are able to recognize both the recombinant and the bacterial protein, confirming the predicted localization of the protein.

To further confirm the presence of the proteins on the bacterial surface and to assess their immunogenicity, sera are analysed by ELISA and FACS. Antibody titres are measured to determine the ability of antisera to bind to the surface of live bacteria.

Why is reverse vaccinology preferred?

One of the main downsides to the conventional vaccine development techniques is how time consuming it is. Every component of the pathogen is tested for immunogenicity. However, it only allows the identification of those antigens which are in abundant quantity and most abundant proteins are not suitable vaccine candidates. Genetic tools required to identify less abundant proteins (BiFC (Bimolecular Fluorescence Complementation), enzymatic reporter assays, etc.) may not be available. In many cases, antigens expressed in vivo, during infection, are not expressed during in vitro culture. This problem can be navigated using reverse vaccinology.

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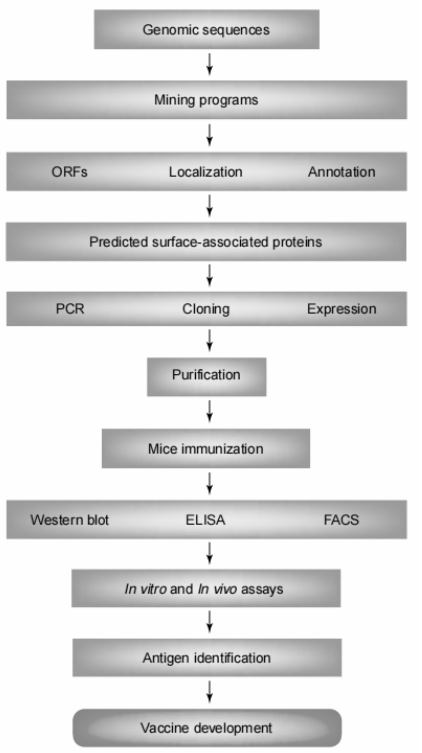

Figure 1: Flow chart of the genome-based approach to vaccine development

Differential in-vitro expression

This issue arises mainly because of the critical difference between the lab conditions and the complex environment of a living host. Pathogens go through a huge genetic reprogramming while entering the host body. Genes for adhesion (pili, fimbriae) which act as very important surface antigens, are often expressed only upon contact with host cells or host-specific signals. Pathogens activate these genes to hold onto tissues and avoid getting washed away by bodily fluids. These genes may be downregulated when there are no host cells to adhere to in a liquid culture. Pathogens may/may not have a library of silent genes for different versions of a surface protein. It can switch expression from one gene to another, hence

changing its surface antigenic coat. By the time the host immune system produces antibodies against a certain antigen variant A, the pathogen switches this specific antigen to variant B.

Techniques used for Viruses

Viruses that show high antigen diversity and high mutation rates cannot be produced vaccines against, using traditional methods. Conventional vaccination relies on supplying the immune system with a part (surface protein, for example) / whole of the pathogen so that a memory of these pathogens is developed and the immune system is ready to fight these pathogens. However, with viruses like Influenza, HIV and SARS-Cov-2, different strains of the viruses exist in nature, with each strain having a different set of antigens. Hence, a vaccine developed against one strain is not protective against other strains.

An even trickier part is the high mutation rate, which causes antigenic drift and shift. Such viruses, due to an error-prone replication machinery (RNA-dependent DNA polymerase), are constantly mutating as they spread. Small changes in the virus surface protein accumulate over time and result in a virus that 'looks' sufficiently different to the immune system, compared to the original one. Hence, the vaccine against the original/previous strain can no longer protect an individual from this new, mutated strain. Consequently, new vaccines are required to be developed for every strain. Antigenic shift occurs when different strains infect a single cell, swap gene segments and create a totally new virus. No one is immune against this new strain, thus causing epidemics.

In reverse vaccinology, however, the genomic sequence can give us information about potential antigens whose quantity is too low to be used as antigens using the traditional methods. This is an essential part of fighting such viral epidemics that keep on mutating their spike proteins (which is the usual antigen in viral vaccines). Conserved sequences like the nucleocapsid can be used as potential antigens instead, to deal with such radical mutations.

Techniques used for Bacteria

Neisseria meningitidis is a major cause of mortality as a result of sepsis and meningitis. Vaccines against serogroup B meningococcus (MenB) could not be developed using the traditional methods. Surface-exposed proteins were widely sequentially variable and serogroup B capsular polysaccharide is cross-reactive with human tissues. This serogroup was hence, approached through the lens of reverse vaccinology.

The incompletely assembled DNA fragments were screened to select proteins predicted to be on the bacterial surface by comparing them with the known homologous bacterial factors of pathogenesis and virulence. 350 out of 570 predicted proteins were successfully cloned and expressed. 85 proteins were surface-exposed and 22 could induce complement-mediated bactericidal antibody response, hence acting as potential antigens.

To test whether the antibodies against these antigens could also protect against heterologous strains, "the proteins were evaluated for gene presence, phase variation and sequence conservation in a panel of genetically diverse MenB strains representative of the global diversity of the natural N. meningitidis population" [3]. Most of the selected antigens were able to induce cross-protection against heterologous strains.

Conclusion

The differences between the traditional and reverse vaccinology show a significant upgradation in how we deal with notoriously fast mutations in pathogens. Reverse vaccinology has redefined the starting point: from the petri dish to the computer. Coupling with the traditional methods to confirm the computerised predictions, is where the true potential of the reverse technique lies. Combining computational foresight with experiments, is the new way to respond to the pandemics and epidemics of tomorrow.

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Reversing Cellular Senescence: The Role of Yamanaka Factors in Rejuvenation

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Keywords: Cellular aging, Epigenetic reprogramming, Yamanaka factors, Regenerative medicine, iPSCs.

Introduction

Aging is a complex biological process driven by the accumulation of cellular damage over time. Key factors include **telomere shortening**, which limits cell division, and **cellular senescence**, where "zombie cells" cause inflammation. Genetics, lifestyle choices, and environmental stressors like oxidative stress also contribute to this gradual decline.

For centuries, humanity has dreamt of a fountain of youth. While the mythical fountain remains elusive, scientists may have discovered the next best thing: a way to turn back the clock on a cellular level. Scientists have discovered a way to turn back the biological clock of individual cells, effectively making them young again. This breakthrough, akin to finding a cellular time machine, holds immense promise for treating age-related diseases and transforming regenerative medicine. At the heart of this technology are specific proteins known as **Yamanaka factors**, which can coax a specialized adult cell back into its most primitive, stem-cell-like state.

This process of cellular rejuvenation, which relies on the masterful manipulation of the cell's identity, is a prime example of **epigenetic reprogramming**/ **cellular reprogramming**.

What is Epigenetic Reprogramming?

Epigenetic reprogramming refers to the deliberate modification of epigenetic marks that govern gene expression to reset a cell's biological age or identity. Unlike mutations or changes in deoxyribonucleic acid (DNA) sequence, epigenetic modifications are reversible, making them attractive targets for age-related therapeutic interventions.

Epigenetic reprogramming involves the resetting of epigenetic markers, such as DNA methylation and histone modifications, to a more youthful state. The concept gained scientific interest and traction following the Nobel-prize-winning discovery of **induced pluripotent stem cells (iPSCs)** by **Takahashi** and **Yamanaka**, who demonstrated that somatic cells could be reprogrammed into pluripotent cells using **four transcription factors**:

- **Oct4**
- **Klf4**
- **Sox2**
- **c-Myc**

These are collectively known as **OSKM factors or**, **more popularly**, **Yamanaka factors**. These transcription factors are master regulators of gene expression, and when introduced into adult cells, they initiate a cascade of events that effectively "reboots" the cell's epigenetic programming. This process not only erases the cell's specialized identity but also resets its biological clock, making it, in essence, young again.

Turning Back the Clock: Reversing Cellular Aging

Cellular reprogramming has been shown to reverse multiple hallmarks of aging. Recent research highlights its potential to rejuvenate cells, extend lifespan, and restore tissue function:

1. **Rejuvenate human cells in a lab setting**

   Aging leads to loss of epigenetic information, disrupting gene expression and cell identity. While Yamanaka factors (OSK) can reverse these

changes, genetic modification poses risks. This study identifies **chemical cocktails** that mimic OSK effects without altering DNA. Using the NCC assay, researchers found small molecules that restore youthful gene expression and reduce transcriptomic age, offering a safer, scalable approach.

2. **Extend the lifespan of mice and improve their health**

   Cellular reprogramming with Yamanaka factors has extended lifespan and reversed aging signs in mice. A 2016 study at the **Salk Institute** showed a 20% lifespan increase in progeria-model mice and improvement in aging symptoms like heart rate, muscle strength, and skin/bone integrity. In 2023, **Rejuvenate Bio** extended the lifespan of naturally aged mice using **OSK via gene therapy**, improving safety and avoiding tumors.

3. **Reverse age-related damage in various tissues, including the skin, muscle, and even the brain**

   Scientists have safely reversed aging in tissues without causing cancer. Continuous OSKM expression is lethal, but two safer methods have been effective: **pulsing OSKM** and **continuous OSK expression (excluding c-MYC, which is actually an oncogene).** These approaches have rejuvenated brain, kidney, and muscle tissues, improved vision in aged mice, and extended lifespan—suggesting that cells retain a "**backup copy**" of youthful epigenetic information that can restore function without loss of identity.

Regenerative Medicine and the Future

Cellular reprogramming enables the conversion of adult somatic cells into induced pluripotent stem cells (iPSCs), which are stem cells reprogrammed to an embryonic-like state with the capacity to differentiate into any cell type. This advancement provides a versatile and powerful platform for regenerative medicine.

Using patient-specific iPSCs, researchers can generate healthy, genetically matched tissues to replace those damaged by diseases such as heart disease, diabetes, Parkinson's, and Alzheimer's. Because these cells originate from the patient, the risk of immune rejection is minimized, enhancing the safety and efficacy of regenerative therapies.

Beyond therapeutic applications, iPSCs facilitate the creation of "disease-in-a-dish" models. These models allow scientists to replicate and study disease mechanisms at a cellular level in a patient-relevant context, improving drug discovery and testing processes with greater precision.

Challenges and Risks of Cellular Reprogramming

Cellular reprogramming shows great potential for regenerative medicine but faces important challenges before clinical use. A major concern is the risk of tumor formation, since the regenerative abilities of induced pluripotent stem cells (iPSCs) can also lead to uncontrolled cell growth. Moreover, in vitro studies have shown that reprogramming only works on some specific cells.

Another challenge is developing precise and efficient delivery systems to ensure reprogramming factors reach the right cells without causing off-target effects or toxicity. This is crucial for translating the technology into safe therapies. Researchers are working on safer delivery methods, like non-integrating viral vectors and chemical cocktails, to reduce this risk.

Ethical issues also need careful consideration, including patient consent, fair access to treatments, long-term safety, and preventing misuse. Addressing these concerns is essential for responsible development and application of cellular reprogramming.

Conclusion

Cellular reprogramming is an exciting and rapidly advancing area of biomedical science that offers new ways to reverse aging, repair damaged tissues, and extend lifespan. By using **induced pluripotent stem cells (iPSCs)** and new chemical methods, researchers are developing safer and more effective treatments that could change how we address age-related diseases and injuries. However, there are still

important challenges to overcome, such as the risk of tumors, delivering treatments precisely, and ethical concerns. Ongoing research and improvements in technology are needed to address these issues and ensure these therapies can be safely used in patients. Ultimately, this field has the potential to not only restore cell and tissue function but also transform the future of regenerative medicine and personalized healthcare.

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Petri to Plate: How Gut Microbe Shape the Future of Mental Health

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Keywords: Anxiety, depression, schizophrenia, gut microbiota, probiotics

Introduction

After researching for years, scientists found out that the gut microbiome plays a huge role in human neurophysiology and mental health. About 100 trillion microbes lives in each of us! And that makes about 70-90% of our body! The intricate dialogue between the gut and brain is a reciprocal exchange that extends far beyond gut health, impacting our emotional state, motivational levels, and even higher-order thinking capabilities. This connection between gut microbiome and brain is mediated by gut-brain axis. The tiny microbes in your gut are 'talking' to your brain. They produce special chemicals that can travel through your bloodstream or nerve pathways to reach your brain. And the conversation goes both ways - your brain can also send signals to your gut, changing the balance of microbes and how they work. (Silberner, 2023)

Gut microflora and Mental Health

Mental health represents a critical global priority, with emerging research revealing gut microbiome interactions as key modulators of neuropsychiatric conditions. Neurochemistry and neurologic function are modulated through gut microbiota activity, particularly via metabolic regulation of neurotransmitter pathways involving GABA and neuroactive compounds governing CNS signalling. Clinical correlations now associate specific microbial profiles with depression, anxiety, bipolar disorder, schizophrenia, PTSD, ADHD, and ASD—pathophysiological linkages demanding operational scrutiny. (Xiong et al.,2023)

Neuropsychiatric issues are complex situations influenced through multiple elements, consisting of genetic predisposition and environmental triggers. Several studies have shown that sufferers stricken by intellectual problems (MD), along with depression, tension, and eating issues, show dysbiosis of the intestinal microbiota. Precise microbiota imbalances affect the mind via humoral and neuronal mechanisms, with a specific cognizance at the vagus nerve. Gut microbiota can also exert an effect through endocrine pathways or through changes of the blood-mind barrier (BBB). Microbial metabolites mediate this gut-brain signaling pathway, together with short-chain fatty acids (SCFAs), secondary bile acids, and amino acids, influencing conduct, memory, gaining knowledge of, and locomotion. Moreover, medical and preclinical proof supports the present intestine-mind axis in neuropsychiatric disorders, where fecal microbiota transplantation (FMT) from wholesome donors has verified treasured in relieving depressive and irritating behavior, as well as the use of probiotics. (Delanote et al.)

- **Schizophrenia**

  Schizophrenia biomarkers include *Lactobacillus fermentum*, *Enterococcus faecium*, and *Alkaliphilus oremlandii*, exclusively identified in affected patients. Major depressive disorder manifests elevated *Prevotella*, *Klebsiella, Streptococcus*, and *Clostridium* XI alongside depleted Bacteroidetes—a dysbiosis pattern requiring remediation. Bipolar disorder profiles further demonstrate reduced microbial diversity, marked by *Clostridiaceae* and *Collinsella* dominance and *Actinobacteria* and *Coriobacteria p*roliferation against diminished

Faeccalibacterium and *Ruminococcaceae*. (Xiong et al.,2023)

- **Autism**

  Autism spectrum disorder (ASD) research identifies *Clostridium paraputri*, *C. bolteae*, and *C. perfringens* enrichment in Egyptian pediatric populations. Diagnostic specificity emerges through *C. difficile* and *C. clostridiioforme* exclusivity in ASD cohorts versus *C. tertium* in neurotypical controls. (Xiong et al.,2023)

  Cross-sectional analyses confirm heightened *Actinobacteria*, *Proteobacteria*, and *Bacilli* among ASD subjects—patterns mirrored in anorexia nervosa's Bacteroidetes depletion and microbiota destabilization. (Xiong et al.,2023)

- **Post-Traumatic Stress Disorder**

  Post-pandemic data reveals frontline healthcare implications: symptom recurrance in PTSD patients correlates strongly with uncultured *Eubacterium hallii* and *Bacteroides eggerthii* prevalance. This presents opportunities for targeted microbial interventions. (Xiong et al.,2023)

Probiotics

Emerging evidence suggests gut microbiota modulation through targated nutritional strategies may enhance both mental health and overall wellness. Protactive mechanisms against neuropsychiatric conditions appear strengthened by bioactive compounds including *Lactobacillus*, *Bifidobacterium*, short-chain fatty acids, and phytochemical-rich sources like *Zanthoxylum bungeanum*. Through microbial equilibrium optimization, these components suppress pathogenic strains while amplifying commensal populations—a bidirectional mechanism confirmed across 14 randomized trials. Notably, GABA enhancing modulation via *L. murine* and *L. reuteri* demonstrates hippocampal neuroplasticity improvements, correlating with depressive symptom alleviation. (Xiong et al.,2023)

- **Prebiotics and Postbiotics**

  Clinical observations further validate prebiotic and postbiotic formulations as viable adjuvants in anxiety, ASD, and Schizophrenia management. Multi-strain probiotic synergies—particularly *Lactobacillus reuteri* NK33 paired with *Bifidobacterium* adolescentis NK98—showcased measurable sleep quality enhancements in 156 adults with subclinical symptoms. Parallel findings reveal biotin-augmented probiotic regimens elevate *Ruminococcus gauvreauii* and *Coprococcus* abundances alongside beta-diversity expansion. Such microbial recalibration presents opportunities for personalized mental health intervantions through prceision nutrition frameworks. (Xiong et al.,2023)

  Research indicates dietary fibers may optimize gut microbiota-CNS interactions in schizophrenia patients through microbial modulation. By targeting microbial diversity, such interventions demonstrate potential for enhancing neurochemical signaling pathways critical to psychiatric outcomes.

- **Spices**

  Spices, historically utilized as both culinary enhancers and therapeutic agents, demonstrate diverse bioactive properties including anti-inflammatory and antimimrobial effects. Of particular interest is curcumin from *Curcuma longa*, shown to remediate DSS-induced anxiety behaviors in murine models via gut-brain axis mechanisms. Analysis revealed curcumin partially reversed DSS-induced gut microbiotc alterations while restoring microbial equilibrium. Parallel observational data merits consideration: analysis of 5845 Australian adults revealed a positive correlation between fruit/vegetable consumption and mental health metrics. Complementary research identifies inverse relationships between produce intake

and ADHD symptom severity in pediatric cohorts. Tea varieties (*Camellia sinensis* and alternatives like *Ampelopsis grossedentata*) present additional opportunities—these widely consumed beverages demonstrate neuroprotective properties through polyphenolic action. Such evidance positions dietary modulation as a viable adjunct to conventional psychotherapeutic interventions. However, translational challenges persist; interspecies metabolic variations necessitate cautious extrapolation from preclinical models to human applications. (Xiong et al.,2023)

Conclusion

Emerging evidence confirms the microbiota-gut-brain axis's centrality in mental health outcomes, with microbial metabolites acting as key neuromodulatory agents. Given interindividual microbiome variability, precision microbial profiling emerges as critical priority—therapeutic efficacy demands tailored identification of disorder-specific microbial signatures. Future investigations should prioritize multiset clinical trials evaluating synbiotic and postbiotic formulations, while expanding phytochemical research across dietary categories.

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Engineering Conditional Transgene Expression in *Nicotiana Benthamiana*

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Keywords: Metabolic engineering, molecular farming, *Nicotiana benthamiana*, synthetic gene circuits

Introduction

Over the past two decades, *Nicotiana benthamiana* has emerged as an important biofactory for the controlled production of bioproducts and metabolites in biocontainment. This is due to its ability to accumulate high levels of recombinant proteins – a trait which is linked to its diminished capacity to mount gene silencing mechanisms. Other features that make it so promising are – its high metabolic activity, practical attributes for indoor cultivation, including compact growth habit, rapid biomass accumulation, high germination rate and compatibility with controlled environment systems. The key advantage with *N. benthamiana* is its permissiveness to transient expression vectors, a trait which is linked to its compromised immune system. Thus, this transient gene expression has become the dominant strategy to produce recombinant proteins. Among the transient gene expression platforms, such as those derived from Tobacco Mosaic Virus (TMV), Cowpea Mosaic Virus (CPMV), or geminiviruses like Bean Yellow Dwarf Virus (BeYDV), among others, are particularly effective in *N. benthamiana*, routinely achieving recombinant protein yields between 0.5 and 5.0 mg/g of fresh weight within just 4 to 7 days post-infiltration. This is also characterised by significant production costs since cultivation and maintenance of two separate biological systems, *Agrobacterium tumefaciens* and *N. benthamiana*, and handling of large liquid volumes during the infiltration process is crucial. In the contrary, sustained protein production for multiple plant generations can be obtained by stable transformation. Low transgene copy numbers, gene silencing and potential phytotoxicity from recombinant protein accumulation constrain it. Thus these challenges are being handled by conditional transient expression and consequent bioproduct accumulation as the key strategy in the optimization of N. benthamiana. Advancements in synthetic biology are accelerating the synthetic gene circuits (SGCs) - which is a promising approach. Transcriptional SGCs usually comprise of a sensor module that captures a non-transcriptional signal, either endogenous or exogenous into a transcriptional output (mRNA); then the transcriptional signal is transformed (e.g., amplified, distributed, integrated with other incoming signals, etc.) by other genetic modules collectively referred to as processors; finally, the processed transcriptional signal is transformed by an actuator module into a non-transcriptional output that features the phenotypic response. Recently, some synthetic biology strategies have been designed to enhance transgene expression control in *N. benthamiana*.

New Sensor Modules for *N. benthamiana* Biofactories: Expanding the Signalling Palette

Conditional and responsive gene expression is achieved by synthetic circuits by incorporating sensor modules as input layers that detect the environmental or endogenous cues and translate them. A recent breakthrough by Ferreira and Antunes (2024) further broadened the sensor toolkit by engineering bacterial allosteric transcription factors (aTFs) that repress synthetic promoters in N. benthamiana and they are de-repressed upon accumulation of specific phenylpropanoid metabolites. These biosensors demonstrated up

to 95% repression, followed by sixfold activation upon ligand sensing, highlighting their potential for metabolite regulation in plants. With the release of AlphaFold 3, it has enabled to carry out rational design of sensors with tailored ligand specificity. Recent advancements include precise transgene modulation using electromagnetic signals- the IR-LEGO (InfraRed Laser Evoked Gene Operator) which uses a heat-shock promoter activated by infrared light to carry out precise gene expression. The visible light optogenetics also holds potential in the production but the visible lights interferes with controlled gene activation and expression which has to be handled. An advancement in this direction is the redON system which is based mainly on the interaction between PhyB and PIF6. In this case, red light (660nm) activates the genes but this can be suppressed by far red light (740nm) under daylight conditions. However, this disrupts the endogenous phytochrome signalling. There is also the Dual Light Control System- PULSE which combines redON system along with a dominant blueOFF module which has a EL222 based repressor which is active under blue light. The genes are activated in red light and remains off in blue light rich daylight or darkness. This is more well suited for application in whole plants.

Novel Approaches for Fast Prototyping

The problem lies in the fact that complex biological complex often leads to unforeseen interactions which can be solved by an iterative Design-Built-Test-Learn framework, which guides each engineering cycle through systematic refinement. Prototyping systems, ideally and effectively, ought to be high throughput, facilitating a rapid transformation turnaround, and produce easily quantifiable, robust readouts. Currently, two experimental platforms dominate plant synthetic circuit prototyping: protoplast transformation- typically employing fluorescent reporters and transient *N. benthamiana* transformation, often coupled with bioluminescence- based assays.

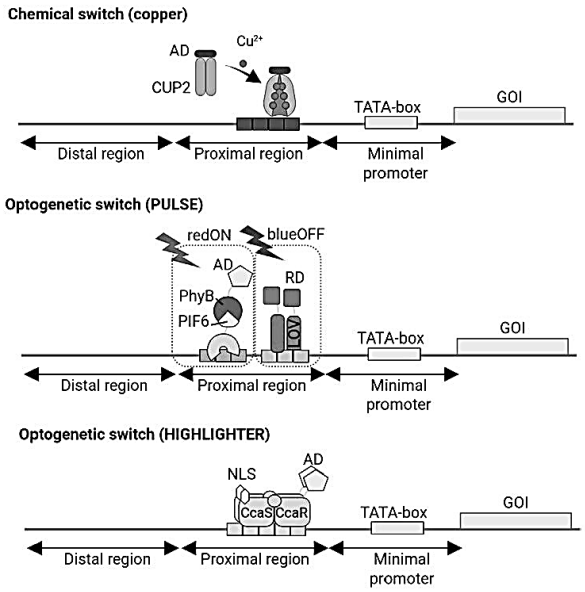

Figure 1: Sensor systems for controlled expression in *Nicotiana benthamiana*. Schematic representation of three inducible switches enabling conditional gene expression. Top: Copper- inducible system based on the CUP2 transcription factor, which activates gene expression upon copper binding. Middle: The PULSE optogenetic system, integrating red light- mediated activation (PIF6- PhyB interaction is mediated by red light) with blue light- repressed transcriptional control (LOV interacts with DNA in the presence of blue light). Bottom: The Highlighter system, repurposes the cyanobacterial CcaS- CcaR two- component system for plant use by engineering CcaS to use phytochromobilin as chromophore and fuse to it a nuclear localization signal (NLS). The figure includes images from Biorender.

Future Prospects for Synthetic Circuit Integration and Plant Transformation in *N. benthamiana*

SGCs offer a transformative approach to optimizing *N. benthamiana* into a biofactory for recombinant protein and metabolite production. By integrating advanced sensing modules with programmable signal processors and targeted metabolic engineering, it becomes possible to address key challenges such as limited yield, transgene silencing and metabolic toxicity. In this expanded role, *N. benthamiana* has the potential to emerge not only as a leading platform for molecular farming, but also as a versatile chassis for novel applications, including- use as a biosensor or as a living dispenser

of informative volatiles, such as pheromones and other signalling compounds. The challenges like the variability among regenerated lines can be addressed by matrix attachment regions (MARS) to mitigate the positional effects. However, generation of transgenic lines is a lengthy process. Traditional tissue culturing systems take approximately six months to establish stable *N. benthamiana* plants, but modern innovations like morphogenic regulator genes, transformation of embryonic axes and meristems, and estradiol induced CRISPR systems can enhance regeneration. Additionally, *Nicotiana* species do not rely on seed-based propagation for maintaining transgenic lines, allowing for the long-term preservation of transformed plants once a stable line is obtained. The SGCs will also help in producing next gen plants with enhanced capabilities.

Conclusion

Challenges like transgene silencing, low yields and metabolic toxicity which greatly limit scalability of production of bioproducts and metabolites, but synthetic gene circuits enable precise transgene expression control, dynamic signal processing and metabolic pathway optimization, thus solving the issue. Recent development of novel sensor systems which respond to chemical and electromagnetic signals, synthetic promoters which have been integrated with programmable transcription factors, and virus derived replicons for transcriptional signal amplification. Plant cell packs and self-sustained bioluminescence systems are some innovative platforms that facilitate rapid prototyping of gene circuits, enabling high-throughput screening and optimization. Future strategies mainly focus on stable genomic integration, positional effect mitigation and accelerated transgenic line generation using morphogenic regulators and CRISPR systems. Many of these challenges are being addressed to unlock the full potential of *N. benthamiana* as a scalable and sustainable biofactory for molecular farming and advanced bioproduction applications in the field of synthetic biology.

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From Tissue To Chip: A Review of Breast Tumor-on-a-Chip Technology

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Keywords: Breast cancer, Human on a Chip, Microfluidics, Drug screening, Nanotechnology, tumour microenvironment

Introduction

The development of drugs for rare diseases remains a major challenge because of the high costs associated with research and the small number of patients involved. Although the passage of the Orphan Drug Act (ODA) in 1983 provided incentives to develop treatments for rare diseases, many of these lacking effective therapeutic interventions. Classical preclinical models often fail to replicate human physiology, leading to poor translational success and inaccurate drug efficacy/safety predictions. Human-on-a-chip (HoaC) is a new generation of microphysiological systems (MPS), used to culture human tissue models in interconnected microfluidic devices enabled by advances in microfabrication, nanotech and stem cell biology. These tools in combination with iPSC (induced pluripotent stem cell) technology make it feasible to establish patient-specific and disease-pertinent models fostered in a controlled, cost-effective environment. By integrating BioMEMS technology, surface chemistry and mechatronic control–HoaCs mimic organ functions & permit on-line non-invasive evaluation of cell and tissue responses with embedded transducers such as microelectrode & microcantilever arrays. HoaCs enable the studies of disease mechanism, drug efficacy evaluation and systemic toxicity prediction by enabling multi-organ interconnectivity & physiological cross-talk amongst tissues. HoaC technology connects classic in vitro/ in vivo approaches to clinical evaluations – and it has the transformative potential to revolutionize rare disease research and accelerate orphan drug development through early-stage implementation of human-relevant phenotypic testing into the discovery workflow.

Modelling the breast tumor microenvironment

Human breast tissue consists of mainly parenchyma and stromal elements. The parenchyma component can be divided into ducts and lobules, while various stromal elements include adipocytes, fibroblasts etc. Most breast cancers are caused by ductal carcinomas (50-75%) while lobular carcinomas (5-15%) represent a smaller demographic and other mixed ductal/lobular carcinomas are even rarer.

Hypoxia

Carcinomas showcase a highly variable structural and cellular heterogeneity; consisting of a population of neoplastic cells, stromal cells (fibroblasts, immune cells, adipocytes) and ECM, all overlaid with a highly complicated vascular network combatting the hypoxic conditions that arise within the tumour. The metabolic demand of neoplastic cells often cannot be met by the existing oxygen supply to the tumour, creating a spatially heterogeneous hypoxic enviroment, where regions receive varying oxygen levels. Oh et al. have developed a single-piece microfluidic device with an integrated oxygen diffusion barrier (PC film) that supports the induction of hypoxia in both 2-D and 3-D patterned cancer cells without an external source of oxygen control.

Metabolic shift

Under hypoxic conditions, HIF-1α (Hypoxia inducible factor 1 alpha) is stabilized, which accumulates (unlike normal conditions, when it usually gets degraded), moves into the nucleus and dimerizes

with HIF-1β. This complex now targets genes which eventually result in the upregulation of glycolysis and inhibition of oxidative phosphorylation via the mitochondria. This eventually leads to the Warburg effect, when tumour cells generate energy preferentially through aerobic glycolysis, glucose is converted directly to lactate. This allows tumour cells to generate ATP independent of the surrounding oxygen levels, varying in different parts of the tumour. The accumulation of excess lactate due to this metabolic shift provides a steady nutrient source for tumour cells, produces an acidic microenvironment that promotes immune cell evasion and upregulates VEGF production, resulting in induction of angiogenesis.

The metabolic profiles of tumour cells were studied during the DCIS (ductal carcinoma in situ) stage, the earliest stage of breast cancer. A microfluidic model that emulated tumour cells trapped within a normal mammary duct was used, and metabolite usage analysed by NMR as well as metabolomic analysis. A PDMS-based microdevice, with three lumens emulating different scenarios: normal, pseudo-DCIS and DCIS, using MCF10A cell line to generate a continuous epithelium for the mammary duct model with DCIS cells being injected into the same. A collagen hydrogel with embedded human mammary fibroblasts (HMFs) mimicked the ECM. A fluorescent glucose analogue NBDG was used to visualise glucose penetration through the tumour, while metabolite consumption through the DCIS model was characterised by analysing media from the lateral lumens in the microdevice by ^{1}H NMR spectroscopy and metabolomic analysis. This method allowed a more detailed conclusion, with the discovery of about fourteen metabolites differing between mammary duct and DCIS models.

Mechanical factors

The interstitial fluid filled spaces and vasculature surrounding tumour cells exert a shear stress on the carcinoma itself, difficult to model via traditional cell-culture methods. Interstitial fluid flow is guided by the hydrostatic and osmotic pressure differences developed due to tumour vasculature. Due to the irregular, leaky vessels created by angiogenesis, interstitial fluid flow is generally more elevated in tumoral tissue rather than the surrounding normal tissues. This high pressure drives outward fluid flow that aligns collagen fibres and forces fibroblasts to contract, stiffening the surrounding extracellular matrix, which directly impacts the shape of the tumour cells, leading to a spindlier, elongated phenotype different from their usual rounded shape, facilitating migration of tumour cells and leading to the development of a more invasive tumour. The shear stress produced by TIF can be reproduced in a microfluidic system using a variety of approaches. Perfusion chips, which can provide high and low perfusion regions, can maintain a gradient varying from high (40–50 s^{-1}) to low (10–20 s^{-1}) shear rates. By adjusting and fine-tuning the perfusion rates, the high-pressure tumour core versus the more compliant periphery can be reproduced.

Applications in drug screening

Breast tumour-on-a-chip systems are a revolutionary method for drug screening and development. The microfluidic devices enable real-time tracking of drug response dynamics, where tumour cells constantly interact with their surroundings. A patient's blood samples or breast tumour biopsies are put into the chip, and treated with different libraries of chemical compounds in a conventional drug-screening process. Thereafter PK/PD analysis, phenotypic alteration & breast cancer biomarkers were used as a metric for evaluating the anti-neoplastic efficaciousness/cytotoxicity of the drug. Using absorbance, fluorescence or luminescence-based read-outs, these assays replicate the in vivo behaviour of a drug within an ex-vivo controlled environment that also gives information on cell viability, toxicity and cellular function. Tumour-on-a-chip models have exhibited a higher drug resistance and cell type specificity than 2D cultures as shown in doxorubicin (DOX) studies. In a similar study, triple-negative breast cancer cell lines (MDA-MB-453, MDA-MB-231 and HCC1937) cultured under perfused versus static conditions showed differential responses with respect to drugs paclitaxel, olaparib and

cisplatin, demonstrating the role of biomechanical/biochemical cues in sensitivities to drug. Integration of CAFs, immune cells and endothelial cells into chip systems improved their physiological fidelity to studying the immune-mediated drug toxicity and CAF-induced therapeutic resistance.

Conclusion

With advances in nanotechnology, the use of 2D and 3D models for cancer studies have become redundant. The traditional techniques fail to replicate the complex tumour microenvironment—lacking fluid flow, tissue deformation, shear stress, and the heterogeneous hypoxia driving angiogenesis. Tumour-on-a-chip technology addresses all of these limitations and also enables the co-culture of heterogeneous cell types within an extracellular matrix. These chips can also be used for high-throughput screening as multiple drugs can be tested on a single chip, as well as different concentrations parallelly, reducing the cost and time of the drug development procedure, paving the way forward for the development of personalised drug therapy.

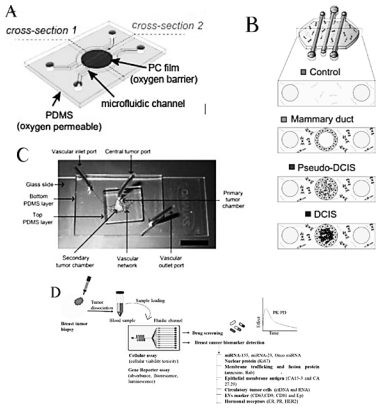

Figure 1: (a) Design of hypoxia microdevice with a polycarbonate (PC) film as the top oxygen diffusion barrier. Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC9299272/#S22 **(b) Schematic illustrating the four conditions from which media compositions were analysed using 1H NMR metabolomics. Source:** https://pmc.ncbi.nlm.nih.gov/articles/PMC6284542/#ab0005 **(c) Tumour-mimetic microfluidic chip containing a realistic vascular network. Source:** https://pmc.ncbi.nlm.nih.gov/articles/PMC8172385/#s0140 **(d) Workflow of breast tumour-on-a-chip for drug screening and biomarker detection. Source:** https://pmc.ncbi.nlm.nih.gov/articles/PMC8172385/#ab0015

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Messenger for a Cure: Harnessing mRNA Vaccine Technology for Cancer Immunotherapy

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Keywords: Cancer vaccination, Tumour-Associated Antigen (TAA), Tumour-Specific Antigen (TSA), Neoantigen, Lipid Nanoparticle (LNP), mRNA-LNP formulation

Introduction

Cancer remains a major global health challenge that causes nearly 10 million deaths worldwide annually. By 2070, it is estimated that there will be 34 million new cancer cases. Thus, the quest for an even more significant advancement in cancer treatment emerges as the central focus for researchers. Immunotherapy, which leverages the immune system to identify and destroy cancer cells, is a promising arena in this context.

Cancer vaccination strategies can be classified into preventive (prophylactic) vaccines and therapeutic vaccines. The former induces immune memory in healthy individuals to prevent cancers caused by viral agents. Examples are FDA approved HBV and HPV vaccines for liver and cervical cancers, respectively. However, not all cancers are associated with a virus and so, this approach poses a limitation. The latter of the two strategies aims to treat the disease by boosting or reactivating the patient's immune system. Approved examples include the BCG vaccine for bladder cancer and the Sipuleucel-T (DC-based) vaccine for castration-resistant prostate cancer. A comprehensive list is maintained at clinicaltrials.gov for further reference.

Cancer vaccines target tumour antigens that can trigger both cellular and humoral immune responses. These responses aid in suppressing tumour growth and also help eliminate tumours. Tumour antigens can be of two types: Tumour-Associated Antigens (TAAs) and Tumour-Specific Antigens (TSAs). Tumour associated antigens are non-mutated proteins that are overexpressed or abnormally expressed in cancer cells and can belong to many subtypes such as differentiation antigens, products of silent genes, universal tumour antigens and onco-viral antigens. However, vaccines targeting these had limited clinical successes and harbor a risk of autoimmune toxicity due to some normal cells also expressing TAAs. TSAs, on the other hand, are exclusively expressed by tumour cells. These antigens have high affinity for MHC molecules, strong immunogenicity, can elicit tumour-specific T-cell responses with minimal off-target effects and have thus become the main focus for recent cancer vaccine development.

In general, there are four major categories of cancer vaccines. Cell-based vaccines utilize whole tumour cells to stimulate the immune system. Genetic modifications can be done by adding cytokines, chemokines, co-stimulatory molecules and silencing immunosuppressive genes. E.g., Dendritic Cell Vaccines. They contain Monocyte-derived antigen-presenting DCs or Leukemia-derived antigen-presenting DCs, both loaded with tumour antigens like DNA, RNA, proteins and peptides. The Peptide-based type uses synthetic tumour specific peptides. APCs present these peptides to T cells to trigger an immune response. Examples include HBV and HPV vaccines for liver and cervical cancers respectively. Additionally, another type can be viral vectors like Adenoviruses, Poxviruses and Alphaviruses which are engineered to carry tumour antigens that elicit strong innate and adaptive immune responses. The oncolytic viruses, like T-VEC herpes simplex virus and adenovirus, infect and kill tumour cells and stimulate immunity. However, a few cons related to

these types of vaccines include anti-viral immunity development, not procuring enough cells to generate a strong immune response, etc. which necessitate the use of the fourth type, that is, Nucleic Acid based Cancer Vaccines. DNA vaccines deliver TAs via DNA/RNA. The DNA enters the nucleus, gets transcribed and the antigen is presented to APCs. This approach is safe, relatively low-cost and can encode multiple antigens. Examples include VGX3100, GX-188E (cervical cancer), etc. Trials for prostate and breast cancers are going on. On the other hand, mRNA vaccines directly inject corresponding mRNA which is translated directly in the cytoplasm and the nucleus is not needed. This type of vaccine has slightly higher immunogenicity than DNA vaccines and the antigen is only transiently expressed for safety. Clinical examples include TriMix and BNT111 for melanoma, mRNA-252 for lymphoma, personalized mRNA vaccines like mRNA-4157 (by Moderna that encodes 34 neoantigens) and BNT122 (by BioNTech that encodes 20 neoantigens) for the ongoing colorectal cancer trials [3].

mRNA Vaccines as a useful tool for cancer immunotherapy

The rapid success of mRNA-based vaccines against SARS-CoV-2 during the COVID-19 pandemic has renewed interest in mRNA cancer vaccines. Advances in understanding of immunological mechanisms have further led to the development of novel vaccine platforms [8].

- **The emergence of mRNA vaccines as an advantageous alternative to other vaccines**

  The successful development of the first mRNA cancer vaccine dates back to 1995. This vaccine encoded for a carcinoembryonic antigen (CEA) in mice which urged scientists to further explore the potential of immunotherapy against cancer [4]. The mRNA vaccines hold various advantages over conventional virus-based vaccines. They are safer, cost-effective, have enhanced purity, pose minimal risks of vaccine resistance and genome integration. Moreover, they exhibit similar translational efficiency in both dividing and non-dividing cells while altogether evading the requirement for nuclear entry. Their mechanism of cytosolic translation of TAAs minimizes potential cellular damage and enables robust immune activation. It is important to note that mRNA vaccines encoding full-length tumour antigens can generate broad-spectrum T cell-mediated immune responses independent of HLA types. In 2024, Phase III trials and potential for first regulatory approvals of personalized mRNA cancer vaccines started.

- **Strategies for Optimizing Target Antigen Selection**

  Several strategies have been employed to optimize target antigen selection. One of these strategies include full-length cancer-specific mutant proteins or Neoantigens being targeted for mRNA sequence design. Multi-epitope strategies that encode multiple TAAs within a single mRNA construct for a broader immune response may also be employed. Recent studies have even introduced patient-specific mRNA platforms in which these sequences are tailored to encode neoantigens carrying different somatic mutations specific to individuals. This invariably enables a highly-targeted, adaptive immune response.

- **Post-Antigen Selection Workflow**

  After the antigen sequence has been identified, it is inserted into a plasmid DNA vector that is derived from the tumour gene. Construction of the mRNA molecule follows incorporation of an open reading frame (ORF). In-vitro mRNA transcription (IVT) from the linearized plasmid DNA template is the most important step. Chemical modifications of the IVT mRNA need to be done to enhance the translational efficiency, stability, and immunogenic profile of the vaccine. Alterations include base modifications like Pseudouridine (Ψ) and N1-methylpseudouridine ($m^1\Psi$) (slightly better than pseudouridine as it achieves elevated protein production and evades TLR 3/7). Modifications to bases

like 5-methylcytidine (m^5C), 5-methyluridine (m^5U), N6-methyladenosine (m^6A) and novel modifications recently highlighted in studies like 2-thiouridine (s^2U) also ensure optimized vaccine performance through structural stability and immune evasion. mRNA extremities (5' Cap and Poly(A) Tail) along with 5' UTR and 3' UTR regions are engineered strategically to ensure efficient recognition and stability in host cells. These modifications are followed by subsequent purification steps. A notable innovation in this field is the development of self-amplifying mRNA (SAM) constructs. This invention has allowed sustained intracellular amplification of mRNA that has led to prolonged antigen expression using the host ribosomal machinery [3].

- **The mode of delivery**

  The generated mRNA is inherently very fragile, prone to degradation by nucleases in the body and thus it necessitates protection with directed delivery to the APCs. Gene delivery vectors can be either viral or non-viral. Viral vectors are known to exhibit higher efficiency in transfection and immune activation while artificial, non-viral vectors do not elicit unwanted immunogenic response, being much safer. But owing to its negative charge and large size, mRNA's cellular uptake itself is quite a challenge. Doxil was the first lipid-based nanoparticle (LNP) formulation that encapsulated the mRNA molecules and released it intracellularly. Cationic lipid amphiphiles with ionizable head groups and polymer-based vectors like PLL, PAA, PBAEs and PEI have also been explored in this context. As recently exemplified by Pfizer-BioNTech in the COVID-19 vaccine platform, Charge-Altering Releasable Transporters (CARTs) helped combine mRNA with cytosine-phosphate-guanine (CpG) motifs (known to be synthetic TLR9 agonists) and they have been used in nanoparticle formulations that proved to be effective in transporting antigen-coding mRNA to APCs in melanoma immunotherapy. Furthermore, polymer-based nanoparticles, such as those made from PLGA can provide sustained mRNA release. They may also be combined with adjuvants to enhance immunogenicity. For mRNA–LNP synthesis, lipids and mRNA are dissolved in ethanol and an acidic aqueous phase which is pH 4.0 citrate buffer. They are combined via a microfluidic device at a ratio of 1:3. This allows self-assembly where the negatively charged mRNA electrostatically interacts with protonated ionizable cationic lipids while helper lipids like cholesterol, phospholipids and PEGylated lipids stabilize the nanoparticles. The ionizable lipids then become neutral at physiological pH, reducing toxicity. The solution is consequently buffer-exchanged to reach neutrality. Moderna's mRNA-1273 vaccine highlights the effectiveness of such LNP delivery systems. Novel PEG-free nanocarriers and another delivery platform known as Lipid–Polymer Hybrid Nanoparticles (LPHNPs) are some of the promising next generation delivery systems [5].

- **Mechanistic pathway of action**

  The vaccine enters target cells via endocytosis and the encapsulated mRNA is released into the cytoplasm. There, the host ribosomes translate the mRNA into the corresponding antigenic protein. The proteasome complex is responsible for degrading the protein into peptide epitopes which are loaded onto MHC class I molecules within the endoplasmic reticulum; these MHC Class I- Peptide complexes then help to activate $CD8^+$ cytotoxic T cells. Alternatively, the antigenic protein can undergo endosomal degradation and the resulting fragments are presented by MHC class II molecules to T-helper cells. Activated T-helper cells, capable of stimulating B cells, lead to the production of antibodies that neutralize cancer-specific antigens [3].

Discussions on Preclinical and Clinical Advances

Pre-clinical studies reported a novel LNP formulation (113-O12B). This formulation exhibited improved lymph node targeting compared to conventional LNPs. Combination strategies that incorporated

multiple cytokines such as IL-15, IL-12 and IFN-⍺, proved to enhance CD8+ T-cell infiltration, granzyme B production and antigen-specific T-cell expansion. Furthermore, induction of durable immunological memory was also reported that led to effective tumour regression in preclinical melanoma models. The liposomal RNA vaccine Melanoma FixVac BNT111 was assessed in the Phase I Lipo-MERIT trial (NCT02410733). It targeted four common non-mutated melanoma-associated antigens. Also, personalized mRNA vaccines such as mRNA-4157 administered with pembrolizumab demonstrated enhanced T-cell responses to neoantigens in patients with resected high-risk melanoma. The peptide vaccine, GP2, achieved a 100% 5-year survival rate in patients with HER2-positive breast cancer in a Phase II study. Combining mRNA vaccination with checkpoint inhibitors and CAR T-cell therapy have been shown to enhance anti-tumour immunity vaccines (e.g., RO7198457, BNT122 and CARVac). Ongoing trials targeting triple-negative breast cancer (TNBC) based on this show a promising future. Pancreatic cancer is a key focus of mRNA vaccine development as it had been, traditionally refractory to immunotherapy. Personalized vaccines, such as iNeST, were created to target patient specific neoantigens and are administered along with LNPs. KRAS-targeted mRNA vaccines, like mRNA-5671/V941 and mRNA-1521 have shown efficacy in preclinical colorectal cancer models. Furthermore, in Non-Small Cell Lung Cancer (NSCLC), mRNA vaccines CV9201 and CV9202 which target multiple TAAs, elicited antigen-specific T-cell responses in 63–84% of participants. [3].

Conclusion

mRNA cancer vaccines have emerged as a highly versatile and promising modality in cancer immunotherapy. The rapid/scalable production, favourable safety profile and potential for personalization of these vaccines underscore their therapeutic promise. Preclinical and clinical studies have demonstrated encouraging efficacy, particularly in neoantigen targeted and personalized aspects. However, challenges related to mRNA stability, efficient in-vivo delivery and targeted tissue specific uptake still pose as critical barriers. To realize the potential of mRNA vaccines fully as a transformative tool in cancer therapy, there needs to be combinatorial strategies with other immunotherapies, comprehensive clinical evaluations and continued optimization of delivery platforms which will undoubtedly bring positive changes in this field, for the greater good of humanity.

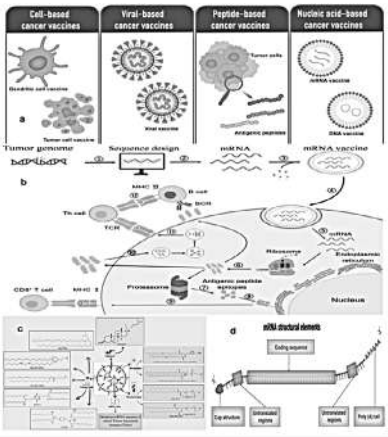

Figure 1: Integrated overview of mRNA cancer vaccines. (a) Different types of cancer vaccine platforms [1] (b) Schematic representation of the design and mechanism of mRNA vaccines within target cells [3] (c) Key components involved in mRNA-LNP formulation [1] (d) Structural elements of mRNA molecules [3]

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Blood-Borne Couriers: Advances in Red Blood Cell-Based Therapeutic Delivery

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Keywords: Red Blood Cells, Drug Delivery, Therapeutic Strategies, Red Blood Cell Membrane (RBCM)

Introduction

Modern advances in drug delivery systems have emerged to overcome several limitations of traditional methods, such as inadequate targeting, instability of drugs, and unwanted side effects. Engineered RBCs and derivatives provide targeted and efficient delivery, avoiding these constraints and acting as promising vehicles for new therapies

Physical and Physiological Characteristics of RBC

Red blood cells being the most numerous cell types in blood, account for a quarter of the total number of cells in the human body. There are many unique characteristics of RBC that shows its relevance to drug delivery:

i. ability to circulate to various regions
ii. elimination of old or damaged RBCs by cells of the reticuloendothelial system
iii. biocompatibility
iv. a long circulatory half life (~120 d in humans and ~50 d in mice)
v. a large surface area of ~140 ìm^2 with a favorable surface-to-volume ratio
vi. absence of a nucleus, mitochondria, and any DNA.

These characteristics can be exploited to make engineered RBCs. Engineered RBCs can be produced either by foreign peptide encapsulation or surface protein fusion with target antibodies. RBCs and their derivatives act as drug nanocarriers, but this comes at the expense of plasma membrane integrity.

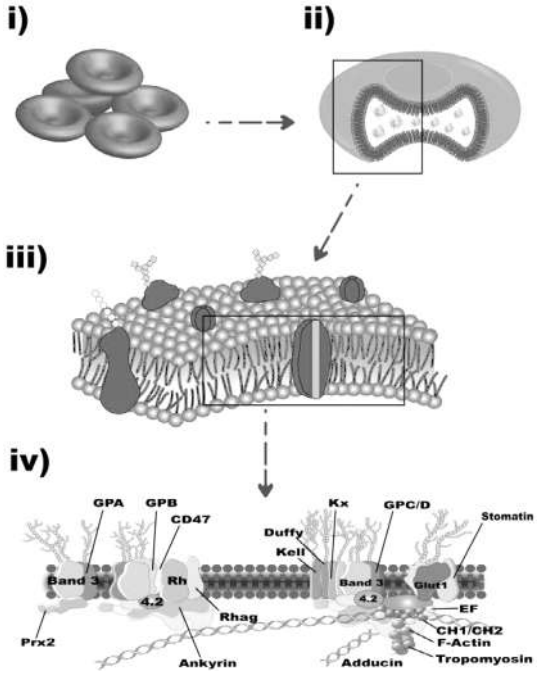

Figure 1: i) Biconcave disc shape of RBCs. ii) and iii) Composite structures of the lipid bilayer composed of amphipathic lipid molecules. iv) Various functional proteins anchored on the lipid bilayer of RBCM, potential binding sites for drug coupling. Source: https://www.sciencedirect.com/science/article/pii/S2452199X25000210#tbl1

To express the modified proteins present on the plasma membrane of mature RBCs, erythroid precursors are used. These modifications do not inhibit erythroid differentiation and are not targeted for degradation during the extensive membrane remodeling that occurs during enucleation and at the later reticulocyte stage.

Molecular Structure of the Red Blood Cells (RBCs) and its application in drug delivery

1. **Lipids**: The major component of RBCM is phospholipids (60% of membrane lipids) and cholesterol (33% of membrane lipids

containing neutral fats). RBCM outer leaflet is dominated by phosphatidylcholine (PC) and sphingomyelin (SM) whereas inner leaflet consists of phosphatidylserine (PS), phosphatidylethanolamine (PE) and traces of phosphatidylinositol (PI).

a. **Phosphatidylcholine (PC) and phosphatidylethanolamine (PE)**: The head of PC contains a choline group, which is involved in membrane-mediated cellular signaling and activation of other enzymes. PE, the most abundant lipid in the RBCM, ensures the smooth exchange of substances and transmission of information between the inside and outside of the cell.

b. **Phosphatidylserine (PS)**: PS shifts from the inner leaflet to the outer leaflet during RBCs' senescence. This is due to calcium imbalance, ion pump dysfunction or reduced cholesterol. The externalization of PS triggers macrophage-mediated phagocytosis which reduces the RBCs' lifespan. For drug delivery using RBC, PS externalization has to be prevented for longer circulation. To enhance its targeting efficiency to the liver and spleen, various structures on the engineered drug-loaded RBCM are altered.

2. **Surface Proteins of RBCM**: The membrane of the RBC contains a large range of proteins to maintain the physiological functions of RBCs. The membrane proteins can be broadly categorized into 3 groups on the basis of their function-structural proteins, physiological function proteins, and immunological recognition proteins.

a. **Structural Proteins**: The RBCM skeleton is primarily composed of a protein network essential for maintaining the biconcave disc shape of RBCs, maximizing the surface area for oxygen exchange and providing physical stability to prevent RBC damage. The primary components of RBCM skeleton include ankyrin, Band 3 protein and protein 4.1, which are interconnected at nodes to spectrin, thereby forming the intact structure of the RBCM. Monoclonal single-domain antibodies (sdAbs) can specifically identify Band 3 and coupling these sdAbs to the Complement Receptor 1 (CR1), where activated complement C3b present on RBCs can bind. This method can extend the in vivo half-life of small therapeutic proteins by leveraging the natural mechanism of CR1 to improve the therapeutic efficiency.

b. **Immunological Recognition Proteins**: Proteins like CR1, Glycophorin A (GPA), CD59 and Glucose Transporter 1 (GLUT1) are present on the surface of RBCs. These proteins act as potential binding sites for therapeutic agents. Also, various membrane proteins contribute to mechanisms of immune evasion.

(i) **CD47**: It is an integrin-associated transmembrane glycoprotein, which is divided into three segments-
- Extracellular N-terminal IgV domain responsible for interacting with SIRPá
- Transmembrane domain for stable embedding within cell membrane
- Intracellular C-terminal domain that can interact with specific ligands, mediating a range of biological processes

(ii) **Complement Regulatory Proteins**: CR1 is a multifunctional protein on surface of RBCs primarily involved in the regulation of complement system. CR1 acts as a bridge for the clearance of immune complexes and entry point for certain pathogens. RBCM can serve as an adsorbing material and detoxifying agent. When the RBCM is coated onto polymer nanoparticles form a biomimetic nanosponge. This nanosponge adsorbs and neutralizes a number of hemolysin toxins with different structures.

(iii) **Glycophorin A**: GPA is one of the most abundant proteins on RBCM and is one of the primary sialoglycoproteins on RBCM. With a minimal modification at the extension of the N terminus of GPA with Glycine residues to make it a suitable sortase substrate.

(iv) **Glucose Transporter 1 (GLUT1)**: It has demonstrated its potential site as a site on the surface of RBCs for connecting drugs. Glucose analogs like glucosamine can help modified Glc-Insulin bind to GLUT1 that can rapidly release insulin in high glucose environment. GLUT1 shows competitive binding with glucose. This leads to rapid release of insulin, thereby responding quickly to high blood sugar levels, mimicking the function of pancreatic β-cells

c) **RBCM-camouflaged nanoparticles**: RBCs are lysed using hypotonic solution, membranes purified, and fused with nanoparticles. RBCM has a limited capacity for loading for multi-drug therapy.

3. **Hemoglobin**: Due to its high biocompatibility, hemoglobin can be used as a drug carrier in a number of ways-
   a. Drug-loaded Hemoglobin nanoparticles being synthesized through non-covalent interactions
   b. Using PEGylated hemoglobin nanoparticles to enhance in vivo performance
   c. Using surface modified hemoglobin for stability of the tetramer structure.

Conclusion

Red Blood Cell-based drug delivery systems (RBC-DDS) have promising applications in cancer treatment and immune disorders. ERY-ASP (L-asparaginase encapsulated in RBCs) prolongs enzyme half-life and inhibits allergic reactions. Dexamethasone-loaded RBCs can relieve symptoms while lowering steroid toxicity.

Despite advances, RBC-DDS encounter issues with effective drug loading, large-scale and low-cost production and control of drug delivery. Delicate handling, stability in storage, and evolving regulatory guidelines further limit clinical translation, requiring stringent preclinical and clinical trials before they can be mass utilized.

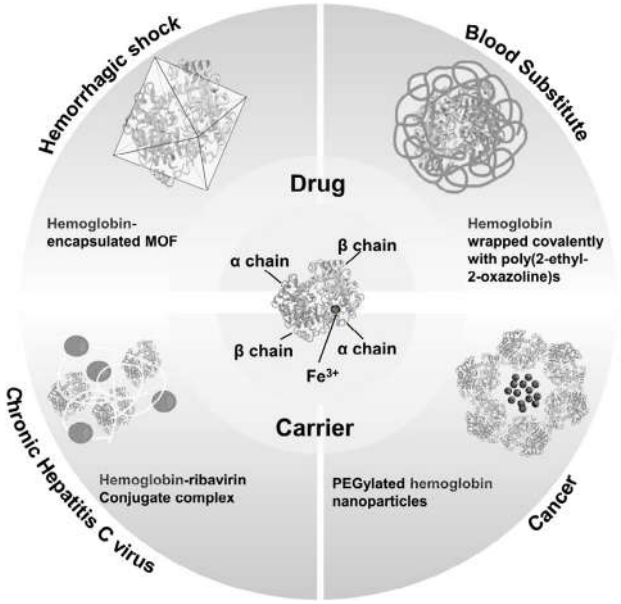

Figure 2: Illustration of structure and novel medicinal approaches of hemoglobin
Source: https://www.sciencedirect.com/science/article/pii/S2452199X25000210#tbl1

Table 1: Main drug loading pathways for RBCs-based carriers

Source: https://www.sciencedirect.com/science/article/pii/S2452199X25000210#tbl1

Location	Method	Description
Surface	1. Coupling (Crosslinking agent, Biotin-Avidin cross-linking) 2. Affinity Interaction 3. Enzyme-Linked Interaction 4. RBCs-hitchhiking	1. Using cross-linking agents like polyethylene glycol or binding sites like Glycophorin A to covalently link drugs to the Red Blood Cell Membrane(RBCM) proteins, or by using Streptavidin to cross-link multiple biotinylated molecules 2. Coupling of the cargo to the RBCM through direct interaction of antibody-protein 3. Using Sortase to catalyze the reaction of covalently linking proteins to the RBCM. 4. By physically adsorbing nanocarriers onto RBCM or adsorbing nanocarriers that has dual affinity for erythrocytes and target cells
Inside	1. Hypotonic Method 2. Electroporation 3. Lipid Fusion 4. Cell Penetrating Peptides (CCP)	1. Formation of pores in nanometers on RBCs surface 2. Exposing the RBCs to high voltage electric field in order to allow drug molecules to enter from extracellular fluid 3. Based on the principle of mutual solubility between phospholipids, RBCs are fused with drug-loaded liposomes 4. Proteins covalently bound with CCP allows internalization into cells through endocytosis without changing the structure or function of RBCs.
Cytoplasm and Surface	Genetic Engineering	Genetically transforming HSCs or progenitors to produce proteins/peptides in the membrane or cytoplasm of engineered RBCs.

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Tolerogenic Dendritic Cells: Redefining the Future of Autoimmune Therapy

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Keywords: Immunologic Tolerance, T cells, Autoimmunity, Tolerogenic Dendritic Cells, Immunotherapy

Introduction

The immune system protects our body from foreign invasion by orchestrating a dynamic network of effector responses upon recognizing pathogenic threats. Although our immune system primarily eliminates harmful invaders, it also establishes tolerance toward self-antigens and commensal microorganisms. This delicate balance between immune activation and tolerance is essential to prevent the emergence of autoreactive responses. A breakdown of immunological tolerance can result in the activation of immune cells against self-antigens (Ags), leading to autoimmune diseases such as Type 1 Diabetes (T1D), Rheumatoid Arthritis (RA), Multiple Sclerosis (MS), and Inflammatory Bowel Disease (IBD).

Dendritic cells (DCs), body's most efficient antigen-presenting cells (APCs), play a pivotal role in maintaining this equilibrium. Besides initiating immune responses, DCs can promote immune tolerance through their tolerogenic phenotype. This ability positions tolerogenic dendritic cells (TolDCs) as promising candidates for therapeutic intervention in autoimmune disorders. This article aims to discuss the mechanisms underlying TolDC-mediated immune tolerance, examine their application in autoimmune diseases and evaluate the future prospects of TolDC-based therapy.

Immunologic Tolerance: A Brief Overview

Normally during infections, Antigen presenting cells (APCs) such as macrophages, dendritic cells, and B cells present the processed antigenic peptide on their MHC Class II molecules to the T cell receptors present on the T Helper cells (CD4+ T cells). Once activated, these Th cells provide essential signals that 'license' the B cells and Cytotoxic T cells (CD8+ T cells) to undergo differentiation and clonal expansion. The resulting effector cells hence eliminate the pathogen.

Thus, significant threat would arise if the lymphocytes start attacking self-antigens, making immune tolerance crucial. Here, two main mechanisms come into play as seen in Fig. 1.

1. **Central Tolerance:** During development in the bone marrow and thymus respectively, self-reactive B and T cells undergo clonal deletion via apoptosis or programmed cell death.

   - **Positive selection:** Developing Double Positive (CD4+ CD8+ DP) T cells undergo positive selection where only those T cells are selected which bear the receptors capable of binding self MHC molecules (Self-MHC restriction). Cells with low affinity die by apoptosis, a process called "death by neglect"
   - **Negative selection:** The T cells with high affinity for self-peptides presented on self MHC molecules, undergo clonal deletion through induction of apoptosis. T cells with low affinity were positively selected as functional T cells and those with intermediate affinity, became regulatory T (T-reg cells) with the upregulation of FoxP3 gene.

Similarly, immature B cells encountering self-antigen may undergo deletion to prevent auto-reactivity.

2. **Peripheral Tolerance:** Despite central tolerance, the risk of auto-reactive T cells escaping still remains. T cells with low affinity TCR to tissue antigens can potentially cause autoimmune disease once they reach the peripheral lymphoid organs. So peripheral mechanisms serve as additional checkpoints to prevent autoimmunity:

   - **Anergy:** Self-reactive lymphocytes become unresponsive due to lack of adequate co-stimulatory molecules on APCs.
   - **Suppression by Tregs:** Regulatory T cells inhibit activation of self-reactive T cells through production of immunosuppressive cytokines like IL-10 and TGF-β.
   - **Activation-induced cell death (AICD):** Repeated stimulation of self-reactive T cells triggers apoptosis via the death receptor Fas and FasL (Fas Ligand) interactions.
   - **Clonal ignorance:** Self-reactive lymphocytes that escape deletion, manage to migrate to the periphery. However, they never come in contact with the appropriate antigen as certain tissues sequester the antigens, denying lymphocyte access and preventing activation.

Role of Dendritic Cells in Immune Regulation

Research on dendritic cells has revealed that DCs are critical in supressing immune responses and maintaining peripheral tolerance by generating anergic and regulatory T cells. This response is fine-tuned by altering the Th1/Th2/Th17 balance.

1. **Central Tolerance:** Thymic dendritic cells play a crucial role in shaping T-cell tolerance. They are the only thymus residing cells that express MHC class II molecules, which mediate negative selection. Experimental results confirmed that

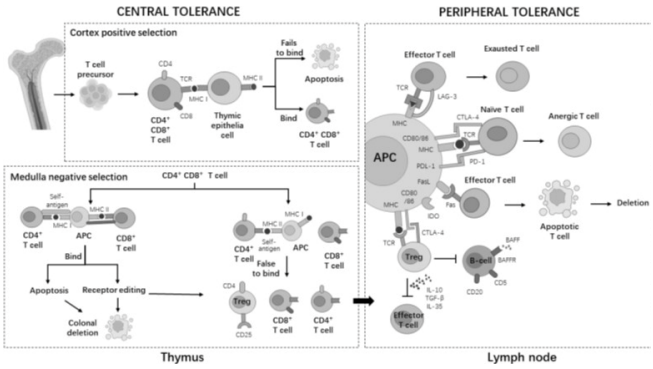

Figure 1: Mechanisms of maintaining immune tolerance
Source:https://doi.org/10.5415/apallergy.0000000000000128

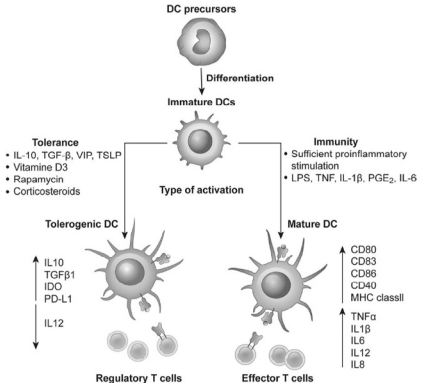

Figure 2: Maturation Stages of Dendritic Cells
Source: https://doi.org/10.3389/fimmu.2019.02393

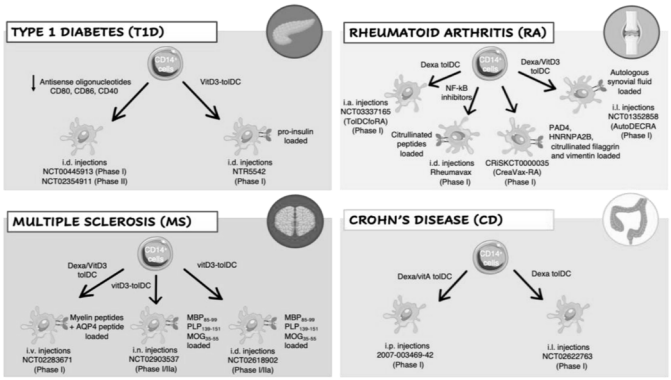

Figure 3: Applications of Dendritic Cell Therapy
Source: https://doi.org/10.3390/ijms22168415

elimination of rare $CD11c^+$ cortical DCs, impaired clonal deletion. Additionally, DCs induce $FoxP3^+$ Treg cells, in response to thymic stromal lymphopoietin (TSLP) produced by Hassall's corpuscles. Together, these processes ensure that most self-reactive T cells are removed or reprogrammed before they exit to the periphery.

2. **Peripheral Tolerance**: Peripheral DCs induce T-cell anergy, deletion, and Treg proliferation. Experimental ablation of DCs in mice leads to spontaneous fatal autoimmunity, demonstrating their essential role in preserving immune equilibrium.

3. **Maturation** Stage of DCs Under steady-state i.e. non-inflammatory conditions, immature DCs display their tolerogenic phenotype (TolDCs), expressing low levels of MHC II and costimulatory molecules. This promotes T-cell anergy or tolerance. Immature DCs stimulate tolerance by either deleting autoreactive T cells or expanding Treg cells. Any inflammatory or danger signal triggers the maturation of DCs, which express high levels of costimulatory molecules and promote effector T-cell activation. Interestingly, certain stimuli can induce mature DCs that still secrete anti-inflammatory cytokines such as IL-10, retaining their tolerogenic function. The differential maturation stages can be observed in Fig. 2.

4. **DC Subsets:** DCs comprise several specialised subsets distributed throughout the body, each uniquely maintaining immune tolerance. For example, immature Plasmacytoid DCs (pDCs) suppress immune activation by Treg cell production whereas indoleamine-2,3-dioxygenase (IDO) expressing DCs inhibit T cell proliferation. This is because IDO catabolizes and hence depletes Tryptophan, an essential amino acid t for T cell development.

Therapeutic Potential of Dendritic Cells

Dendritic Cell Therapy is an advanced form of immunotherapy which fosters immune tolerance rather than suppression. This focuses on using patients' own DCs, which can be manipulated into a tolerogenic state by anti-inflammatory cytokines and immunosuppressive factors such as IL-10, TGF-β etc. Experimentally, ex vivo–generated tolDCs using these mediators have successfully prevented autoimmune diseases like type 1 diabetes and multiple sclerosis. Treatment ensues as:

i. **Cell collection:** Monocytes are procured from the patients' blood.

ii. **Cell transformation:** These monocytes differentiate into DCs when subjected to specific growth factors and cytokines in laboratory settings.

iii. **Antigen Exposure:** The transformed DCs are loaded with disease-specific autoantigens that are retrieved from patients' own tissues.

iv. **Reintroduction:** The modified DCs are introduced back into the patient, where these interact with the T cells to maintain tolerance.

Administration of Dendritic Cell therapy

1. **Type 1 Diabetes:** In T1D, autoreactive T cells progressively destroy insulin producing β-cells. Tolerogenic DCs, generated from patients' monocytes are loaded with β-cell derived autoantigens. This retrains the immune system to restore tolerance. Early clinical studies have shown that intradermal administration of autologous TolDCs is safe and well-tolerated, with a modest increase in T cells. This does not produce any systemic immune suppression or adverse effects on the remaining β-cell function.

2. **Rheumatoid Arthritis:** In patients with rheumatoid arthritis, the immune system mistakenly attacks the synovial lining of joints. Tolerogenic dendritic cells loaded with autoantigens, such as type II collagen, can retrain the T cells to stop the immune attack. Clinical trials have shown that TolDC therapy can minimize disease activity and lower dependence on conventional immunosuppressants

3. **Multiple Sclerosis:** In patients suffering from multiple sclerosis, the immune system attacks the myelin sheath surrounding nerve fibres.

Thus, TolDC therapy focuses on inducing antigen-specific immune tolerance to myelin proteins, such as myelin oligodendrocyte glycoprotein (MOG) or myelin basic protein (MBP). Phase I clinical studies, demonstrate that this approach is safe, well-tolerated, and associated with reduced pro-inflammatory cytokines and relapse rates without weakening the overall immune system

4. **Inflammatory Bowel Disease:** Crohn's disease and ulcerative colitis are two major forms of IBD in which immune responses against the gut microbiota and intestinal tissue cause chronic inflammation of the gastrointestinal tract. TolDC therapy seeks to restore mucosal tolerance by modulating T cell responses in the gut. Pilot studies in patients with severe IBD have shown that injecting autologous TolDCs can reduce inflammation and promote mucosal healing

The applications have been demonstrated in Fig. 3.

Conclusion

Compared to Traditional immunosuppressants, dendritic cell therapy provides precise, antigen specific modulation of the immune system. This minimizes side effects while preserving overall immune function. Beyond its current applications, TolDCs hold possess great potential for the development of new therapies, including genetically engineered DCs, approaches that leverage viral factors and advancement in nanomedicines. Together, these advances position Tolerogenic dendritic cell therapy as a transformative approach in restoring the balance in autoimmune diseases.

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Printing Bones: Biomimetic 3D - Printing Strategy for Bone Tissue Engineering (BTE)

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Keywords: 3D bioprinting, Biofabrication, Biomimetics, Tissue-specific bioink, Osteochondral regeneration.

Introduction

The development of three-dimensional (3D) bioprinting has opened a new arena in manufacturing 3D cellular constructs which impersonate the structural and functional and characteristics of natural body tissues. Bioprinting has considerable application in the field of tissue engineering and regenerative medicine, which includes repairing and replacing damaged tissues or organs by creating biological substitutes using scaffolding and biomaterials, to restore normal function. The musculoskeletal system consists of a wide range of tissues like bone, cartilage, skeletal muscle, tendon/ligament and other connective tissues. These come and work together, allowing synchronous locomotion, providing mechanical stability and protecting vital organs. Musculoskeletal disorders are pervasive and are major contributors to global disability with approximately 1.71 billion people suffering from them. Nowadays, people across all age groups indulge in sports and acrobatics alongwith an increasingly aging population, orthopedic surgeries have become common for the treatment of patients with musculoskeletal trauma, injuries or degenerative ailments. Autografts remain the standard treatment in orthopedic clinics, but nowadays tissue engineering have evolved to become an advantageous alternative.

Various 3D bioprinting technologies to generate cell-laden constructs

Biofabrication refers to production of digital blueprints of complex biological structures using CAD (computer-aided design) to generate tissue constructs with complex geometries through assembling of living and non-living components such as cells, biomaterials and biochemical factors. A brief overview of the 3D bioprinting techniques and biomaterials utilized in this process is as follows:

- Inkjet-based bioprinting can extrude nano- or micro-liter volumes of cell-laden droplets in drop-on-demand (DOD) mode. This technique allows drop-by-drop deposition of bioink on the substrate to form a specific pattern of 3D biological structures. The inkjet printing heads maybe thermal, using a heating pulse from a thermal actuator to create a vapour bubble and push the droplet or piezoelectric, a piezoelectric actuator gives a mechanical pulse, which pressurizes the ink out of the nozzle.
- Laser-based bioprinting makes use of a laser source to deposit solid materials to create biological structures. The two methods include (i) stereolithography system that employs ultraviolet or visible light to solidify the preordained regions of a photosensitive solution and form the desired construct using layer-by-layer photopolymerization, which causes crosslinking and solidification only in the exposed areas, (ii) laser-assisted bioprinting uses a laser pulse to direct the deposition of components on the receiving substrate to build 3D structures. The printing system is composed of a pulsed light source, a ribbon resembling a laser absorbing layer, printable biomaterials and a collecting substrate.
- Extrusion-based bioprinting releases the ink

through a nozzle in a continuous manner using pressure or dispensing apparatus such as air, a piston or screws. It involves coordinated movements of the printing heads and the substrate along the three axes which facilitates deposition with high precision. This is widely used in orthopedic tissue engineering due to its ability to deposit biomaterial inks with a huge range of viscosities (30mPa.s to over 6×107mPa.s) and high cell densities, which is common within musculoskeletal tissues.

Advanced biomaterials for 3D bioprinting of orthopedic tissues

The choice of ink material is crucial to promote tissue regeneration for successful bioprinting of regenerative implants. 'Bioink' refers to a bioprintable material that contains single or collection of cells where it maybe combined with hydrogel biomaterials or bioactive compounds to create cell-friendly microenvironments with required physical and biochemical properties.

- **Synthetic polymers**: Biocompatible synthetic polymers such as polycaprolactone (PCL), polylactic acid (PCA) and polyurethane (PU). PCL is an FDA-approved biomaterial that has extensive use owing to its biocompatibility and slow degradation rate, however the release of acidic byproducts is a disadvantage. PU materials are popularly used biomedical synthetic polymers with high elasticity, tunable physiochemical and degradable traits - used in tubing, catheters and cardiovascular devices.
- **Hydrogel-based advanced bioinks:** They form 3D-hydrophilic polymer networks that can absorb and retain large amounts of water to maintain structural integrity. They form cell-favourable matrix to imitate the native complex microenvironments.
- Alginate, a natural polysaccharide obtained from brown algae induce instant crosslinking using divalent cations like calcium. Alginate-based bioinks are modified via RGD (Arg-Gly-Asp) functionalization to improve bioactivity.
- Collagen type I hydrogel is widely used for musculoskeletal tissues due to its ability to thermally gel at 37°C and biodegradability with minimal immunological responses.
- Gelatin, a non-cytotoxic and water-soluble natural protein derived from denatured collagen such as skin or bone is used due to its low immunogenicity and presence of RGD motifs. To improve the printing quality, methacrylated gelatin (GelMA) is extensively used due to its rapid crosslinking under UV exposure.
- Tissue-specific decellularized extracellular matrix (dECM) forms printable bioink formulations to create heart, cartilage and adipose tissues showing high cell viability and tissue-specific gene expression.

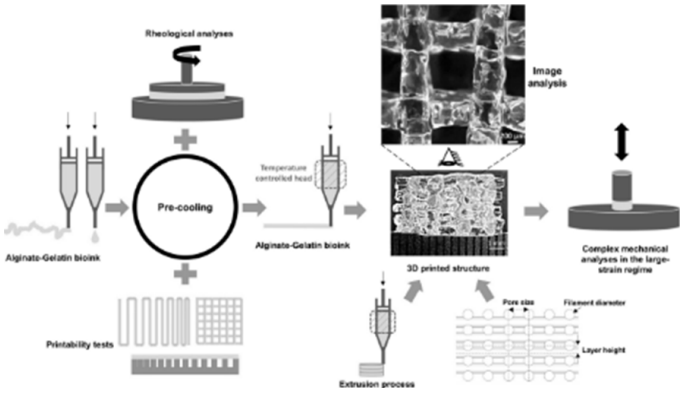

Figure 1: Schematic diagram of the essential steps used to optimize the printing process Source: https://www.nature.com/articles/s41598-023-38323-2

3D bioprinting strategies used in bone tissue engineering applications

Designing a 3D bioprinting scaffold for bone tissue engineering must include the pore properties, scale, structural and compositional organization, biomechanical features, biodegradability and biological elements like cell sources and ink materials.

Bone loss and injuries maybe caused by aging, trauma, healing of bone defects and fractures. Autografting used commonly, is now being slowly replaced by customized scaffolds for bone tissue regeneration. 3D printed scaffolds are prepared

using bioceramics which includes hydroxyapatite (HA) and beta-tricalcium phosphate (β-TCP), to improve osteoconductivity and osteogenesis. Hyperelastic bone (HB) ink is prepared using HA powder and PCL/poly lacticco glycolic acid (PLGA). Few instances observed were as follows:

- When human mesenchymal stem cells (MSCs) were put in HB constructs and the composite was implanted in a macaque calvarial defect for four weeks, it showed new bone formation with vasculature and rapid tissue networks- an increased osteoinductive potential.
- Through the use of 3D bioprinting, replicating the microcellular ECM and mineralized bony environments with the 3D bioprinted structures was shown. 3D porous human adipose stem cell (hASCs) constructs were prepared using a collagen/bioceramic-based bioink via extrusion bioprinting. (Fig. 2a). To demonstrate the feasibility of bone tissue constructs, in vivo implantation of the constructs was done in a rodent model with mandibular and calvarial bone defects. Results showed mature bone formation with a newly formed vascular network within the entire construct after five months in vivo, displaying effective bone repair. (Fig. 2b). When methacrylated bone dECM is used with 3D hASC-laden bioprinted cell construct, it replicated the mineralized environment, provided good biocompatibility with improved osteogenic gene expression and calcium deposition in vitro (Fig. 2c). The bony environment was now being mimicked using 3D porous PCL/PLGA/TCP scaffold using 3D bioprinting, coated with a dECM hydrogel. It showed new bone formation over the entire implantation site, about 85% with 70% bone density (Fig. 2d).
- The designing of the osteoinductive inks for bone tissue engineering is vital alongwith vascularization, which plays an important role for nutrient and oxygen diffusion and regenerative processes. Biomimetic-assisted scaffold formation by spatial organization is also significant.

Conclusion and future prospects

Orthopedic disorders are prevalent in today's society and may causing long-term pain, loss of mobility and other complications. Several aspects such as understanding the level of biomimicry in bioprinted tissues, proper vascularization, signaling strategies, biofunctionality and neurological impact on these constructs should be considered for clinical practices. With its advantages, the expansion of 3D bioprinting strategies could lead to extensive changes in bone tissue engineering, regenerative medicine and biotherapeutics.

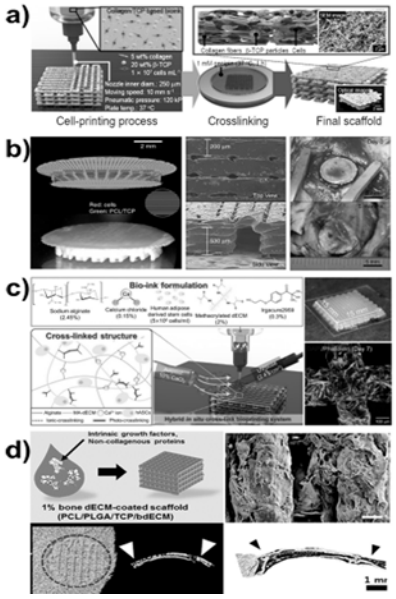

Figure 2: a) Cell-printing and construct making b) Bone formation after 5 months c) Methacrylated dECM cell-laden structure d) Final 3D bioprinted scaffold
Source: 156, pp. 11. https://doi.org/10.1016/j.actbio.2022.08.004.

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The Smallest Architects: How Microbes Could Help in Planetary Terraforming

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Keywords: Terraforming, Ecopoiesis, Extremophiles, Cyanobacteria, Synthetic biology

Introduction

Terraforming, which is the process of engineering an alien planet to resemble Earth has long been a staple of science fiction. This once distant dream is now being actively pursued by figures like **Elon Musk**, whose company SpaceX is developing the technology to establish a human presence on **Mars**. We may think that the scale of such a project is immense using giant orbital mirrors and atmospheric processors while the true pioneers of planetary transformation might be the **smallest life forms** we know: **microbes.**

The concept of using microorganisms to kickstart a biosphere is known as **ecopoiesis**, the creation of a self-sustaining ecosystem. These tiny, resilient life forms are Earth's original terraformers, having transformed our own planet's anoxic atmosphere into the oxygen-rich air enabling the emergence of more complex lifeforms we see today. Here's how we could do it again on a planet like **Mars.**

Role of microorganisms in terraforming

Microbes can be used for terraforming in basically two phases:

Phase 1: The Pioneer Microorganisms

The first wave of microbial colonists would need to be incredibly tough. These organisms, known as **extremophiles**, thrive in conditions that would be lethal to most other life. The initial goal would be to alter the planet's atmosphere and surface chemistry.

Atmospheric Engineering: The primary candidate for this job are **primitive cyanobacteria,** such as ***Chroococcidiopsis*** which will act as a pioneer microorganism for terraforming Mars. Its morphology is simple but shows a wide range of variability, and it resembles certain Proterozoic microfossils. ***Chroococcidiopsis*** **is probably the most desiccation-resistant cyanobacterium, the sole photosynthetic organism in extreme arid habitats.** It is also present in a wide range of other extreme environments like, Antarctic rocks, thermal springs and hypersaline habitats, but it is unable to compete with more specialized organisms. Genetic evidence suggests that all forms belong to a single species. These microbes are **photosynthetic masters.** They can also survive high levels of UV radiation and low temperatures. Its presence and tolerance of environmental extremes make *Chroococcidiopsis* a prime candidate for use as a pioneer photosynthetic microorganism for terraforming of Mars. The hypolithic microbial growth forms, i.e., which lives under stones of a desert pavement could be used as a model for development of technologies for large-scale Martian farming.

- **Oxygen Production**: Through **photosynthesis,** cyanobacteria would consume carbon dioxide (CO_2) from the Martian atmosphere and release oxygen (O_2) as a waste product. This would be the very first step toward creating a breathable atmosphere for other lifeforms to evolve.
- **Nitrogen Fixation**: Some cyanobacteria can also fix atmospheric nitrogen (N_2), converting it into nitrates and ammonia which will act as essential fertilizers for future plant life.
- **Soil Creation:** These microbes would form

biofilms on the Martian regolith (the loose layer of dust and rock). As they live and die, their organic matter would begin to form the first true soil, enriching the barren ground with vital nutrients.

Phase 2: Building a Biosphere

Once the first wave of cyanobacteria has established a foothold and slightly increased the atmospheric oxygen and soil nutrients, a more diverse team of microbes can be introduced:

- Algae: Extremophilic algae can be used for further biogenic oxygen production and carbon dioxide sequestration. We may enhance the algal strains' resilience and metabolic efficiency, including genetic modification and the development of bioreactors for controlled growth in extraterrestrial environments.
- Decomposers: Bacteria and fungi would be introduced to break down dead organic material from the pioneer cyanobacteria. This creates a crucial nutrient cycle, preventing essential elements from being locked away in dead biomass.
- Specialized Bacteria: Other bacteria could be engineered to perform specific tasks, such as metabolizing toxic perchlorate salts found in Martian soil or releasing trapped water (another essential component of life) from minerals.
- Lichens: A powerful follow-up would be lichens, which are a symbiotic partnership between fungi and algae or cyanobacteria. They are expert rock-eaters and soil-creators, capable of accelerating the breakdown of regolith into fertile ground.

Use of Synthetic Biology for Terraformation of Endangered Ecosystems on Earth Along with Terraformation of Extraterrestrial Planets

Synthetic biology can be applied across three distinct scales. At the planetary level, it explores engineering microorganisms to slowly build a habitable biosphere on a planet like Mars, while also using scientific realities, like the insufficient CO_2 in the polar caps to underscore the immense technological challenges. Similarly on Earth, the same principles can be applied to ecological restoration, envisioning engineered organisms designed for targeted tasks like cleaning up pollutants to save collapsing ecosystems. Finally, the concept can be scaled down to the microscopic level, proposing the engineering of the human gut microbiome, where synthetic microbes could be introduced to create a healthier internal environment.

Challenges and The Long Road Ahead

Terraforming with microbes is not a quick process. It's a process that would likely take centuries, if not millennia just like how life evolved on Earth and faces significant hurdles:

- Hostile Environment: Mars is incredibly cold, has a very thin atmosphere, and is bombarded with cosmic radiation and solar radiation due to **lack of a magnetosphere.** The first microbes would need to be housed in protected biodomes before they could survive on the open surface. The solar wind also blows away the Martian atmosphere. **So, even if we do coax microbial life into producing oxygen and other gasses, much of it will simply float away into space.**
- Unintended Consequences: Methods used should focus to track and avoid accidental delivery of Earth's harmful microorganisms and genes to extraterrestrial areas. Also, evolution in an alien environment could produce unexpected and potentially harmful strains of microorganisms.
- Ethical Considerations: A major debate surrounds the ethics of terraforming, focusing on whether humanity has the right to fundamentally alter another world. This issue is particularly critical if Mars hosts native microbial life, as introducing Earth-based organisms could potentially destroy an alien biosphere. This concept is a core part of **planetary protection protocols,** which aim to prevent biological contamination between celestial bodies.

Conclusion

Considering all these, the most practical and scientifically viable approach to terraforming a planet like Mars begins with microbes. The strategy would use tough, **extremophilic** microorganisms, specifically **cyanobacteria**, to kickstart the process. Their primary functions would be to produce oxygen (O_2) to modify the atmosphere and to create the first organic soil from the barren planetary **regolith**. While this long-term plan faces significant challenges, including the harsh environment and the ethical guidelines of **planetary protection**, it remains the foundational method. Therefore, using these tiny biological engineers is the most realistic strategy for the monumental task of creating a self-sustaining ecosystem on another world. Furthermore, these techniques of synthetic biology can also be used to restore endangered ecosystems already present on Earth and to create a healthy human gut microbiome.

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From Molecules to Masterplans: The Rise of Human-Directed Biology

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Keywords: Evolution, Microbiology, Synthetic Biology, Biochemical pathways, iGEM, de novo synthesis.

Introduction

Evolution on Earth has been driven by random genetic variation and natural selection for long. According to the "engineering is evolution" perspective, humans are now active creators of biological change rather than mere passive recipients of it. Since Waclaw Szybalski coined the term in the 1970s, synthetic biology has advanced remarkably over the past few decades. At its core, the field focuses on designing new biological systems and components, such as enzymes, metabolic pathways, and genetic circuits, to carry out useful functions like drug, pharmaceutical and biofuel synthesis, bioremediation, or aiding environmental cleanup. To develop innovative solutions to challenging biological issues, it lies at the interface of numerous research domains like functional genomics, protein engineering, bioinformatics and many more. In this article we shall dive deep into the various applications of Synthetic Biology aimed at overall human welfare.

The Future of Evolution – From Random Mutation to Human-Directed Design

Directed evolution, a powerful laboratory approach that simulates Darwinian selection, enables to rapidly refine natural enzymes and proteins to enhance their activity, specificity and stability, incorporate UAAs to expand the diversity in proteins, produce alternative biosynthetic pathways and even to generate entirely new biocatalysts. It has therefore made notable advancements in the field of synthetic biology by evolve desired complex traits in industrial organisms. This approach has been continually called upon to bridge gaps between current biological understanding and practical applications, making it possible to achieve traits that nature doesn't produce. Huang (2024) looks at how synthetic biology is used to improve enzyme catalytic efficiency through directed evolution.

Genome editing, particularly through the CRISPR-Cas9 system, has emerged as a pioneering discipline in molecular biology which reigns as a foremost technology, attracting substantial attention. This technology initiated a transformative era in genome editing, offering an efficient and explicit mechanism to manipulate genes due to its unwavering potential in unraveling genetic mechanisms and developing therapeutics. Recently, it has enabled the first approved gene therapy, Casgevy, to cure sickle cell disease and transfusion-dependent beta thalassemia. It has successfully corrected gene mutations associated with conditions like retinitis pigmentosa, paving way for a future with on-demand gene-editing therapies for individuals with until-now untreatable genetic disorder s. These groundbreaking advancements drove CRISPR to the spearhead of primary research endeavors and therapeutic approaches, playing an important role in transforming the realm of genetic modifications. CRISPR is becoming a mainstream methodology used in many cancer biology studies because of the convenience of this technique," said Jerry Li, M.D., Ph.D., of NCI's Division of Cancer Biology. Beyond medicine, genome editing also possesses the potential in agriculture—engineering disease-

resistant crops and modifying vectors of infectious diseases—marking a paradigmatic shift in both health and environmental biotechnology.

BioBricks and standardization: Engineering life like Lego blocks

BioBricks refers to the directed assembly of biological parts which is made into an artificially engineered metabolic network. This helps in producing desired phenotype where a host organism or biological system serves as the platform (biological chassis) into which genetic parts or networks are introduced and tested. There are two ways to access these biobricks. First, one may access public databases like GenBank, UniProt, or BRENDA. Such databases are enormous collections of genetic material, and researchers sift through them meticulously searching for sequences that could be useful, then modify them to fit their experiments. Or, pre-existing BioBricks can be used from repositories such as the iGEM Parts Registry or BioMaster. These parts have been tested and are standardized, so they can be implemented immediately, which is less time- and labor-consuming. Basically, mining is like digging up an enormous library to find the exact piece of DNA, while pre-designed parts can be thought of like a special store that sells ready-made Lego pieces. Each piece has been tested to fit perfectly in your project. With these techniques, building new biological systems becomes faster and more efficient. The engineered biobricks can be obtained by PCR or de novo – synthesis of complex molecules from simple molecules. The other steps include assembly into circuits, computer modeling and rational design and inserted into live cells and fine tuning. Widely used host organisms in synthetic biology include strains of *Escherichia coli* and *Saccharomyces cerevisiae*.

There are several applications of Biobricks which includes, synthetic organisms which are living organisms which have artificially engineered genomes for example engineered *Escherichia coli* strains are designed to produce insulin for use in therapy, in biotechnology and medicine where it helps in producing vaccines like those developed for COVID-19 (mRNA virus) to produce viral proteins and also environmental implications where microbes are modified to metabolize and degrade toxic waste products reducing harmful environmental pollution.

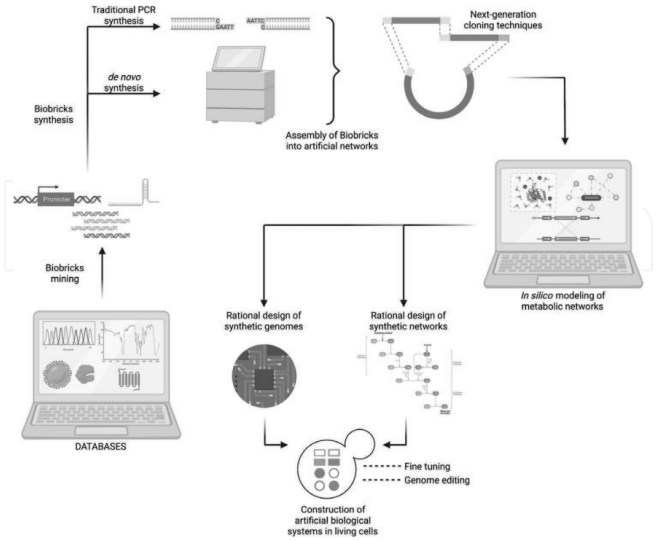

Figure 1: Frequently used steps to engineer artificial biological systems and synthetic genomes using BioBricks as building blocks (Reyes & Fernández-Niño, 2022)

Molecular solutions for a planet in crisis

Synthetic biology aims at creating biological parts and systems that do not exist in nature. This includes the design and realization of new enzymes and metabolic networks or pathways . This expands the biochemical capabilities of natural metabolism. One of these examples is the CETCH Cycle. This includes synthetic CO_2-fixing in vitro reaction network that requires 20% less energy compared to the Calvin cycle and features enoyl-CoA carboxylases/ reductases that are an order of magnitude more efficient than Rubisco, the CO_2-fixing enzyme of photosynthesis.

Synthetic CO_2 is fixation in CETCH Cycle is faster and more efficient than the Calvin Cycle, where two reductive carboxylation reactions take place to fix two molecules of CO_2 into one glyoxylate molecule. Starting from propionyl-CoA to produce ethylmalonyl-CoA and subsequently methylmalonyl-CoA, leading to a small 2 carbon the final product glyoxylate. This is a platform molecule where cells can build amino acids, sugars and other essentials required. Reaction intermediates like

ethylmalonyl-CoA and methylsuccinyl-CoA fix CO_2 into them in this cycle. Like other biochemical cycles, the intermediates like crotonyl-CoA are regenerated to perpetuate these reactions in order. This is called Anaplerosis.

The carbon capturing efficiency of the CETCH cycle can be applied to carbon sequestration. Synthetic and systems biology (SSB), which enables manipulation of cellular phenotypes. This offers us powerful approach at reducing atmospheric carbon. the ability to design and program biological systems to carry out prespecified functions. The potential for SSB to synthetically modify plants to convert CO_2 to a stable nonrespirable form rather than returning it to the atmosphere offers a potentially important opportunity to moderate climate. Roughly 120 gigatons of carbon (GtC) per year are cycled between the atmosphere and terrestrial life and another 90 GtC between the atmosphere and the ocean's mixed layer. Genetic modification of relevant plant traits (e.g., biomass yield, root system architecture, root depth, lignin content, suberin content, photosynthetic, and water- and nitrogen-use efficiency) to achieve even a small perturbation in the 120 GtC respired to the atmosphere each year can have a pronounced impact on its carbon capturing ability.

Conclusion

Synthetic biology is changing science by moving evolution from chance to choice. With tools like CRISPR, BioBricks, and synthetic pathways, we can tackle health, energy, and climate issues. However, the real challenge is using this power responsibly. We need to find an efficient way to balance innovation with ethics and responsibility to create a future that supports life.

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When Life Reaches Mars

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Keywords: Martian Microbes, Extremophiles, Cyanobacteria

Introduction

Life, in all its forms, has always reached beyond its boundaries. From the very first cells in Earth's oceans to the forests and cities we know of today, life forms have evolved and explored. But how far can that instinct stretch? Could life, even in its simplest form, find a home in worlds that are not its own? These questions have pushed scientists to turn their gaze toward Mars. Unlike the gas giants or scorching Venus, Mars holds a fragile balance. It is cold and barren, yet with evidence of frozen water beneath its surface, ancient rivers, and a thin atmosphere rich in carbon dioxide. As Earth faces mounting challenges of climate and resources, curiosity has sharpened into urgency. Can Mars teach us not just about the origins of life in foreign atmospheres, but also about its endurance?

Climatic conditions on Mars

Mars is a cold, desert-like planet with an average temperature of –63°C, a thin CO_2 dominated atmosphere, low surface pressure (~0.6% of Earth's pressure), and intense UV radiation. Yet it offers key resources like carbon dioxide, nitrogen traces, abundant regolith, and water locked in ice. For long-term human presence, importing supplies from Earth is unsustainable. This challenge fuels the idea of In Situ Resource Utilization (ISRU), where life, especially microbes, transforms local Martian resources into breathable air, food, fuel, and construction material.

Microbial Candidates for Mars

1. **Cyanobacteria (Oxygen Factories)**

   These are frontline candidates. They capture CO_2 via photosynthesis, fix nitrogen (in some species), and produce oxygen and biomass. In lab tests: *Anabaena* sp. (strain PCC 7938) has been studied for growth under Mars-like atmospheres and low pressure. *Nostoc muscorum* can grow on Martian regolith simulant (MGS-1) and help fertilize growth media for other bacteria (like *E. coli*) in experiments. But their efficiency depends on how processed the Martian atmosphere is (ratio of N_2, CO_2, pressure) and the mass of their containing reactors.

2. **Extremophiles like *Chroococcidiopsis***

   This cyanobacterium is known for exceptional resilience surviving desiccation, radiation, and extreme cold. It was tested on the ISS exposure experiments (EXPOSE-R2), and its pigments (carotenoids) had survived high UV exposure for 15 months. *Chroococcidiopsis* has been proposed as a model genus for Mars experiments, especially for its durability and possibilities for genetic engineering by researchers like Daniela Billi. Other extremophiles, such as *Deinococcus radiodurans* (radiation-resistant) and *Halobacterium salinarum* (thrives in high salinity), are models for engineering tolerance to Mars' UV exposure, cold cycles, and nutrient scarcity. *Deinococcus radiodurans*, which is nicknamed as "Conan the Bacterium," can withstand intense radiation and repair its own DNA.

Synthetic Lichen / Co-culture Systems

One of the most innovative new approaches: combining cyanobacteria with filamentous fungi to create living materials. A 2025 preprint describes a "synthetic lichen" that grows solely on Martian regolith simulant, air, light, and minimal liquid medium (no extra carbon or nitrogen inputs). The cyanobacteria fix CO_2 and N_2, feeding the fungi; fungi help bind mineral ions and create structural materials.

NASA also describes biomineralization-enabled self-growing building blocks: cyanobacteria produce carbonate ions and organic compounds, fungi bind metal ions and act as nucleation sites, and together they glue regolith particles into blocks, floors, walls, or furniture. Texas A&M's team is also developing synthetic lichens to glue regolith particles and combine with 3D printing to build habitats or furniture, autonomously.

Recent Discovery and Possible Martian Microbes

In 2025, NASA's Perseverance rover discovered "leopard spots" in a Martian mudstone (Jezero Crater), which may be mineral signatures of ancient microbial activity (vivianite, greigite).

If those spots are indeed biosignatures, they hint that microbes might once have lived on Mars — making our engineered microbes perhaps the returning guests, not newcomers. Until the samples are returned to Earth, it remains ambiguous, but it is one of the strongest signs yet of possible ancient life.

Recent theoretical work also proposes symbiotic engineering between terrestrial microbes and hypothetical Martian life (if any exist). Engineered partnerships might be formed to help both species flourish under Mars's conditions.

Challenges for Microbial Survival on Mars

Microorganisms face significant obstacles to survival and function on Mars despite their resilience. The Martian surface is exposed to very high levels of cosmic and solar radiation due to the absence of a protective magnetic field and a very thin atmosphere. Most microbial species cannot tolerate such exposure without additional shielding. Hence, bioreactors that are situated underground or covered with regolith have been proposed as protective environments. The scarcity of accessible liquid water poses a critical limitation. While ice and briny deposits are known to exist, considerable energy input would be needed for the extraction and processing of these resources. Issues of scalability also remain unresolved. Current studies only show microbial growth and resource production only at small laboratory scales; effective application on Mars would demand cultivation at volume several orders of magnitude larger. Finally, ethical and planetary protection concerns must be acknowledged. In the event that native Martian microbes are present, the introduction of terrestrial species may irreversibly alter or obscure native ecosystems, thereby making the hunt for extraterrestrial life more difficult.

Synthetic Biology as a Link

Even if Mars' complete terraforming is still a long way to go and possibly a contentious goal, synthetic biology has the potential to bring about a lot of changes. We can see how straightforward Petri dish experiments could lead to planetary-scale changes by sowing tiny, contained ecosystems that capture carbon, improve soil, or produce oxygen. Editing genomes can create microbes that are not just survivors, but multi-functional pioneers.

For example: radiation-resistant photosynthesizers which include cyanobacteria engineered with DNA-repair genes from *Deinococcus radiodurans*; bioplastic factories and strains that turn CO_2 into polyhydroxyalkanoates (PHAs), forming lightweight, moldable building materials; biofertilizers that include microbes releasing essential nutrients into regolith to support higher plants.

Conclusion

We often picture towering beings with glowing eyes and oversized craniums when we imagine aliens. However, the true future of space colonization might not lie in giant organizations but in the tiniest

ones. Synthetic biology bridges the smallest and the largest scales, from rewriting a single gene in a Petri dish to envisioning the entire biosphere on distant planets. It represents the spirit of “From Petri to Planet”, where a journey that starts with molecular design extends into the wide unknown of space. If humanity ever breathes comfortably under the Martian sky, it might be thanks to not only the rockets and robots but also the living blueprints we first learned to draw in the lab.

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The Biological Camera: A Brand-New Way to Record and Store Information

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Keywords: DNA, Data Storage, CRISPR-Cas, biological camera, *E. coli*

Introduction

In today's era of technology and digitalization, humans are constantly searching for ways to store vast amounts of information in smaller, compact and more robust forms. Advancements in technology have led to development of various devices suitable for storing data in large quantities, be it in the form of magnetic tapes or silicon chips. Yet, there is no surpassing the most brilliant storage device perfected by nature over billions of years ago; **the DNA molecule**. Just one gram of DNA can theoretically store more than 200 million gigabytes of data. Due to its remarkable storage capacity, durability, and stability, DNA has emerged as a suitable alternative to traditional storage media. This notion drove scientists to develop a way to utilize DNA from live cells and create something known as a "**biological camera**"; an apparatus that records spatial data from outside and encodes it directly into the DNA of a living organism. In a groundbreaking achievement, a team from the National University of Singapore (NUS) brought this vision to life, developing a mechanism that merges biology and digital technology. Utilizing the CRISPR-Cas system of bacteria, they came up with a way to convert light signals into a time-encoded series of genetic code. The revolutionary research, published in detail in the journal "*Nature Communications*" on July 3, 2023, was led by Associate Professor Poh Chueh Loo, the Principal Investigator at the College of Design and Engineering at NUS. This article explores the mechanism behind this technology and discusses its applications in various fields of biology, while considering the challenges that exist to perfecting these living cameras.

DNA: The molecular recorder

Before one can go about constructing a biological camera, a storage medium, or "film," is required. DNA is composed of four chemical bases—Adenine (A), Guanine (G), Cytosine (C), and Thymine (T), and they can be used to translate any type of digital data, which ultimately is a string of 0s and 1s. DNA is particularly ideal owing to its astounding information density, long term durability and high energy efficiency. It can easily outlast any form of digital storage technology present today. Moreover, if properly synthesized, DNA needs no power to be stored, as opposed to data centres, which need continuous power to run and cool. These characteristics make DNA the perfect medium for a biological data recorder.

Following this, scientists proceeded to search for something that could take information and encode it into genetic sequences.

CRISPR-Cas: The molecular scribe

The innovation for a molecular scribe came from the bacterial immune system. To protect themselves from attack by bacteriophages, most bacteria employ **CRISPR-Cas** mechanism (Clustered Regularly Interspaced Short Palindromic Repeats and CRISPR-associated proteins).

A bacterium, when invaded, grabs a short stretch of the virus's DNA. The CRISPR system, using proteins such as **Cas1** and **Cas2**, copies the viral DNA fragment into a unique part of the bacterium's own genome, the **CRISPR array**. This array is a collection

of foreign DNA snippets from previous infections. So, if the same virus attempts to infect, the bacterial cell generates CRISPR RNA from the pre-existing DNA fragments in the array, which subsequently identify and kill the invading viral DNA.

Inspired, scientists successfully hijacked this system. They realised that instead of allowing the cell to capture viral DNA, they could provide their own engineered DNA sequences. And if they could control when such sequences were to be provided and incorporated, they would have a molecular recorder at hand. The CRISPR-Cas system thus became the "writer," and the bacterial genome became the "tape."

Working of the Biological Camera

The first real test of a biological recorder was performed in 2017, by scientists at Harvard University. Led by geneticist George Church, they built a functional biological camera, utilizing a population of ***E. coli*** bacteria. They attempted to encode a moving 5-frame GIF of a galloping horse, into the bacterial DNA. Their success proved that the system was capable of storing not only static images but also moving ones. The sequence of DNA fragments in the CRISPR array thus acted as a molecular timeline of stored data.

The synthetic biologists at NUS then proceeded to demonstrate that DNA can not only be used to take and store images, but that these pictures can later be retrieved via sequencing techniques. The researchers were able to create "a biological analogue to a digital camera" which they called the **BacCam.**

Previous endeavours had been made by scientists around the world, to take advantage of the vast storage capacity of DNA. However, most efforts along these lines involved in-vitro synthesis of DNA that would be manipulated to store information. Though the process turned out to be well-tested, it was unfortunately expensive, complicated, and often prone to errors. A new technique soon emerged that negates the need to synthesize DNA, by working with living cells of *Escherichia coli.* They contain so-called "**optogenetic**" circuits capable of recording the presence or absence of light within DNA.

The technique uses light-sensitive enzymes, such as the recombinase system of living cells. This system responds to the presence or absence of blue light as an external signal and subsequently records the response into DNA itself via site-specific DNA editing. The cells are arranged in wells, and the presence or absence of light in each well corresponds to a pixel in the image. To enable the encoding of a 2-dimensional image, along with the recorded signal, a barcoding scheme is implemented, which assigns unique sequences to each well containing the cells and allows their differentiation, thereby 'digitizing' the image and allowing for its resolution upon retrieval via sequencing methods. As a result, this recombinase-based DNA recorder, coupled with a barcoding scheme, enables the capture and storage of information via light into DNA itself. Furthermore, the NUS team was able to use red light to project a separate image on the same segments of DNA, demonstrating that multiple images could be captured, stored, and deciphered from a single genetic sample.

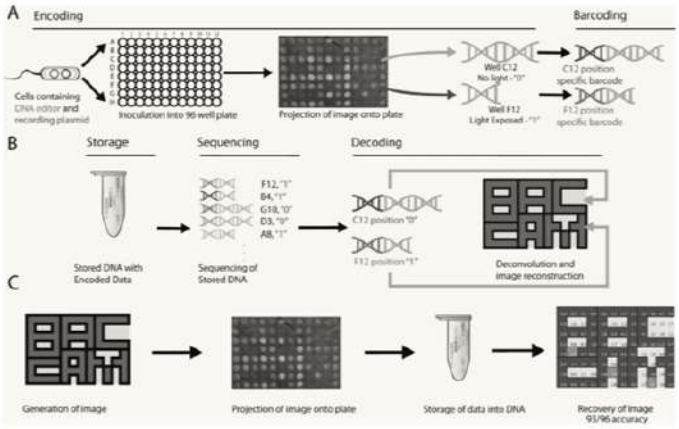

Figure 1: Working Mechanism of a Biological Camera

Source: https://www.nature.com/articles/s41467-023-38876-w/figures/1

Conclusion

The potential to convert living cells into an efficient recording equipment is revolutionarily vast. The innovation of the biological camera is capable of

fundamentally reshaping the data-storage industry by allowing direct encoding and storage of images within DNA. This “living digital camera” offers a host of future applications in computing and nanotechnology. In addition, this technology can have a huge impact in the fields of developmental biology, neuroscience, environmental monitoring and so on. However, the technology is still developing and has some significant obstacles to overcome. The process of recording images and other data has a notable error rate, and the capacity of information that can be stored is restricted by the size of the CRISPR array. Moreover, the speed of recording is relatively slow, with the current pace spanning from several hours to even days. Logically, the next big step requires enhancing the fidelity, capacity, and speed of this novel molecular recorder. Although challenges exist, the very idea behind creating a molecular recorder has opened newer possibilities for collecting and storing data, as well as other uses of the ingenious and beautiful molecule that is DNA.

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Mitochondrial Transplant – A Breakthrough in Lung Cancer Treatment

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Keywords: Mitochondrial transplant, cisplatin, non-small cell lung cancer (NSCLC), tumour microenvironment.

Introduction

In order to improve lung cancer treatment scientists have found that chemotherapy can be made more efficacious by transplanting healthy mitochondria into tumours. When this advanced method was combined with cisplatin which is a potent platinum-based chemotherapy drug belonging to the drug class of alkylating agents and operates by damaging the DNA of cancer cells to stop them from growing and multiplying, researchers reversed harmful tumour metabolism and empowered immune cells to fight back, all without added toxicity. This innovative treatment focuses on strengthening immune functioning, overcoming chemotherapy resistance. That apart it reduces the toxic side effects.

Globally, lung cancer causes highest number of deaths related to cancer, of which non-small cell lung cancer (NSCLC) accounts for 85% of the cases. While chemotherapy remains as the foundation of lung cancer treatment, it often debilitates the immune system and also has toxic side effects. Chemotherapy affects the immune system predominantly by killing rapidly dividing cells including cells which are pivotal for fighting infection such as healthy white blood cells like neutrophils etc, hence resulting in the reduction of white blood cell count, a condition called neutropenia and leaves patients immunocompromised. The range of this effect depends on three factors, namely, the specific chemotherapy drugs, the dose, and the length of treatment. Compounding the issue, tumours can expropriate the mitochondria of immune cells through nanotube-like structures, further lessening immunity. There is no doubt that immunotherapy has a positive outcome for some, but there are many patients who still fail to respond. Owing to these shortcomings, need of the hour is to have certain strategies that restore immune power and metabolic balance during chemotherapy. This weakness can be turned into strength just by transplanting healthy mitochondria into the tumour environment. In case of advanced non-small cell lung cancer (NSCLC), amalgamating mitochondrial transplantation with cisplatin not only boosts immune cell infiltration but also reverses tumour metabolism and ameliorates the drug's effectiveness. This pioneering approach transfigures the role of mitochondria from a mere energy supplier to an active ally in cancer therapy, there by revealing prospects of treating aggressive lung tumours.

Researchers from Tongji University School of Medicine and Nantong University published a study in Cancer Biology & Medicine examined whether direct mitochondrial transplantation could increase the effects of chemotherapy in advanced NSCLC. They combined functional mitochondria with cisplatin and aimed to not only improve tumour response but also restore immune vigour inside the tumour microenvironment. The findings upon examination, is considered a significant step towards integrative treatments that energize both cells and immunity.

The functional mitochondria from human cardiomyocytes, cells known for their high energy output were isolated and then transplanted into NSCLC tumour models, both in vitro and in vivo. Upon examination it was found that the mitochondrial transplantation alone did not harm cancer cells.

On combining with the mitochondria with cisplatin it was observed that the tumour suppression enhanced. This synergy reduced the IC50 of cisplatin from 12.93 μM to 6.7 μM, revealing greater drug sensitivity. In order to examine weather, the findings of the above experiments done in vitro were equally applicable for in vivo similar experiments were carried on mice. The tumours in mice shrank more drastically with the combination therapy than with chemotherapy alone, and immune infiltration strikingly increased. A major shift can be observed in the tumour metabolism during transcriptomic analysis: downregulation of glycolysis and hypoxia genes, and upregulation of oxidative phosphorylation pathways -- reversing the Warburg effect. Suppression of markers of cell proliferation (Ki67, P53) and stemness (HIF-1α, CD44, CD133) was observed. Crucially, mitochondrial transplantation also revitalized mitochondrial activity in immune cells, strengthening the response of T cells and natural killer (NK) cells. Additionally, no negative impacts on the levels of toxicity, body weight and organ viability were observed. Therefore, it is proven that mitochondria can serve not only as a metabolic but also as immunologic reinforcements, changing the tumour landscape into an environment more susceptible to immune attack and chemotherapy.

It was stated by Dr. Liuliu Yuan that incorporating functional mitochondria to the immune cells, it not only enhances the energy of the immune cells but also restores their ability to fight. The vulnerability of the tumour cells towards chemotherapy also increases. According to him, for the patients who do not respond well to conventional treatments, this is a promising avenue.

Conclusion

A devastating illness like lung cancer starts with the uncontrolled growth of cells in the lungs. While most of the cases are caused due to tobacco smoking, non-smokers might also suffer from this illness due to other environmental and genetic risk factors. As mentioned earlier this type of cancer is the leading cause of cancer-related death globally.

Unfortunately, lung cancer often goes undiscovered in its early stages and symptoms appear only after it has advanced and spread. A formidable challenge is thrown to the medical science and public health due to the aggressive nature of the disease and late diagnosis.

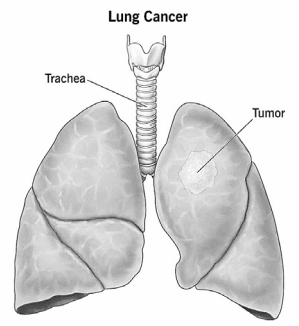

Figure 1: Tumor in the superior lobe of the left lung is observed.Source: Cleveland Clinic 2022

This discovery lays the groundwork for a new therapeutic paradigm - one that harnesses the mitochondria's unique biology to augment cancer treatment. Mitochondrial transplantation could improve the effects of existing chemotherapy drugs while reducing immune suppression, in case of patients suffering from advanced NSCLC. Apart from lung cancer, this approach may extend to other tumours as well, in case where immune dysfunction and metabolic reprogramming acts as barriers to treatment success. Mitochondrial transfer could evolve into a multifaceted platform for combination therapies which helps in moving beyond the current limits of cancer care and into a new era of bioenergetic and immune restoration. With the expansion of cancer research, this study would be a guiding light and a revolutionary pathway to transformative treatment. The mitochondrial transplantation can create new possibilities for therapeutic innovation which in turn empowers patients to reclaim their lives. It also shifts the perspective of this devastating disease. These findings not only hold profound promise but also provides a brighter future for affected persons and a testament to the relentless pursuit of medical advancement in a world impacted by cancer.

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The Private Investigator of Nucleic Acid: SHERLOCK

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Keywords: CRISPR, Nuclease, Nucleic Acid, Gene Editing, Dengue Fever, SHERLOCK

Introducing CRISPR- Clustered Regularly Interspaced Short Palindromic Repeats

Phages have been infecting bacteria for millions of years. To combat this foreign DNA, bacterial systems developed a rather interesting defence mechanism.

When a bacteriophage injects its DNA into bacterial cells, the bacteria integrate small segments of this phage DNA into its own genome in a particular repeat known as CRISPR arrays. Upon subsequent viral attacks, the cell utilizes these regions to generate certain CRISPR RNA sequences (crRNA). crRNA binds to Cas9 proteins forming a crRNA-Cas9 complex. This complex now binds to the viral DNA at specific sites and the Cas9 protein (endonuclease) cuts the DNA, thus neutralizing the infection.

CRISPR was first discovered in *Escherichia coli* by Japanese scientists (Ishino et.al) in 1987. Doudna et.al implemented this defence mechanism in various Genome Editing methodologies.

For editing the genes of humans, two components are used: an RNA guide (gRNA) and a nuclease, in this case Cas9. This RNA guide is designed complementary to the target DNA (part of the sequence which is to be edited). This gRNA binds to Cas 9 and brings it to the target DNA sequence. Cas 9 protein then cleaves the DNA, leading to various phenotypic expressions. This is a common step in all CRISPR tools.

The next step is case specific. Various methods of gene manipulation and inactivation can be used to treat various chromosomal aberrations, cancers and retroviral infections.

Cas 9: It is a 160 KDa Protein majorly associated with the anti-viral activities of bacterial cells. Cas9 is an RNA-Guided DNA Endonuclease enzyme. It is associated with Mg^{+2} ion for binding with viral DNA for endonuclease activity. However, it only has a nuclease activity when a gRNA is bound to it (conformational changes).

Boundaries of CRISPR-Cas9 genome editing mechanism

1. Off-Target Effects: One major side-effect of CRISPR-Cas9 is the high frequency of Off Target Effects (OTEs) which are unwanted, often detrimental alterations to the DNA sequence. Such changes include deletions, insertions and translocations leading to frameshift mutations in the target DNA.
2. Potential DNA Damage: CRISPR Therapy might lead to double strand breaks (DSBs) that activates an apoptotic pathway. This phenomenon was first observed in human pluripotent stem cells.
3. Immune Response: Due to antibody production of the acquired immune system in humans, CRISPR therapy might fail. Charlesworth et.al first demonstrated that more than 50% of their test subjects possessed anti-Cas9 antibodies in their system due to prior bacterial infections. This is still a field of active research and its clinical applications is yet to be determined.

Furthermore, the CRISPR-Cas9 system is restricted to precise applications in DNA editing. However, it is unable to edit RNA- Sequences. To tackle this issue a similar system involving the Cas13 protein has been developed: Regarded as Specific High Sensitivity Enzymatic Reporter unLOCKing: SHERLOCK.

What is SHERLOCK?

Discovered by Feng Zhang, Omar Abudeyyeh and Jonathan Gootenberg, this technique replaces the traditional Cas 9 protein with Cas 13. This involves a prior amplification of nucleic acids for more efficient binding with either target DNA or target RNA sequences.

"This platform, turned Specific High Sensitivity Enzymatic Reporter Unlocking (SHERLOCK), allows for multiplexed, portable, and ultra-sensitive detection of RNA or DNA from clinically relevant samples." - Max J Kellner et.al .

Cas13: Cas13 indiscriminately cuts its RNA target sequence in ssRNA. This is perfect for attacking mRNA. Another property is that it can temporarily change gene expression, unlike cas9 whose effects on DNA are permanent.

Brief Working Procedure

1. Preparation of sample and extraction of nucleic acid: A fluid/tissue sample is collected from the test subject. The cells are lysed using detergent buffers or certain digestive enzymes. The DNA and RNA is then eluted using water and tris buffer. Quality is checked through spectrophotometry and gel electrophoresis.
2. Pre-amplification of nucleic acid: To amplify the target DNA, Recombinase Polymerase Amplification (RPA) is carried out at a temperature of 37 - 42 °C. In the case of RNA, it is converted to cDNA via reverse transcription and then amplified.
3. Preparation of the CRISPR enzymatic detection system: The Cas 13a (or Cas 12a for DNA) is complexed with the guide RNA complementary to the target sequence. Also a fluorophore oligonucleotide sequence is attached for visual detection. This system is termed as the "CRISPR Detection Mix".
4. Detection of the target: The CRISPR Detection Mix and the amplified DNA (or cDNA) sequence is taken together in a suitable buffer and incubated. If the target is present, the gRNA attaches to the genome sequence cleaving both the Cas enzyme and the fluorophore primer. Only if fluorescence is present, can one infer that the sequence alignment has happened and the target genome sequence is present.

SHERLOCK's Investigation of Dengue Fever: Application of CRISPR-Cas13a

Dengue is a female *Aedes sp*. mosquito (Tiger mosquito) borne disease whose incidence is quite prevalent in tropical areas like West Bengal during monsoons. Recent studies have revealed that the Dengue virus (DENV) has four distinct variants or 'serotypes': DENV1, DENV2, DENV3, DENV4. These 4 variants interact with and harm the human body in their own different ways. Despite diagnostic tools like ELISA or PCR, CRISPR-Cas13a method has been able to isolate distinct gRNAs complementary to the different serotypes of DENV.

Furthermore, recent research is underway to completely eradicate the ailment. Using the CRISPR-Cas13a mechanism, this goal can be achieved. The target gene is the NS3 region (Non-structural protein 3), which is crucial for viral replication, protection from the host immune system and for spreading the infection. The experiment involves the basic principle of SHERLOCK by binding the CRISPR-Cas13a and guide RNA system with the NS3 gene into human cells infected with DENV (Li et.al - reference 8). Results showed that the gRNA system successfully recognised and cleaved the NS3 domains reducing their levels of toxicity in human cells. Also, the human genetic material was not affected by this process owing to the high specificity of this procedure.

Conclusion

The viral infections which have been plaguing humanity for millennia are no longer fatal. Development of drugs which work against chronic diseases such as AIDS have been discovered. The usage of CRISPR-Cas13 has paved a new way for research and drug discovery. Its applications in treating viral infections such as Dengue shows us its

potential. No doubt, SHERLOCK is a tool to unlock many hidden mysteries, no pun intended.

Whether it is a boon or a bane to humanity depends on how we decide to use it. Indeed, an ethical question must be raised in order to prevent unregulated usage of this technology.

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Human Animal Chimeras a Boon or a Ban?

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Keywords: Human-animal chimeras (HAC), Autologous Transplantation, Cognitive Thinking, Emotional Intelligence.

Introduction

Organ transplantation is a highly utilized treatment for many medical conditions, but in recent years, the wait list for receiving an organ has increased significantly. To reduce the wait time, scientists have started seeking other technologically advanced techniques using gene editing methods. Animals have been used for drug safety tests for many years, but recently scientists have been seeking more. Human pluripotent stem cells have been injected in mouse embryos with the gene for pancreas being disabled through techniques like CRISPR, this creates a developmental niche for the new organ (the most common target is the Pdx1 gene which is essential for pancreatic development). These induced pluripotent cells are guided by the mouse's developmental signals to fill the niche and differentiate into appropriate cell types to form human pancreas. When these cells were transferred into immunodeficient mice, they were able to mature into fully functional, glucose responsive beta cells. This resulting tissue can secrete human insulin and reverse diabetes in mouse models. This experiment was the breakthrough point as it led scientists to wonder that if human pluripotent stem cells can lead to formation of organs in closely related other species, then it might be possible to grow human organs in such animals and extract them for patients on the waitlist for organ transplantation.

What are chimeras?

Chimeras developed for human organ production can be created in various ways, including blastocyst complementation (the above-mentioned example), xenotransplantation, but they are not a result of sexual reproduction. A type of chimers called mosaicism or micro-chimerism happens when genetically distinct cells are present in a single organism. Chimerism is a natural phenomenon since it happens in human pregnancies between mother and the fetus, at times between fraternal twins.

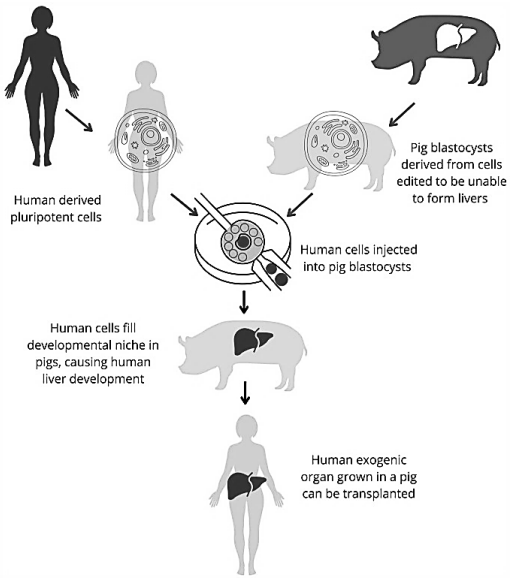

Figure 1: Generating exogenic human organs in interspecies chimeras using blastocyst complementation

Source:https://pmc.ncbi.nlm.nih.gov/articles/PMC10467371/figure/fig1-09636897231183112/

A neural chimera is a chimera that independently forms a part of the central nervous system, the brain and the spinal cord.

Why should chimeras be created?

Creation of these chimeras would provide a model for evolving traditionally used methods for treating neurological disorders for a large population and

would resolve the most important issue of consent regarding studying of these disorders. Moreover, using animal models to study diseases unique to humans are imperfect predictors of therapies. Even using the most genetically close nonhuman primate for testing vaccines has failed most times. Currently the practice of keeping large lab grown organs alive outside the human body for more than a few days has not improved significantly. Chimeras will significantly increase the rate at which organs are grown as the development time for these animals like pigs and sheep are less than the gestation time of human. Autologous transplantations are better suited as the cells are immunologically more viable, and the chances of immunosuppression are extremely less which in turn reduces the chance of organ rejection. Further, under the National Organ Transplant Act, organ donor means a human being who is the source of the organ for transplantation into another human being. If the donor were a chimeric animal, it would not fall under the auspices of NOTA and hence there would be no issues regarding consent.

Laws regarding HAC

In March 2019, Japan modified its laws to allow the creation of human or non-human chimeras inside the uterus of another species beyond 14 days, eventually until term. According to the law passed in 2001, HAC could only be created for primary research only, and these referred embryos were not allowed to grow beyond 14 days, when the primitive streak comes around, they cannot be transferred to the uterus of an animal. With the recent change in the law, it now allows the creation of chimeras with human brain cells which was earlier forbidden. The prior prohibition was based on the belief that "producing a brain derived from human cells in the body of an animal may have an effect on the animal behavior and should be regulated even at stages before individuals are generated" (*Mizuno et al.*, 2015). Currently the regulations of Japan allow the growth of such organisms for indefinite time.

The Japanese expert panel in bioethics in the cabinet office carefully considered the moral, ethical as well as the future of humans. The main concern in generating human organs in animals lies in the possibility of these animals' gaining human like credibility and emotional intelligence, when dealing with neural chimeras. However, we are yet to discover certain specifications regarding this issue. We lack the precision as to how many human brain cell would actually be required for the organism to gain human like cognitive skills. Or exactly at which point in its growth will it generate emotional intelligence. Infact if the transfer happens postnatally the possibility of the animal having human like capacities is pretty much impossible. In the Rochester study, where mouse was introduced with the human glial cells in their brains. Researchers revealed that the mouse remained a mouse the human cells only increased the efficiency of the mouse's own neural networks.

The British academy of medical sciences stated that 'merely demonstrating quantitative enhancement of one's aspect of an animal's cognitive function

	Animal cells transferred into another animal	Human stem cells transferred into mammalian (nonprimate) blastocyst, embryo, or fetus	Human stem cells into nonhuman primate blastocyst, embryo, or fetus	Human progenitor cells into brain/CNS of nonprimate animals	Transfer of an animal somatic cell nucleus into a human oocyte	Animal cells into human blastocyst/embryo	Live born human with animal haploid cells	Relevant state statutes
California		P	P	17 CA ADC § 100070				
Illinois		P	P	77 Ill. Adm. Code 995.90				
Virginia				VA Code Ann. § 32.1-162.22, § T. 23, Ch. 22.1				
Mississippi				Miss. Code. Ann. Ch.27 § 97-27-10				
Arizona	P	P	P	A.R.S. § 36-2311, § 36-2312, 35-196.04				
Louisiana	P	P	P	LSA-R.S. 14:89.6, § 89.6., RS 40:1300				
Montana				MCA 50-11-103				
South Dakota				SD Codified L § 34-14-22 (2019)				
North Dakota				Section 12.1-39				
Missouri				V.A.M.S.340.220				
Oklahoma				§63-1-727, §63-1-749, §63-1-270.1				
Arkansas			P	§ 20-16-1001, § 20-16-22				

Figure 2: Aspects of chimera related science prohibited by existing legislature in each state
Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC10467371/table/tble3-09636897231183112/

does not imply its cognitive is approaching that of human' (Academy of Medical Sciences, 2011, p. 47). In a study in 2016, Hyun (2016) it was discussed that it takes an infant brain to develop completely years with the correct social nurturing even after all its cells being human, so in no way would a HAC be able to develop that level of social consciousness. This is called anthropogenic arrogance.

Despite of all this, United Kingdom does not permit the placement of a chimera in the uterus of either an animal or human.

Conclusion

Modern science has now developed to the point where creating all the creatures from our bedtime stories is now possible. Man with the head of a lion, sounds fictitious but not with the boons of gene editing and HAC. However, is it legally, morally and ethically, correct? That remains unanswered. It has always been the thirst for knowledge of discovering the unknown that has led to some of the most legendary as well as deadly discoveries. Evolution, an ongoing process of nature. No matter how much we statistically try to analyze the probabilities of these organisms' gaining human like capabilities, it's not under our control. There are no rights protecting these organisms. We all saw how the anthropogenic arrogance failed miserably when covid rampaged the humankind for months, a mere virus. Now we are blurring the lines between different species, what came from a mere idea of saving humans by extracting organs could lead to the creation of an entirely different species of "super humans". Thus, HAC whether it will provide to be a boon or a ban it's for the researchers and the future to decide.

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New Patterns in Membrane Protein Behavior Unlocked

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Keywords: Protein-designing technique, molecular motif, transmembrane helix packing.

Proteins are an integral part of the fluid-mosaic structure of cell membranes. They are scattered (like mosaic stones) on the lipid bilayer. The fluid character comes from the fact that the hydrophobic fatty-acid tails of the individual lipids can rearrange among themselves, providing a certain degree of mobility or fluidity to the membrane structure. Membrane proteins are of the following types (as per their position on the bilayer)

i. Peripheral-membrane proteins, that lie afloat on the outer surface of the lipid bilayer

ii. Integral-membrane proteins, that are embedded within the bilayer

Transmembrane proteins are a class of such integral proteins that stretch across the entire membrane.

Membrane-proteins play many important roles including transporting substances in and out of the cell, transmitting signals, catalyzing reactions and helping in cell-cell adhesion. Malfunctioning of these membrane-proteins can cause serious diseases such as cancer, thereby making them attractive drug targets.

Why is it challenging to study membrane-proteins?

Understanding how membrane-proteins behave and function can be challenging due to their position within the lipid membrane and the tendency to "fall apart" when broken out of the cell. Their hydrophobic nature requires detergents to maintain their structure and preserve them outside the cell. It is also difficult to crystallize them due to their fragility. Moreover, cells have low protein yield that further makes it challenging to obtain and purify in large quantities.

Advancements in the field of protein study

Cryo-electron microsopy allows for the study of membrane-proteins in their membrane-like environment and has significantly advanced structural determination by providing higher resolution structures from non-crystalline samples.

Synchroton radiation and X-ray crystallography have improved the ability to collect diffraction data from membrane-protein crystals.

Scientists have recently developed a computer-driven strategy to understand the working of proteins at an atomic level. This technique involves designing new synthetic proteins "from scratch" with computer programs to approximate the behavior and structure of natural membrane-proteins.

General structure of membrane-proteins

They consist of multiple helices that are folded and tightly-packed (like strands of a rope). The study of various membrane-proteins revealed that there is a common pattern (motif), i.e. a small amino-acid which repeats after every 7 amino-acids in a protein chain. This pattern implies that these specific amino-acids are present in the same position on every second turn of a given helix. Scientists hypothesized that such motifs represent "sticky spots" that enable protein helices to bind to each-other and organize within their membrane folds.

Role and features of the motif

To understand why this motif is so conserved and how the atoms create stability, researchers

used a computer program to design idealized versions of the motif to study in labs. Once the synthetic proteins were produced, they folded as predicted, supporting the “sticky spot” hypothesis. Like-wise it was shown that when the motifs were given the most optimal sequences, the resulting proteins were found to be extremely stable and remained intact even under boiling conditions. The motif’s stability is driven by an unusual type of hydrogen bond that is typically very weak, but when the motif is repeated, these weak H-bonds all add up to make a very stable interaction.

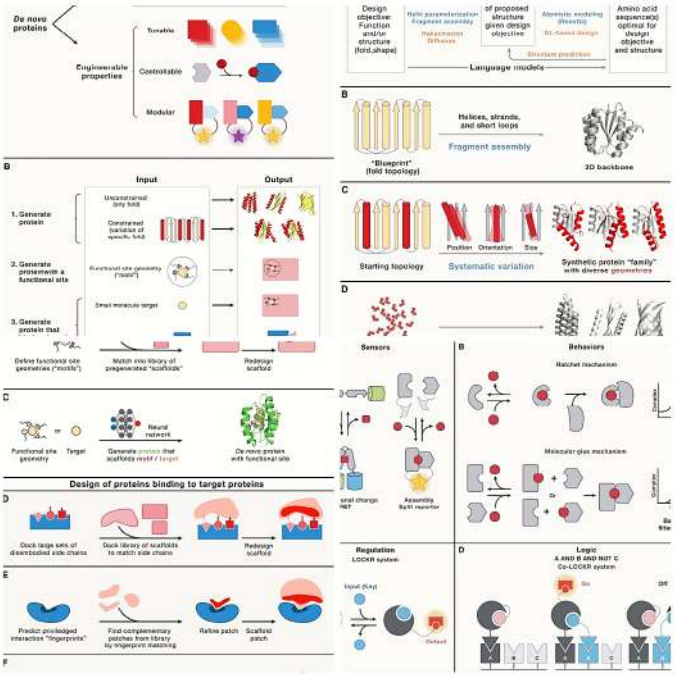

Figure 1: The above image is a collage of 4 figures that show the various steps of protein designing. *de novo* protein design in the age of AI, Protein design concepts and approaches, *de novo* design of molecular functions & *de novo* design to control cellular functions

Significance of the obtained result

The protein-design approach decoded a sequence-structure relationship underlying transmembrane helix packing. It uncovered how Small-X_6-Small consensus sequences (i.e. the special patterns or motifs) encode antiparallel folds and stability. The findings offer chemical rules and computational strategies to interpret and manipulate membrane-protein folding and function with implications for therapeutic targeting and biotechnological applications like engineering nanopores and lipid-embedded miniblinders. Researchers even believe that this information may be useful in identifying and understanding genetic mutations that can potentially cause genetic diseases. Scientists are now looking forward to designing molecules to directly target membrane-proteins within the cell. This approach encourages and accelerates the necessary urge to discover more about the inner workings of membrane-proteins and how to make better therapies.

In conclusion, it is worth noting the following detail of the research undertaken

A fragment-based data-mining and sequence statistical inference method (including cross-evolutionary structure-aligned covariance) was used for engineering de novo TM protein assemblies by successfully encoding Gly-X_6-Gly and Ala-X_6-Ala building blocks. A highly-stable glycine-based design’s X-ray structure hosts -C-H- - - - -O=C- (i.e. H-bonding) alongside extensive backbone-directed van der Waals packing, idealizing features of this motif in nature. Data-driven design navigates sequence space to directly inquire upon how to encode and stabilize vital membrane-protein structural elements, facilitating effective construction of lipid-embedded architecture of increasing complexity.

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Synthetic Biology Fighting off Antibiotic Resistance : The Teixobactin Breakthrough

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Keywords: Antimicrobial Resistance, Teixobactin, Synthetic biology, Horizontal Gene Transfer

Introduction

The discovery of antibiotics has been a great boon to us. From sailing towards back to 1928, when Alexander Fleming brought forth the golden age of antibiotics which not only saved so many lives but also provided the structural foundation of overall new antibiotics. However, everything has a dark side besides its good side. Slowly, antibiotic resistance became an inevitable and a complex issue. Due to the success of antibiotics, it was once thought that bacterial infections would be fully curable. Decades later, clinical research and tests found that almost resistance against all current antibiotics is possible. To overcome antibiotic resistance, alternative treatments are needed to diversify treatment options, which can potentially alleviate our dependence on antibiotics. Here, synthetic biology can play a major role in overcoming this.

Synthetic Biology is about using biology's way of redesigning biological systems/organisms for our own benefit or purposes. This article review mainly deals with the quantitative and synthetic biology which can improve diagnosis and treatment of bacterial pathogens in light of the antibiotic resistance crisis.

What are the different ways in which bacteria develop antibiotic resistance?

Bacteria uses various intricate pathways to acquire and propagate **Antimicrobial Resistance** (**AMR**), a significant challenge to global public health. One of the pathway is **genetic mutation**, wherein spontaneous modifications within the bacterial chromosomal structure can permute drug targets, reduce drug uptake, or boost up the efflux pump activity. For example, point mutations in the ribosomal subunit - encoding genes may confer a certain amount of resistance to macrolides, class of antibiotics used to treat sinusitis and other skin infections in humans. Another more rapid and coherent method is Horizontal Gene Transfer (HGT), where bacteria acquires resistance genes, new metabolic pathways and hence increase pathogenicity through transfer of mobile genetic material— such as **plasmids, transposons, or integrons**—between similar strains of bacteria, or across different species. Three vital HGT mechanisms are **conjugation** (direct cell-to-cell transfer), **transformation** (uptake of extracellular raw DNA) and **transduction** (bacteriophage-mediated transfer). These genes encode special enzymes called **beta-lactamases**, which inactivates the antibiotic chemically or alternative proteins that ignore the drug's action mechanism and potential. Further, **biofilm** formation by some bacterial strains develop AMR by acting as physical barriers that prohibits drug penetration, allowing genetic exchange and survival under extreme antibiotic pressure.

Some novel strategies of synthetic biology to combat AMR

Synthetic Biology is developing as a powerful fight back against antimicrobial resistance (AMR) by offering innovative alternatives to traditional antibiotics. Synthetic Biology approaches its aim to be modular: with proper design and implementation, individual modules such as sensing, processing and effector modules which can be replaced by depending on design goals without drastically

affecting functions of other modules. Some novel strategies of synthetic biology for combating AMR include:

Engineered bacteriophages: Usually wild type phages are inefficient in penetrating bacterial biofilms which are a major contributor to antibiotic resistance. Bioengineering can remodel or redesign phages equipped with genes that produce biofilm degrading enzymes, aiding in more effective bacterial killing.

CRISPR-Based genome editing: This technique is highly significant in biotechnology. Phages can be genetically modified to carry CRISPR-Cas systems that specifically target and destroy ARGs and make the bacteria once again vulnerable to conventional drugs, while preserving the beneficial microbiota.

Activating BGCs: Many fungi and bacteria carry silent or "cryptic" biosynthetic gene clusters (BGCs) as they have been previously undetectable or transcriptionally silent. BGCs encode for unknown natural products, some of which may have antimicrobial properties. Synthetic Biology offer new options to fight the rapid emergence of AMR by genetically engineering bacteria through recombination techniques. Thus it allows for the modification of modular pathways, such as non-ribosomal peptide synthetases (NRPS) and polyketide synthases (PKS), to create novel antimicrobial structures.

Quorum quenching: Bacteria use a special mechanism called quorum sensing (QS) to communicate and coordinate their behavior as a population where cells release and detect signaling molecules (auto-inducers). Quorum quenching helps in overcoming antimicrobial resistance by interfering with this communication process, thus blocking the bacteria's ability to coordinate group behaviors like biofilm formation and virulence factor production, which makes bacteria more vulnerable to host immune responses and less resistant to existing antibiotics. Quorum quenching can be achieved with the help of synthetic biology by designing engineered bacterial cells such as synthetic biosensors or targeted drug delivery, and phage mediated QQ carrying lactonases as enzymes by inhibiting signal production of bacteria.

Effective use of existing antibiotics

Improving use of antibiotics such as adjusting doses and combining drugs can make treatments more effective, delay antibiotic resistance or even can reverse it. Scientists are now using computer models to predict how bacteria respond to different treatments, helping design better drug combinations and dosing schedules. Understanding how bacteria can evolve resistance also allows doctors to choose antibiotics that slow or prevent this process.

Beyond antibiotics, synthetic biology offers new solutions like **phage therapy**, using viruses that infect bacteria. Phages can multiply inside the infection, evolve with bacteria, and target specific harmful microbes while leaving good ones unharmed. Phages are often engineered also to break down biofilms (protective coverings or layers bacteria form) or destroy antibiotic resistance genes using **CRISPR-Cas** technology which can precisely target ARGs of bacteria and help preserve healthy ones. Hence, "such treatments enhance the longevity of antibiotics against evolving targets".

Teixobactin-the newest antibiotic on the block!

Synthetic biology plays a key role in the discovery of teixobactin - a powerful new antibiotic by helping scientists study and produce compounds from bacteria that could not be grown in normal lab conditions. Traditionally most soil bacteria from where many antibiotics come are unculturable directly in the lab. Synthetic Biology tools allowed scientists to create special devices like the **iChip** or isolation chip, which allows these "unculturable" microbes to grow in their natural environment. This led to the isolation of a new bacterium, *Eleftheria terrae*, which produces teixobactin, showing strong antibacterial activity.

Teixobactin, a "head-to-side-chain cyclo-depsipeptide" with its unique chemical scaffold deals with multi-drug-resistant bacterial infections. Unlike many conventional antibiotics that target

bacterial proteins, teixobactin binds to conserved, non-protein components of the cell wall that are essential for survival, thus targeting less mutable molecules.

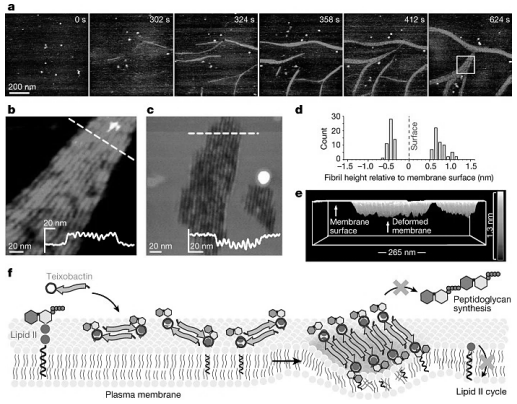

Figure 1: Evidences showing Teixobactin sequestering Lipid II into supramolecular fibrils and its mode of action.

Source:https://pmc.ncbi.nlm.nih.gov/articles/PMC9365693/

Teixobactin has a "dual-pronged" action. It targets Lipid II and Lipid III and inhibits synthesis of bacterial cell walls. Upon binding teixobactin molecules self-assemble to form a unique fibrillary structure which disrupts the cell membrane, ultimately killing the bacteria. Many antibiotics can bind to proteins within bacteria. However, efflux pumps located in the bacterial cell walls can efflux unwanted molecules from the cell. Teixobactin when attach to the outside surface of bacteria avoid this efflux mechanism. For a bacterium to survive, it would need to develop a resistance mechanism against two separate, critical targets at once, which is an extremely difficult "evolutionary hurdle".

Conclusion

Most of the new antibiotics in late stage of development belong to the existing classes. So there is "nothing new under the Sun". Advances in diagnostics and treatment are critical to enhance withstanding the AMR crisis. Synthetic biology provides various novel strategies to augment existing antibiotics and fight against antibiotic resistance. Advances in quantitative and synthetic biology offers unique approaches treating resistant pathogens or even reversing it. Extensive research is still going on to develop next-generation diagnostics and new discoveries and inventions which will furnish better ways to overcome such problems, securing the future of anti-infective medicine.

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AI-Engineered Ecosystems: Algorithmic Design for Synthetic Biospheres

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Abstract

By facilitating the generative design and dynamic control of self-sustaining ecosystems, artificial intelligence (AI) is revolutionising synthetic biology. Real-world implementation for carbon reduction and pollution control is made easier by combining deep learning with evolutionary algorithms and using digital twins and hybrid modelling. To guarantee that this technology functions as a responsible instrument for resilient planetary engineering, addressing three crucial issues—evolutionary drift, biosafety, and computational sustainability—requires hybrid governance and Green-AI principles.

Keywords: Artificial Intelligence, synthetic ecosystems, evolution, Deep Learning, digital twins, biosafety.

Introduction

Artificial Intelligence is no longer limited to fields of data analysis and content creation-it's reshaping the way we design life. The growing problems of biodiversity loss, climate change, and environmental degradation calls for innovative solutions that go beyond conventional approaches to ecosystem management.

The convergence of artificial intelligence and synthetic biology heralds the construction of synthetic ecosystems where intelligent algorithms and communities of living systems co-develop in a dynamic, adaptive partnership which increases efficiency while reducing external output-a revolutionary vision for a self-evolving biosphere. By imitating nature's own process of selection and change, AI-driven evolutionary models allow for the creation of ecological systems that are adaptable, strong and optimised function well in environmental, social, and economic settings.

The Concept of Synthetic Ecosystems

From microbes to humans, living systems form strong, interconnected networks that are vital for carbon storage, nutrient recycling, and maintaining the resilience of entire ecosystems. One of the major aims of modern biology is creating synthetic ecosystems- "intentionally designed biological systems that combine biodiversity and technology, involving organisms with little or no shared evolutionary history, to create functional ecological communities engineered for specific purposes."

Even a two-species interaction, however, is extremely complex due to the interdependence of metabolic cross-feeding, competition, spatial gradients, regulatory crosstalk, evolutionary drift, and environmental perturbations. Conventional "trial-and-error" engineering soon becomes unfeasible. Simultaneously, machine learning (ML) and artificial intelligence (AI) have advanced in their ability to guide design in other fields (such as drug discovery and materials science) and analyse big, noisy, high-dimensional datasets. The design-build-test-learn (DBTL) cycle may be closed more quickly and consistently thanks to the growing convergence of bio-design and AI.

A class of optimisation techniques known as evolutionary algorithms draws inspiration from theories of biological mutations, recombination, natural selection and survival of the fittest. Its analyses a population of potential solutions that represent different ecosystem configuration based on fitness criteria like economic viability, biodiversity richness, and carbon sequestration.

The evolutionary computation approach, inspired by natural selection, is a crucial mechanism enabling Artificial Intelligence to tackle the immense complexity inherent in designing synthetic ecosystems.

Algorithmic Roles of AI in Synthetic Ecosystem Design

The complexity inherent in designing synthetic ecosystems, which involves managing resource competition, metabolic cross-feeding, and evolutionary drift , makes AI essential for navigating the combinatorial design space.

Generative Design and Consortia Assembly

At the molecular level, Deep Learning (DL) architectures are used to learn quantitative mappings from sequence (DNA/RNA/amino acid) to function , enabling the generative design of novel biological components, such as optimised enzyme kinetics or novel circuit components like toehold switches. These generative models are crucial for finding high-performance sequences that exist beyond the scope of rational design, often jointly optimising for both functional fitness and necessary sequence diversity.

For multi-species systems, the task shifts to network optimisation. Constraint-based metabolic models (CBMs) are combined with evolutionary algorithms (EAs), like genetic algorithms, to iteratively improve the consortium composition or environmental conditions in order to attain a desired phenotype. Designers can reconcile competing objectives, such as optimising functional yield while reducing manufacturing complexity, by using the Multi-Objective Optimisation (MCO) technique. Advanced frameworks, such as GENIA (Genomically and Environmentally Networked Intelligent Assemblies), apply Graph Neural Networks (GNNs) to rationally design synthetic communities. GNNs are uniquely suited to model the non-Euclidean nature of biological interaction networks. By integrating genomic data with pathway complementarity and functional redundancy minimisation, GENIA has successfully predicted optimal nine-member consortia for the sustainable degradation of persistent multi-pollutants, including lignin, atrazine, and PFAS. This systematic, network-aware design mitigates the risk of competitive instability and evolutionary drift.

Digital Twins, Hybrid Modelling, and Adaptive Control

To ensure designs generalise reliably from the controlled laboratory environment to complex field settings, **Hybrid Modelling** (Scientific Machine Learning) is utilised. This technique combines ML surrogates to handle complex, high-dimensional, and noisy sub-processes with mechanistic models (based on known physics and biology) to define large-scale constraints. Fast, multi-scale simulation of evolutionary dynamics and perturbation responses is made possible by this integration, which makes it easier to create Digital Twins—dynamic, virtual prototypes of the biological system and its surroundings. In order to ensure model robustness for translational deployment, digital twins are essential for closing the generalisation gap.

Once deployed, synthetic ecosystems require real-time, adaptive management. Reinforcement Learning (RL) controllers offer model-free control, meaning they do not require a detailed a priori mechanistic model of all species interactions. Instead, the RL agent learns an optimal policy (e.g., controlling nutrient influx via simple on-off “bang-bang” actions) by maximising a reward signal from the environment. Importantly, RL controllers have proven to perform better than conventional proportional integral (PI) controllers, especially in situations where system measurements are delayed or infrequent (long sampling periods). The deployment of autonomous and resilient synthetic ecosystems is now economically feasible due to the robustness to low-frequency measurement, which lowers the operational cost barrier.

Biological and Ethical Challenges in Deployment:

- **Generalisation Gap:** The Generalisation Gap is a fundamental problem. Machine learning models that were trained on limited lab datasets

found it difficult to handle the complexity and variation of the real world. These models must be improved by incorporating mechanistic constraints through hybrid modelling in order to increase their predictive accuracy.

- **Evolutionary Drift:** Evolutionary drift can lead to the emergence of undesirable, or "cheater," biological strains, making it challenging to maintain long-term stability. We must use evolution-aware simulations and put in place genetic protections like kill-switches and enforced dependencies to guarantee ecosystem resilience.
- **Computational Sustainability:** Deep neural networks' large energy footprint raises environmental issues. Achieving a positive ecological balance requires strict adherence to Green - AI principles, which include effective model architectures and renewable computing infrastructure.
- **Biosafety and Dual-Use Risks:** Advanced AI tools can be severely misused enabling the development of harmful gene variants which necessities an adaptive governance framework that enforces model access control, traceable audit systems and automatic biosecurity screening.

Conclusion

The combination of artificial intelligence and synthetic biology, is already providing the resources necessary for a new generation of resilient and self-sufficient artificial ecosystems. Just as with any new paradigm there will be a need for responsible stewardship of these initiatives for success in this direction. Generative design with GNNs and model-free control with RL could only be examples of how AI-based bio-design could be assured an agent of transformative change for planetary health through, hybrid modelling for generalisation, prioritising Green -AI for less of a computational burden, and rapidly design and implement a function-based screening hybrid prerequisite to close the biosecurity gap.

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Engineering *Saccharomyces cerevisiae* : The Insulin Revolution

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Keywords: *Saccharomyces cerevisiae*, Insulin, Recombinant DNA technology

Introduction

A diagnosis of Type I diabetes was a death sentence to patients until 1922, when insulin was first administered to a 14-year-old boy. Till the 1980s, insulin was sourced from the pancreas of animals like pigs and cows, which helped to treat diabetes, but it was not ideal, as the administration of this insulin led to the development of allergies in the recipients and was also expensive. With the advancement in recombinant DNA technology, Genentech scientists successfully cloned the human insulin gene in 1978, resulting in the development of Humulin or human insulin. In 1982, Humulin was approved by the US Food and Drug Administration (FDA). In recent times, insulin has been produced by engineering *Saccharomyces cerevisiae*, demonstrating its significant potential in synthetic biology.

Yeast: The Ideal Pharmaceutical Host

Initially, *Escherichia coli* was engineered to produce insulin, but it has certain limitations.

- Post-translational modifications do not occur in this bacterium.
- It produces inclusion bodies, which include misfolded proteins.
- It adds complex refolding procedures to the process, resulting in increased costs and reduced yield.

Later, Saccharomyces cerevisiae was engineered to produce insulin due to the following advantages:

- Ability to carry out post-translational modifications like proper protein folding.
- Presence of endoplasmic reticulum for protein folding.
- Presence of a well-annotated genome.
- Natural adaptability to harsh industrial conditions.
- Rapid growth time.

About Insulin

Insulin is a peptide hormone required for glucose metabolism. It is formed by the beta cells of the islets of Langerhans of the pancreas.

Insulin is synthesised as preproinsulin, which has a signal peptide that helps to move the preproinsulin into the endoplasmic reticulum (ER). In the ER, the signal peptide is removed to form proinsulin. After proinsulin is folded into an accurate conformation and 3 disulphide bonds are formed, it moves to the trans-Golgi network, where proinsulin is converted to active insulin by endopeptidases, which cleave and release the C-peptide.

Mature insulin is a polypeptide consisting of 51 amino acids with a molecular weight of 5808 Da. It is composed of two protein chains, A (21 amino acids) and B (30 amino acids), linked by disulphide bonds.

Producing this complex structure in engineering hosts is challenging. Formation of mispaired disulfide bonds inactivates insulin. Recombinant insulin must be identical to human insulin; otherwise, immune responses will be triggered.

To overcome these hurdles, two approaches have been adopted.

1. Single-Chain Proinsulin: Proinsulin is expressed as a single-chain precursor, having the C-peptide, which is enzymatically cleaved

to form the two-chain insulin. This process mimics the natural insulin biosynthesis.

2. Separate Chain Production: A and B chains are expressed separately in cultures, purified, and combined in vitro to promote protein folding and formation of disulphide bonds.

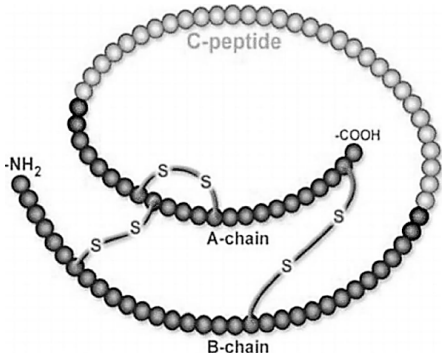

Figure 1: Structure of proinsulin showing C-peptide and the A and B chains of insulin Source: Akinlade, A. T., Ogbera, A. O., Fasanmade, O. A., & Olamoyegun, M. A. (2014). Serum C-peptide assay of patients with hyperglycemic emergencies at the Lagos State University Teaching Hospital (LASUTH), Ikeja. International Archives of Medicine, 7(50). https://doi.org/10.1186/1755-7682-7-50

Laboratory Techniques

1. Gene construction: The human insulin gene is located on chromosome 11 and encodes proinsulin. As genetic language varies, human-preferred codons are replaced with yeast-preferred codons without changing the amino acid sequence. The proinsulin gene is inserted into the yeast plasmid containing a promoter, signal peptide, selectable markers, and terminator.

2. Transformation and selection: The yeast cell wall is temporarily made permeable by either the lithium acetate method or electroporation to get the engineered plasmid into the yeast cells (transformation). Only transformed cells survive on the selective medium. Transformed cells are verified for proper construction.

3. Expression optimisation and screening: To pick out the best producers, small-scale screening is performed using protein detection methods like Western Blotting, ELISA, or SDS-PAGE. Clones are selected based on high insulin yield, stable expression, and balanced growth rate.

4. Fermentation and protein expression: Engineered yeast cells are cultured in large bioreactors under suitable temperature, pH (5.5-6.5), and oxygen saturation to produce insulin precursors in large quantities. Chemical inducers are used for promoter activation and proper expression.

5. Purification Techniques: A series of downstream processes is executed to form the mature active insulin from the precursor by enzymatic cleavage of the C-peptide. Various chromatography methods (ion-exchange, HPLC) are used to achieve high purity for therapeutic substances.

From Petri To Planet

Microscopic organisms like Escherichia coli, yeasts (*Saccharomyces cerevisiae*), and others, once grown in petri dishes, have expanded their dominance to large-scale planetary applications. This huge success of recombinant technology in the production of insulin had acted as a trigger for the trials of producing different complex therapeutic proteins: a “Domino Effect”.

The Key Impacts:

1. Wide Range of Access and Affordability: Microbe-based insulin precursor production has expanded its accessibility, especially to low and middle-income countries, making it cost-effective, with a stable supply compared to the lower output from animal pancreas.

2. Eco-friendly, improved quality and purity: Standardised fermentation processes involving yeasts ensure purity and quality, reducing allergic responses due to foreign origin, and are eco-friendly for curbing the frequency of animal slaughter and resolving different religious concerns.

Facing The Challenges

The complex structure of the insulin, consisting of two polypeptide chains (A and B), linked by the disulphide bonds, and the variability in the yeast protein processing machinery, pose a major challenge in protein folding. Insulin is naturally produced as proinsulin with C-peptide, but engineered yeasts sometimes form a single-chained precursor, producing misfolded proteins, creating problems with insulin signalling, endoplasmic reticulum stress, and beta-cell dysfunction. Modified precursors with altered C-peptide or fusion partners, expression of chaperones, and improved amino acid substitution, like TyrA14Glu, enhance the thermodynamic stability and ensure correct protein folding.

The Kex2 endoprotease of yeast leads to the secretion of incorrectly cleaved or hyperglycosylated precursors due to incorrect cleavage. Using a protease-deficient strain of yeasts, the addition of spacer peptides like EEAEAEAP between the leader peptide and insulin precursor can improve the cleavage efficiency.

One of the concerns regarding the yeast expression system is that the proteins synthesised have higher mannose N-glycosylation than humans, which reduces their efficiency and action-life, activating certain immune responses in the body, as these substances are foreign materials in our body. Humanisation of yeast by modifying the glycosylation pathways can lessen its immunogenic effects.

Conclusion

Research still continues for betterments, suitable for the human body, to reduce the treatment burden. The future research directs towards introducing modifications in proteins, exhibiting alternate expression (transgenic plants) and delivery systems to prevent protein degradation in the digestive system, digital and personalised approaches (AI utility) to meet the unmet needs of diabetes management, and to bridge the economic gaps, making it more affordable and accessible. Yeasts like Pichia pastoris are favoured for their strong protein expression system and protein secretion without hyperglycosylation. Innovations on insulin analogues for developing long-acting, rapid-acting, and smart-glucose responding insulin are undergoing trials. Insulin, one of the most important therapeutic proteins, a lifesaver for millions of people, has come a long way since the 1920s, from being an animal pancreatic secretion to finding its way of production using molecular technology and petri-borne microbes, creating a paradigm of petri dish dominance over the entire planet.

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Microbial Strategy against a Global Crisis: An Epic Breakthrough in *Ideonella sakaiensis*

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Keywords: *Ideonella sakaiensis*, PET (polyethylene terephthalate) degradation, *Is*PETase, protein engineering

Introduction

Plastics are ubiquitous, flooding our planet from mountain peaks to ocean depths. Every year, millions of tons of plastic waste are produced, with polyethylene terephthalate (PET) plastic contributing significantly to it, and accumulating in landfills and oceans. PET plastic is both a convenience and a curse to humanity; although lightweight and durable, this polymer is resistant and virtually indestructible in the environment.

In 2016, in a Japanese bottle recycling facility, scientists made a groundbreaking discovery of a bacterial strain, *Ideonella sakaiensis* 201-F6, that can degrade PET into individual monomeric units by using the PET-hydrolysing enzyme *Is*PETase. This pioneering discovery offered a biological solution to one of the burgeoning waste management crises of modern society.

Microbe And Enzyme

With the discovery of *Ideonella sakaiensis*, it was found that these bacteria grow on low-crystallinity (1.9%) PET films, compared to the 30-40% crystallinity of bottle-grade PET. This bacterial strain possesses two enzymes for PET degradation- PET hydrolase (PETase) and mono-(2-hydroxyethyl)terephthalate hydrolase (MHETase). The degradation occurs via a two-step process. The process is initiated with PETase acting on polyethylene terephthalate (PET) and hydrolysing it into mono(2-hydroxyethyl) terephthalate (MHET) and other compounds. MHETase then hydrolyses MHET into ethylene glycol (EG) and terephthalic acid (TPA).

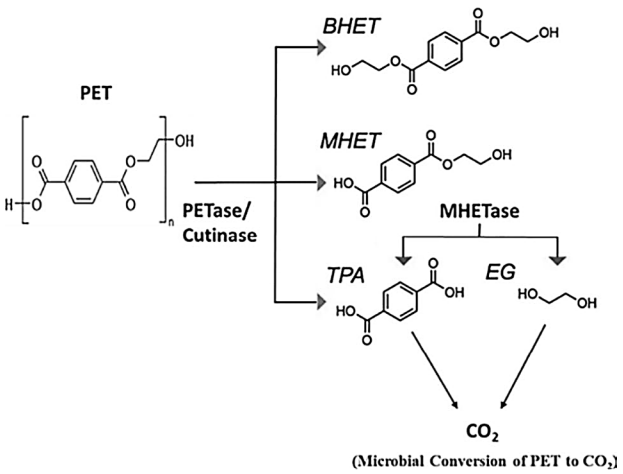

Figure 1 : Enzymatic degradation of Polyethylene Terephthalate (PET) by PETase/Cutinase Source: Mohanan, N., Montazer, Z., Sharma, P. K., & Levin, D. B. (2020). Microbial and enzymatic degradation of synthetic plastics. Frontiers in Microbiology, 11, Article 580709. https://doi.org/10.3389/fmicb.2020.580709

After PET hydrolysis, MHET tends to accumulate, which is prevented by MHETase. This enzyme degrades MHET into ethylene glycol and terephthalic acid. These smaller, non-toxic compounds are utilized synergistically by various microorganisms as their carbon and energy sources, thus promoting a circular bioeconomy. This approach of degrading PET through a synergistic microbe-enzyme system is environmentally friendly, with a better performance than individual microbe or enzyme treatment.

X-ray crystallography has indicated that *Is*PETase (enzyme derived from *Ideonella sakaiensis*) is a member of the α/β-hydrolase superfamily, having a catalytic centre with a catalytic triad formed of Ser160-Asp206-His237. *Is*PETase can hydrolyse PET at room temperature as it exhibits optimal activity at a temperature of 30–40 °C, and its catalytic efficiency decreases at a temperature above 40 °C.

Need For Bioengineering

Natural *Is*PETase has certain limitations:

1. It is a heat-labile enzyme and hence it works best at room temperature; beyond 40 °C, *Is*PETase gets deactivated. In moderate temperatures, the degrading activity of *Is*PETase decreases after 24 hours of incubation. A long incubation period and high temperatures around 50-65 °C are required for PET processing, which makes it inefficient for industrial applications.
2. *Is*PETase works best at a slightly alkaline pH (around 7.5-8.0), and its enzymatic activity decreases with an acidic pH (below pH 6.5).
3. PET has a semi-crystalline structure, which reduces the catalytic efficiency of PETase. Thus, pretreatments are necessary to increase the number of amorphous regions within the molecule.

To improve thermostability, enzymatic efficiency, and robustness of the enzyme, there is a need for bioengineering.

Engineering Approaches

1. Site-directed mutagenesis
    - R280A mutation: Substitution of arginine with alanine at position 280 reduces steric hindrance and electrostatic repulsion, changes the conformation of the enzyme, and improves substrate access. This mutant achieved a 22.4% increase in PET hydrolysis after 18 h, and a 32.4% increase after 36 h under laboratory conditions.
    - I179F mutation: Substitution of isoleucine with phenylalanine improves π-π interactions, resulting in a 2.5-fold increase in substrate affinity and a 3-fold increase in degradation rate than the wild type enzyme.
2. Multi-Site Mutations
    - S121E/D186H/R280A triple mutant: This mutation introduces hydrogen bond donors and stabilizes electrostatic interactions within the enzyme molecule, resulting in a 13.9-fold increase in PET degradation efficiency at raised temperatures.
    - S238F/W159H double mutant: This mutation introduces aromatic residues that promote π-stacking interactions, resulting in a 1.7-fold increase in crystalline PET degradation.
    - W159H/F229Y mutant: This mutation increases thermal stability of the enzyme and increases the formation of the degradation product by 40-fold at 40 °C over a 24-h period.
3. Advanced Engineering
    - To increase the thermal stability of the enzyme, thermostable variants have been developed, like FAST-PETase (melting temperature- 63.3 °C), and HotPETase (melting temperature- 80.5 °C).
    - Immobilization strategy: The PETase enzyme was immobilized with hybrid nanoflowers using $Co(NO_3)_2$ and $CuSO_4$. $Co(NO_3)_2$ -immobilized PETase exhibited better storage capacity, and $CuSO_4$-immobilized PETase showed better reusability.

Lab Techniques

These mutations require several analytical methods, which are as follows:

1. X-ray crystallography: For the determination of the overall structure and catalytic centre of the PETase enzyme.
2. Assays: For screening novel PETase.

    Types:
    - Low throughput: Agar plate-based methods
    - Moderate throughput: Titrimetric methods
    - High throughput: Fluorescent assays
    - Ultra-high throughput: Fluorescence-Activated Cell Sorting

3. Heterologous expression platforms: For screening variants of PETase.
4. Scanning electron microscopy (SEM): For surface characterization.
5. Molecular docking and molecular dynamics simulation: For predicting the performance of mutant PETase.

Real-World Applications

1. Industrial recycling: Degrading post-consumer PET into monomeric units by enzymatic recycling generates virgin-quality plastics and is much more efficient than conventional recycling.
2. Microbial valorization: Pseudomonas species are engineered to convert terephthalic acid into polyhydroxyalkanoates (biopolymers), thus promoting a circular bioeconomy.

Key Challenges

1. High production costs: The cost of enzyme production is quite high. For example, recombinant *Escherichia coli* yield PETase at significantly high prices due to their complex fermentation and purification processes.
2. Substrate pre-treatment: To date, experimental studies have only been performed on PET films, powders, and fibers. Pretreatment of PET to convert intact PET products into smaller amorphous residues is necessary for easier accessibility of the enzyme to the substrate.
3. Environmental sensitivity: PETase shows optimal activity at slightly alkaline pH (around 7.5-8.0) and at moderate temperatures (30–40 °C). Real-world settings like landfills and oceanic environments show fluctuations in pH and temperature, thus limiting the catalytic efficiency.
4. Bio-safety concerns: Release of genetically modified organisms (GMOs) into the environment can disturb the ecosystem, transfer modified genes to other species, and cause disruption to microbial communities. National and international regulations like the Cartagena Protocol on Biosafety govern the approval for the deployment of GMOs into the environment, which further increases costs.

Conclusion

The revolutionary discovery of *Ideonella sakaiensis* in 2016 marked the beginning of a remarkable journey from petri plate to planetary solution. Through protein engineering and synthetic biology, *Is*PETase mutants have achieved up to a 40-fold increase in catalytic efficiency, transforming an enzyme into a powerful tool for PET plastic degradation. Yet there are crucial challenges that need to be addressed- thermostability of the enzyme must improve, production costs must decrease, and biosafety frameworks must evolve to ensure safe deployment of genetically modified organisms into the environment. As interdisciplinary research progresses, *Is*PETase illustrates how a bacterial enzyme, discovered in a Japanese bottle recycling facility, offers hope for a circular plastics bioeconomy- from laboratory innovation to planetary ecological remedies.

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Third parent to fight Faulty Mitochondria

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Keywords: mtDNA, mitochondrial replacement, reproductive technology, mitochondrial donation technology

Introduction

Mitochondria which is often referred to as the powerhouse of the cell is an intracellular organelle having its own genome. The mitochondria has few repair systems and thus are more vulnerable to genetic mutations which lead to disease in approximately 1 in 5000 people. Mutations in the mitochondrial DNA leads to related diseases and it is inherited almost exclusively from the mother. This can affect organs that are dependent on energy from metabolism and cause various incurable diseases. They are difficult to diagnose and thus remain untreated affecting adults as well as children. Three parent baby is a technique where an offspring is produced from the genetic material of one man and two women through use of assisted reproductive technologies. It involves mitochondrial replacement therapy (MRT) and three-person in vitro fertilization (IVF).

The Technique

In mitochondrial substitution technique nuclear genome is withdrawn from the oocyte of the biological female parent who carries mutated mitochondrial DNA and is implanted in a normal enucleated donor. The nuclear genome transfer from oocytes or zygotes is carried out using techniques such as pronuclear transfer (PNT), spindle transfer (ST), polar body transfer (PBT) and germinal vesicle transfer (GVT). Following are the detailed discussion on each techniques :

Pronuclear transfer: After occurrence of oocyte fertilization, two pronuclei (PN) having defined membranes each with a haploid set of chromosome become visible and migrate towards the center of zygote. In this technique, two pronuclei are removed from the zygote containing mutated mitochondria. They are transferred to a normal zygote with previously removed PN. The fusion of the PN and cytoplasm is carried forward by electrical pulse or inactivated Sendai virus. To retain nuclear integrity in PNT, small amount of mtDNA transfer is inevitable leading to heteroplasmy. In the first human study of this technique, it was able to reduce the rate of mutant mtDNA to 2% in most reconstructed zygotes.

Spindle transfer: During the second meiotic division, maternal spindle or the spindle-chromosome metaphase II (MII) complex is formed within the oocyte. In this technique, the spindle is removed and transferred to an oocyte in MII with previously removed spindle. Fusion of the spindle to the cytoplasm is ensured by electrofusion or inactivated Sendai virus.

Polar body transfer: The polar body (PB) is a small residual structure of the meiotic division in females. Appearance of the first polar body occurs after ovulation while the second polar body appears after fertilization of the oocyte with spermatozoa. Both the polar bodies contain exact genetic copy to that of oocyte nucleus. In the polar body I (first polar body, PBI) transfer (TPBI), polar body is removed from the oocyte in MII and transferred to another oocyte in the MII with previously removed spindle. Following this the fertilization of reconstructed oocyte is carried out. During the transfer of polar body II (second polar body, PBII) transfer (TPBII), the polar body is removed from the zygote in

pronucleus stage and it is transferred to zygote containing maternal nucleus having PBII removed. This technique has greater efficiency and greater disease prevention potential as the amount of residual mtDNA transferred is minimal. There are no recorded TPBII study on human zygotes as it might be strenuous differentiating the maternal and paternal nuclei. This makes it difficult to select and accurately extract the maternal nucleus to assist the occurrence of the technique.

Germinal vesicle transfer: The nucleus of the immature oocyte in prophase I of first meiosis is referred to as the germinal vesicle. In the above mentioned technique, germinal vesicle is removed and transferred to an oocyte with its own germinal vesicle previously removed. The reconstructed oocyte is then subjected to in-vitro maturation following which it undergoes fertilization. Initially this technique was invented to treat infertility in older women.

Ooplasm transfer: Cytoplasmic transfer was the first technique curated to treat infertility. This involves the transfer of 5 to 15% of the cytoplasmic content of a healthy donor which consists of mtDNA, proteins, mitochondria and other organelles to the oocyte of the female with mutated mitochondria. Initially it was developed using animal models with the goal of improving oocytes with low cytoplasmic quality

Scope and Future Prospects

With the current limited options for the prevention of transmission of disease with mitochondrial origin, MRT opens up a vast scope. Pre-implantation genetic diagnosis (PGD) is a viable option for prevention of mitochondrial disorders in cases of assisted human reproduction (AHR) but they are not feasible in most cases such as those where the female parent exhibits homoplasmy (where all the offsprings are affected) or high levels of heteroplasmy (due to difficulty of selection of embryo with low mutational load). In contrast to this, in the MRT, due to the small amount of mutated mitochondria loaded during application of the technology and the bottleneck effect, it may decrease the chances of transmission of diseases due to mitochondrial DNA mutation. However, considering that the mutational loads may be different from cell to cell and tissue to tissue, reoccurrence risks are troublesome to estimate. Also, with advanced age of women there is an increase of infertility, embryonic and fetal losses. Reports point that in the embryos of older women, the mtDNA levels are lower at the cleavage stage and higher at blastocyst stage in comparison to that in younger women. Considering the above reports a relation is drawn between mitochondria and infertility and thus it is considered that introduction of mitochondria donated by younger women may have potential to restore fertility of older women's gamete.

Several queries were raised about the communication between the mothers nDNA and the donors mtDNA and their potential of having deleterious effects on the mixing genomes and potential incompatibilities arising between them. As of date, there has been little evidence of MRT being detrimental due to deleterious mito-nuclear interactions as the procedure in humans have led to normal gene expression in the blastocysts stage. Also, in normal reproduction, the interaction of mitochondria with nuclear environment is new due to them never having experienced half of the father's nuclear genome. As this interaction lead to no abnormalities, the same is expected for the interaction of the half of the nDNA donated by the mother with the donors mtDNA.

Conclusion

Mitochondrial replacement therapy (MRT) can thus be seen as a breakthrough to the diseases caused by the mutation in the mitochondrial DNA and thus prevent the prevalence of the mutated mtDNA in the progeny to a certain extent. Also, this technology does not cause significant change in the percentage of parentage of the baby with parental DNA percentage being approximately 99.8% while donor DNA range from 0.1 to 0.2% thus effectivity keeping ethical values. MRT can also assist older women with a better probability of having progeny with healthy physical state. Although reports have

a positive feedback, due to lack of extensive study and experiment there are still questions about the amount of mtDNA load during the procedure. Also due to lack of ample study of the procedure in human there are still queries about its long-term effect on the health of the progeny thus created. Hence, more studies must be performed in humans to demonstrate its effectiveness in preventing mitochondrial mutation induced diseases.

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From Trisomy to Neurodegeneration: Pathophysiology of Alzheimer's in Down syndrome

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Keywords: Alzheimer's disease, Down syndrome, Amyloid Precursor Protein, amyloid-beta peptides, biomarkers

Introduction

Alzheimer's disease (AD) is prevalent in persons with Down syndrome (DS) to a much larger degree than it occurs in the general population. AD usually affects about 10% of people above the age of 65, while nearly all DS adults show the amyloid pathology of AD after reaching their forties. Cognitive impairment occurs in midlife or beyond. The link between DS and AD was established in the 1980s, when neuropathological examination demonstrated extensive amyloid plaques and neurofibrillary tangles (NFTs) in the brain of middle-aged DS patients (Mann, 1988). These findings changed the view of DS from being exclusively a developmental disorder to also being a genetic model of early-onset AD (EOAD). This article highlights how DS increases susceptibility to dementia and the extensive clinical and epidemiological work being carried out for elucidating the more rapid disease course of DS in contrast to sporadic AD.

Genetic cause of AD in DS

The genetic basis of AD in individuals with DS is fundamentally associated with trisomy 21, the presence of an additional copy of chromosome 21, and a consequent increase in the dosage of genes located on this chromosome. Particularly significant is the amyloid precursor protein (APP) gene on chromosome 21, the triplication of which leads to elevated expression levels and subsequent overproduction of amyloid-beta (Aβ) peptides, particularly the amyloid-beta 42 (Aβ42) isoform. These peptides aggregate to form amyloid plaques. Presenilin 1 (PSEN1), and Presenilin 2 (PSEN2) are also recognized contributors to AD risk in the general population. PSEN1 and PSEN2 genes code for presenilins that compose the catalytic subunit of the γ-secretase complex. γ-secretase, along with β-secretase, cleaves APP to form Aβ. Mutations or variations in these genes can increase amyloidogenic peptides and exacerbate plaque formation.

APOE ε4 allele is a lipid transporter associated with a more severe form of AD in DS. Despite potential early cognitive benefits linked to lipid metabolism, the presence of this allele may induce late-onset AD (LOAD).

Further modifiers involved in inflammatory processes, lipid metabolism, and neuronal signalling pathways have been identified. These factors contribute to the clinical heterogeneity observed across persons with DS, despite a common trisomic background.

Neuropathological features

In DS, alterations such as endosomal enlargement, defective synaptogenesis and reduced neurogenesis are observed early, including the fetal brain; thus, AD neuropathology develops well before clinical dementia manifests. "AD is characterised by synapse loss, followed by the atrophy of neurons throughout the cerebral cortex, with the medial temporal lobe being the most severely affected" (Sheppard & Coleman, 2020). The degeneration begins at the hippocampus and entorhinal regions and then expands throughout the fronto-temporal cortices.

Extracellular Aβ plaques, made of mostly Aβ42 and a smaller percentage of Aβ40 peptides, initiate a cascade of events that disrupts synaptic plasticity

and transmission. This is the major cause of autosomal dominant forms of EOAD (AD-EOAD), showing clinical signs before the age of 65.

Aβ plaques trigger abnormal phosphorylation of tau protein by activating cyclin-dependent kinase 5 (CDK5) and glycogen synthase kinase 3 (GSK-3). This forms NFTs, causing a synergistic cognitive deficit. Aβ induces the cleavage of tau by caspase-3 (CASP3) to result in neurotoxic oligomers. Tau oligomers bind to microglia and astrocytes; Aβ itself is structurally similar to antimicrobial peptides (AMPs) that stimulate glial cells. These factors induce pro-inflammatory cytokine release and consequent neuroinflammation.

Aβ oligomers cause mitochondrial fission and fusion imbalance, leading to mitochondrial dysfunction and oxidative stress. Aβ deposition in cerebral and leptomeningeal vessels causes cerebral amyloid angiopathy (CAA) in DS adults, and its progression may weaken the vessel walls inducing microbleeds.

Clinical manifestations and Diagnosis

There can be a significant gap of 20+ years between the start of Alzheimer's pathology and the appearance of the first symptoms in individuals with Down syndrome. However, recognizing the early and later stages of dementia is difficult due to variances in pre-existing intellectual disability. In addition to behavioural alterations, avoidance and depression are early clinical signs linked to amyloid-beta and NFT pathology.

This clinical progression can be insidious, as seen in a case study where an individual progresses from depressive symptoms at age 48 to a full dementia diagnosis by 55. Diagnosing Alzheimer's remains challenging, as caregivers often mistake early symptoms for the individual's baseline intellectual disability. Currently, there are no universally accepted diagnostic criteria specifically for this population, making early and accurate diagnosis exceptionally difficult. Evidence suggests that direct, performance-based cognitive tests, such as the modified Cued Recall Test, are more sensitive for detecting early decline than informant-rated measures.

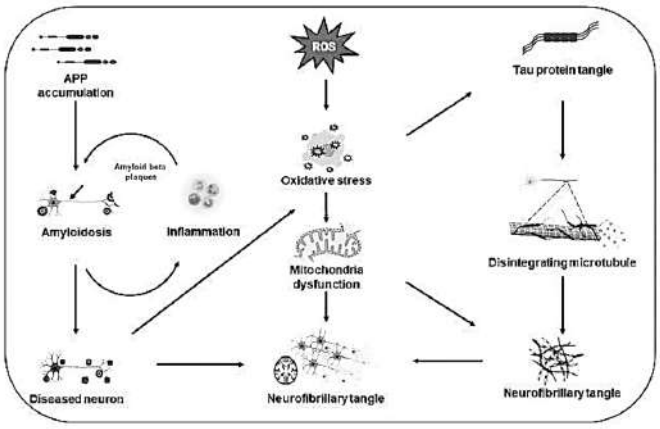

Figure 1: The proposed neurobiological mechanisms involved in the pathogenesis of AD

Source: https://www.aginganddisease.org/article/2024/2152-5250/148464/null/thumbnail/AD-15-1-43-g2.jpg

Biomarkers for AD in DS

To address these diagnostic challenges, researchers use objective biomarkers to stage the disease progression. Biomarkers are crucial for understanding disease progression by evaluating their positive and negative predictive values, starting decades before symptom onset.

Fluid biomarkers detect early changes within the long-standing AT(N) framework (Amyloid, Tau, Neurodegeneration). This cascade has been extensively mapped by longitudinal studies like the Alzheimer's Biomarker Consortium–Down Syndrome (ABC-DS). A gene dosage effect often increases plasma Aβ1-42 and Aβ1-40 levels, causing a significant reduction in the early variability of the Aβ1-42/40 ratio during the preclinical stage. While plasma p-tau181 peaks 10 to 15 years before the expected prodromal AD diagnosis, plasma Neurofilament Light Chain (NfL), which assesses axonal damage, may serve as a good predictor of symptomatic Alzheimer's disease. Additionally, plasma GFAP, an astrogliosis marker, increases around 10 years before positive amyloid PET results, supporting a new expanded AT(N)I framework for inflammation.

Although fluid biomarkers are the earliest indicators, neuroimaging plays a crucial role in confirming the

sequence of abnormal accumulation later in life. Mature neurotic plaques are identified through amyloid PET positivity, which typically begins with increased striatal uptake in the late 30s. Tau PET confirms tau pathology only in amyloid-positive individuals, displaying tau distribution consistent with Braak staging. Neurodegeneration markers include FDG-PET, showing hypometabolism similar to AD in the parietal, praecuneus, and posterior cingulate cortex, and structural MRI, which reveals AD-related atrophy in the hippocampus, thalamus, striatum, and posterior cortical thinning. Features of CAA are frequently observed with imaging. Timely detection, monitoring, and assessment of clinical trial eligibility rely on the comprehensive integration of these fluid and imaging modalities.

Therapeutic and intervention strategies

The ability to identify this long preclinical phase through biomarkers offers an attractive opportunity for therapeutic intervention. However, there are currently no approved drugs for treating AD dementia in people with DS.

DS is arguably the best population for conducting AD prevention trials due to its predictable, high risk for symptomatic AD and uniform pathophysiology, raising a clear ethical obligation to carry out these trials. Future efforts focus on anti-amyloid monoclonal antibodies, with prevention trials of agents like lecanemab, anti-tau, and anti-inflammatory therapies. Because of the high prevalence of CAA in DS, anti-amyloid trials will have to be monitored carefully for amyloid-related imaging abnormalities (ARIA). In addition to clinical management, it is important to treat co-morbidities, as sleep-related and mental health conditions (e.g., depression) have been shown to diagnose and delay the onset of AD in symptomatic patients (e.g., hypothyroidism, sleep apnoea, or seizures).

Conclusion

APP triplication makes DS a unique genetic model of AD. Yet, DS community has been largely excluded from major AD clinical trials, raising ethical and scientific concerns. Future work should prioritize their inclusion in therapeutic drug trials and focus on developing validated cognitive assessments and clinical targets for DS adults. Analysing the factors underlying variable dementia onset and studies integrating neuroimaging, cognitive measures, and clinical outcomes are needed to employ personalized strategies to delay symptom onset and improve quality of life.

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A Historic Win for Immune Science

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Keywords: T_{regs}, FOXP3, CD25, Autoimmune

Introduction

October 2025 saw one of the most thrilling announcements in recent Nobel history. The Nobel Prize in Physiology or Medicine was shared by Shimon Sakaguchi, Mary E. Brunkow, and Fred Ramsdell for their pioneering findings regarding regulatory T cells (T_{regs}) - a unique subset of immune cells that serve as the body's "peacekeepers". Their research revealed how our immune system avoids catastrophic self-attacks, a phenomenon referred to as peripheral immune tolerance. Outside of revolutionizing fundamental immunology, their findings have also led to new therapies for autoimmune illnesses, transplant rejection, and even inflammatory diseases.

Solving a long-standing mystery

Scientists have puzzled for decades about how the immune system does not attack the body's own healthy tissues. They realized that a lot of self-reactive immune cells are weeded out early in life within the thymus (a phenomenon known as central tolerance). But this wasn't the complete picture — a few rogue immune cells broke through this early culling, and individuals still developed autoimmune disorders such as type 1 diabetes, lupus, and multiple sclerosis. Scientists believed that there had to be another mechanism in place — one operating outside the thymus to maintain wayward immune cells in check.

The Discovery of the Peacekeeper Cells

In a major finding in 1995, Shimon Sakaguchi and his colleagues identified a small subset of T cells — white blood cells vital to immune protection — characterized by the molecule, CD25. It was demonstrated that $CD4^{ww}$ T lymphocytes expressing the surface marker CD25, the alpha chain of the IL-2 receptor, possessed immunoregulatory functions. When Balb/c athymic nude (nu/nu) mice were injected with $CD4^+$ cells from spleen and lymph nodes depleted of $CD25^+$ T cells from heterozygous Balb/c nu/+ mice, they developed histologically and serologically evident autoimmune diseases, including thyroiditis, gastritis, insulitis, adrenalitis, and polyarthritis. However, re-constitution with $CD4^+$ $CD25^+$ T cells within a limited period after transfer of $CD4^+$ $CD25^-$ T cells prevented the development of autoimmunity. These findings indicated that the $CD4^+$ $CD25^+$ T cells were essential for maintaining immune self-tolerance. Thus, the existence of a regulatory $CD4^+$ $CD25^+$ T cell subset capable of dampening immune responses was discovered. These were regulatory T cells or T_{regs}, a subset committed to ensuring other immune cells stayed in line. They play an important role to shut off overactive immune reactions and thereby, preventing the immune system from targeting the body by accident.

The Genetic Key: FOXP3

In an interesting project, Mary E. Brunkow and Fred Ramsdell attempted to identify the scurfy mutation (a lethal mutation in mice) using the positional cloning techniques available at the time. A two-base pair insertion in a gene resulting in a frame shift and a premature stop codon was identified by them and the gene was named Forkhead box P3 (Foxp3). , They further generated five transgenic mouse lines carrying the Foxp3 gene, each with a different copy number, and individually crossed them with scurfy mice to prove that the mutation was responsible for the scurfy phenotype. It was

observed that wild-type Foxp3 rescued male scurfy mice from disease. Subsequently, they turned their attention to a rare inherited human disease known as IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, characterized by severe autoimmune devastation in infancy. It was demonstrated that mutations in FOXP3, the human counterpart to the gene mutated in the scurfy mouse, were responsible for IPEX. FOXP3 was thus identified as the master regulator of T_{reg} development and function. Without FOXP3, T_{reg} cells are unable to form, and immune tolerance is broken.

Making the Connection

Following these two discoveries, Shimon Sakaguchi's team demonstrated that Foxp3 was selectively expressed in $CD4^+$ $CD25^+$ T lymphocytes and that retroviral transfer of Foxp3 converted conventional $CD4^+$ T cells to T_{reg} cells and thus established the connection. Thereafter, Ramsdell's group independently showed that T_{reg} cells were absent in the scurfy mice and the mice overexpressing Foxp3 exhibited an increased number of T_{reg} cells.

Biology of T_{reg} Cells

T_{regs} are a specialized subset of $CD4^+$ T lymphocytes characterized by the expression of the transcription factor FOXP3 and surface markers such as CD25 (IL-2 receptor alpha-chain).

They originate through two major pathways:

- Natural T_{reg} cells (nT_{reg}): Developed in the thymus during T cell maturation.
- Induced T_{reg} cells (iT_{reg}): Differentiated from conventional $CD4^+$ T cells in peripheral tissues under the influence of TGF-beta and other signals.

Mechanisms of action:

- Secretion of inhibitory cytokines (e.g., IL-10, TGF-beta, IL-35).
- Direct cell-to-cell contact to suppress effector T cells.
- Modulation of antigen-presenting cells.
- Metabolic disruption (e.g., IL-2 consumption, cAMP transfer).

Therapeutic Potential of T_{reg}

T_{reg}-based therapy aims to restore immune tolerance without causing generalized immunosuppression. Major application areas include:

a. **Autoimmune Diseases**
   T_{reg} deficiency or dysfunction is linked to conditions like type 1 diabetes, multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis. Clinical trials using autologous ex vivo expanded T_{reg} cells have shown encouraging results in delaying disease progression and reducing inflammation.

b. **Organ Transplantation**
   Conventional immunosuppressive drugs prevent rejection but carry risks of infection and malignancy. T_{reg} therapy offers a targeted approach to induce long-term graft tolerance, potentially minimizing the need for lifelong drugs. Early-phase clinical trials in kidney and liver transplant recipients demonstrate safety and feasibility.

c. **Allergic and Inflammatory Disorders**
   T_{reg} cells can control exaggerated immune responses in asthma, allergic rhinitis, and inflammatory bowel disease by suppressing Th2 and Th17 pathways.

d. **Tissue Repair and Regeneration**
   Beyond immunosuppression, T_{reg} cells produce growth factors that support tissue healing, making them relevant for regenerative medicine, including muscle and skin repair.

Breakthroughs in Therapy Development

The past few years have seen rapid progress in turning T_{reg} science into real treatments:

- CAR-T_{reg}: Scientists are engineering T_{reg} cells to target specific tissues, like transplanted organs, using chimeric antigen receptors (CARs).
- Gene editing: Tools like CRISPR are used to make T_{reg} cells more stable and effective.
- Off-the-shelf therapies: Companies are developing a donor-derived universal T_{reg} to make treatment scalable and affordable.

Dozens of clinical trials are now underway across the globe, with early results showing both safety and promise.

Challenges Ahead

Despite exciting progress, several hurdles remain:

- Stability: T_{regs} can lose FOXP3 expression and convert into effector cells under inflammatory conditions.
- Manufacturing: Expanding T_{regs} to therapeutic doses while preserving their purity and function is complex.
- Specificity: Broad T_{reg} activity risks unwanted immunosuppression; precise targeting is essential.
- Regulation: Cell therapies face strict regulatory pathways for clinical approval.

Conclusion

By unveiling how regulatory T cells function, Sakaguchi, Brunkow, and Ramsdell have given medicine a potent tool: the capability to retrain the immune system to tolerance rather than lifelong repression. As medical research continues to evolve, T_{reg} cells may become the foundation of 21st-century medicine, holding out promise for millions of people who suffer from autoimmune and inflammatory diseases. In spite of the hurdles, as clinical research advances at an ever-faster pace, the globe might well be seeing the dawning of a new medical dawn — tolerance therapy. T_{reg}-based treatments will hopefully soon transition from the laboratory into everyday medicine.

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Molecular Music: How Biochemistry May Have Been Sung into Existence by Life's First Catalysts

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Keywords: Vibrational Catalysis, Resonance Catalysis, Primitive Peptides, Bond Vibration, Activation energy

Introduction

Today, when we think of enzymes, we think of precise machines with precisely shaped pockets and grooves that fit substrates and break or form bonds. Reactions in this traditional lock-and-key model are largely determined by the shape of molecules. However, what if life didn't depend on such mechanical accuracy billions of years ago? What if the first catalysts guided chemical reactions through resonance and vibration, much like musical instruments?

This is the essence of vibrational and resonance catalysis, a notion that almost poetically combines physics, chemistry, and the beginnings of life.

The Molecules' Music

Chemical bonds are dynamic at the atomic level. Each bond vibrates at distinct frequencies as they continuously stretch, bend, twist, and oscillate. For example, oxygen-hydrogen bonds vibrate at a slightly higher frequency than carbon-hydrogen bonds, which vibrate at about 3000 cm^{-1}. These vibrations are more than just a normal motion; they are actually the stored energy that can affect the occurrence of a reaction or the breaking of a bond.

These vibrations are cleverly exploited by contemporary enzymes. According to some research, enzymes have the ability to direct energy into particular bond vibrations, which facilitates their breaking. To put it another way, enzymes do more than just keep molecules where they are; they also "nudge" them, sometimes at the proper frequency, to speed up reactions.

According to research on the makeup of prebiotic peptides and amino acids (such as glycine, alanine, and valine) transported by meteorites, the earliest catalysts were probably short, flexible and because of thermal and environmental energy, these early peptides were full of motion and naturally vibrated in a variety of modes despite lacking rigid structures. Their vibrations could couple with a wide variety of bonds in neighbouring molecules due to their flexibility, increasing reaction rates without the need for the specificity of contemporary enzymes. Similar to molecular tuning forks, these peptides may have acted as resonant cues to chemical bonds.

These vibrationally active peptides may have evolved into increasingly specialized enzymes over time due to evolutionary pressures, suggesting that motion and resonance were crucial for the emergence of life.

Finding the Correct Note with Resonance Catalysis

Resonance catalysis occurs when the enzyme's vibrations match the natural frequency of a bond in the substrate. The bond efficiently absorbs this energy, much like a wine glass vibrates and then shatters when the right note is sung.

This match of vibrational frequency is not perfect, even a rough overlap can increase the motion of the bond and reduce the energy needed to break it. In modern enzymes, this effect usually works in concert with the exact structure of the active site. However, resonance might have been the primary mechanism facilitating reactions for primitive peptides, which lacked defined pockets or folded three-dimensional structures.

Vibrational Catalysis: Providing Bonds with Energy

In case of vibrational catalysis, even though their

natural frequencies do not precisely match, the enzyme actively transfers energy to a bond. How does this operate?

Thermal energy and environmental interactions cause all peptides and enzymes to vibrate naturally. Weak forces, such as van der Waals interactions or hydrogen bonds, enable some of the enzyme's vibrational energy to couple into the substrate bond when a substrate molecule approaches. The activation energy required for a reaction is reduced because the bond stretches more than usual.

Considering, pushing a swing. Repeated pushes raise the swing even if the timing is not perfectly aligned. So, the primitive peptides must have operated this way, progressively "pushing" bonds until reactions occurred.

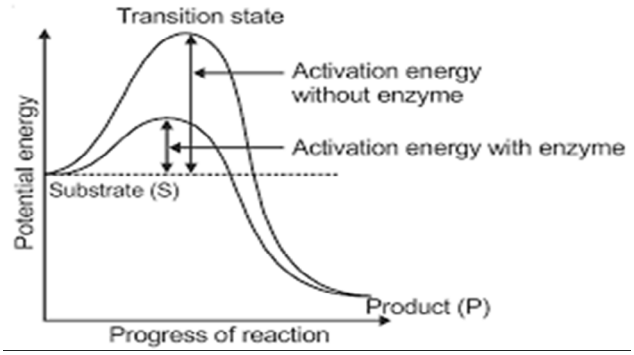

Figure 1: Catalysed and Uncatalysed reaction's energy profiles. Energy profile illustrating the reduction of activation energy by an enzyme
Source: NCERT Biology, Class 11

This idea changes how we think about the beginnings of life. Instead of viewing early reactions as simple structural challenges, we can picture a lively, rhythmic environment where molecules interacted like instruments in an orchestra. Bonds were constantly oscillating, peptides were humming, and occasionally the right alignment would trigger reaction that would eventually give rise to one of the first biochemical pathways in life.

Echoes of this "molecular music" can still be heard in contemporary enzymes. The Catalytic activity and vibrational modes are still a part of the enzymes today, indicating that nature has never completely given up on the power of resonance.

Conclusion

Resonance and Vibration catalysis serves as a reminder that chemistry is about energy, motion, and timing in addition to forms and structures. Despite their primitive nature, early peptides were dynamic, vibrating, resonating, and gradually coordinating the processes that would eventually lead to life.

According to this theory, biochemistry was "sung" into existence by a combination of chance vibrations, environmental energy, and primitive catalysts, making the origins of life less of a static puzzle and more of a symphony of molecules.

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Applications of Synthetic Biology: Vaccine Production

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Keywords: Virus-like Particles, Lambda Red recombination system, Cre-LoxP system, CRISPR-Cas9, recombinant vaccines

Introduction

Biology is a branch of science that focuses on the new abilities of engineering into existing organisms to redesign them for useful purposes. The goal is to design, and build engineered live biological systems that process information, manipulate chemicals, fabricate materials and structures, produce energy, provide food, and maintain and enhance human health, as well as advance fundamental knowledge of biological systems and our environment.

Synthetic Vaccines and Virus-like Particles (VLPs)

The advent of synthetic biology approaches, which have enabled the rapid and reliable design and production of pathogen genomes that can be subsequently manipulated for vaccine production. Synthetic vaccines consist mainly of synthetic peptides, carbohydrates, or antigens. These are proposed to be safer than conventional vaccines due to precise antigen selection, eliminating the risks of infection from live or inactivated pathogens. Synthetic vaccines are associated with higher production rates, simplified manufacturing, less biological contamination, and cost-effectiveness. The two major types of synthetic vaccines include synthetic peptide vaccines, which use short protein fragments, and recombinant vaccines that use DNA technology to produce pathogen antigens in cells or host organisms. The synthetic gene which is synthesized by introducing genetic material (DNA or mRNA) into cells, when transcribed and translated by cells, will act as a synthetic antigen, which will hopefully be recognized by the immune system, activate the T and B lymphocytes, and produce antibodies. Such synthetic vaccines enable the targeting of a wider range of diseases, including cancer and autoimmune disorders

Virus-like particles (VLPs) are non-infectious nanostructures that mimic the shape, size, and surface features of actual viruses but lack genetic material. They are highly related in overall structure to their corresponding native viruses. They may be enveloped or non-enveloped VLPs. The viral structural proteins spontaneously self-assemble into virus-like structures into repetitive units, and this virus-like structure allows them to display antigens. These particles are safe, stable, non-infectious immunogenic that can provoke robust T cell and B cell immune responses. Since VLPs cannot reproduce, they offer a more secure option compared to attenuated viruses. The initial FDA-approved vaccine utilizing VLP technology is designed to prevent Hepatitis B. Vaccines like Gardasil are another example of successful VLP-based vaccines approved to protect against HPV infection. VLPs provide an innovative platform for developing vaccines mimicking viral structures. VLPs have also recently received attention for their successful applications in targeted drug delivery and for use in gene therapy.

Genetic engineering in vaccine development

Genetic engineering has revolutionized vaccines, creating more effective and safer immunizations. Cre-LoxP is a site-specific DNA recombination system comprising two components: the Cre recombinase enzymes and LoxP sites. LoxP sites are specific DNA sequences that are recognized by Cre. Cre-LoxP helps

construct attenuated vaccine strains by modifying viral genome strains through deletion, insertion, or replacement. Wang et al used reverse genetics methods, Cre-LoxP-mediated recombination tools to develop the first VZV skin and neuroattenuated live vaccine candidate for varicella, known as v7D. v7D shows immunogenicity in both in vitro and several small animal species, is tolerated well, and also retains the ability to an elicit immune response in children. Liang and colleagues used the Cre/Lox tool and introduced a novel vaccine development strategy to combat reemerging pseudorabies virus (PRV). This is done by 'precise excision of the marker gene on the viral strain'.

The Lambda Red recombination system found in bacteriophage λ consists of three proteins: Exo, Beta, and Gam. Exo is an exonuclease that degrades ssDNA in 5' →3' direction, thus generating 3' overhangs. Beta is a single-strand annealing protein that facilitates annealing of complementary sequences by binding to these overhangs. Wang et al eliminatedd the genes related to endotoxin synthesis in E coli and introduced HPV L1 protein into the expression frame of endotoxin synthesis-related genes, and thus constructed nine consecutive strains using the Red system. These strains helped construct HPV vaccines by improving the efficiency of expression of L1 protein and reducing endotoxin contamination.

CRISPR-Cas9, initially found in prokaryotes, is an adaptive immune system. It comprises Cas9 nuclease and single guide RNA (sgRNA), forming the ribonucleoprotein complex. Cas 9 can precisely cleave the target sequence with guidance from sgRNA'. The genomes of various DNA viruses such as herpes simplex virus type 1, adenovirus, and pseudorabies virus, can be edited by this system. Gowri Palan et al effectively screened recombinant vaccinia viruses within two weeks by using CRISPR to inhibit virus replication in culture.

Attenuating Pathogens

Vaccines are biological substances aimed at activating the immune system, encouraging the creation of antibodies specific to pathogens, and aiding in the establishment of active immunity. Due to advancements in cell culture methods, numerous live attenuated vaccines were created, such as those for tuberculosis, yellow fever, polio, measles, mumps, rubella, and varicella. Live-attenuated vaccines provoke strong, enduring humoral and cellular immune reactions. Progress in genetic and molecular biology technologies resulted in the creation of recombinant vaccines—e.g., Vaccines for Hepatitis B, anti-HPV, anti-herpes, and anti-rotavirus vaccines. The swift transformation of pathogens (including influenza, Ebola, SARS-CoV-1, MERS, and SARS-CoV-2), their strong transmission potency, and the versatility of virulent strains raise significant concerns regarding emerging outbreaks. Obstacles have spurred the creation of advanced vaccine platforms, utilizing innovations such as nanotechnology to facilitate rapid adaptation, enhance immune responses, and improve dosing regimens. Recent progress in nanotechnology has led to innovative vaccine delivery systems, demonstrating the capability to enhance immune responses more efficiently.

The live attenuation of these viruses was accomplished through an innovative vaccine method called synthetic attenuated virus engineering (SAVE), which involves integrating modifications to the preferred usage of specific codons and codon pairs for encoding design amino acids and neighbouring amino acid pairs into the virus during its synthesis. Selecting the degree of under-represented codons or codon pairs incorporated (which simultaneously leads to an Vaccines are biological substances aimed at activating the immune system, encouraging the creation of antibodies specific to pathogens and aiding in the establishment of active immunity. Due to advancements in cell culture methods, numerous live attenuated vaccines were created, such as those for tuberculosis, yellow fever, polio, measles, mumps, rubella and varicella. Live-attenuated vaccines provoke strong, enduring humoral and cellular immune reactions. Progress in genetic and molecular biology technologies resulted in the creation of recombinant vaccines—e.g. Vaccines for

Hepatitis B, anti-HPV, anti-herpes, and anti-rotavirus vaccines. The swift transformation of pathogens (including influenza, Ebola, SARS-CoV-1, MERS, and SARS-CoV-2), their strong transmission potency, and the versatility of virulent strains raise significant concerns regarding emerging outbreaks. These obstacles have spurred the creation of advanced vaccine platforms, utilizing innovations such as nanotechnology to facilitate rapid adaptation, enhance immune responses, and improve dosing regimens. Recent progress in nanotechnology has led to innovative vaccine delivery systems, demonstrating the capability to enhance immune responses more efficiently.

Increase of rare CpG and UpA dinucleotide occurrences) allows for the attenuation of viruses in cell culture and mouse models in a customizable manner. This method has been broadened to include HIV retroviruses and the bacterium, Streptococcus pneumonia. With the rapid progress in vaccine development, there is a push for a perspective that emphasizes disease eradication, instead of mere control. Initial positive outcomes in viral attenuation using SAVE suggest that investigations into other virus families could reveal SAVE's wide-ranging applicability.

Conclusion

Synthetic biology is a scientific field of blends approaches and concepts derived from classical and advanced scientific disciplines. There is recombination at unintended sites, inconsistent recombination efficiency levels, challenging delivery methods, potential off-target effects, etc. In spite of these limitations, genetic engineering has refined attenuation and vaccine design, thus efficiently addressing new and intricate pathogens, unlike conventional vaccines. Synthetic biology offers a fundamental shift from the empirical and often haphazard methods of traditional pathogen attenuation. It provides unprecedented speed, precision, and control over genetic modifications. Continued advancements in developing powerful biocontainment systems and understanding complex host-pathogen dynamics will help realise its full potential for rapidly and safely combating infectious diseases.

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Quest for The Origin of Life

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Keywords: Panspermia, Spores, Formose Reaction

Introduction

Every night while looking at the stars, I often wondered how it all began. Were we formed by some supernatural boon, rising from a hot, dilute soup, or were transported as spores of life from some other universe? We shall find out. The first form of life appeared on Earth around four billion years ago. To date, several theories have been considered regarding the origin of life. Still, the truth behind it remains a bit foggy.

Theories regarding The Origin of Life

Theory of Special Creation: It was given by Father Suarez. According to this theory, the universe and all living things were brought into being by some supernatural power only within six days.

Theory of Panspermia, or Cosmozoic theory, or Spore theory: It was proposed by Hermann Richter. According to this theory, protoplasm came from some other planets in the form of spores (units of life).

Theory of Spontaneous Generation (Abiogenesis or Autogenesis): It was proposed by Aristotle. The theory claimed, life originated from non-living things spontaneously. Life came out of decaying and rotting matter like straw, mud, etc. Evidence against this theory was provided by experiments conducted by Louis Pasteur, Redi, and Lazzaro Spallanzani.

Theory of Chemical Evolution: It was given by Oparin of Russia and Haldane of England. The theory proposes that life arose from non-living organic molecules through a series of gradual chemical reactions on the primitive Earth.

The Formose reaction: The 160-year-old hypothesis

The primitive Earth was a volatile and inhospitable place marked by extreme temperatures, volcanic eruptions, and a thin atmosphere. Within this chaos, the basis of life, the molecular components like sugars, amino acids, and nucleotides, emerged. Among chemists all around the world, it is widely accepted that among these molecules, a sugar, known as Ribose, which forms the backbone of RNA, was produced spontaneously in a chemical process, namely, the Formose reaction.

The Formose reaction was discovered by Aleksandr Butlerov in 1861. During the reaction, Formaldehyde molecules repeatedly react with each other to create larger molecules; the first two Formaldehydes react to create two-carbon molecules, which then react with another Formaldehyde, and so on.

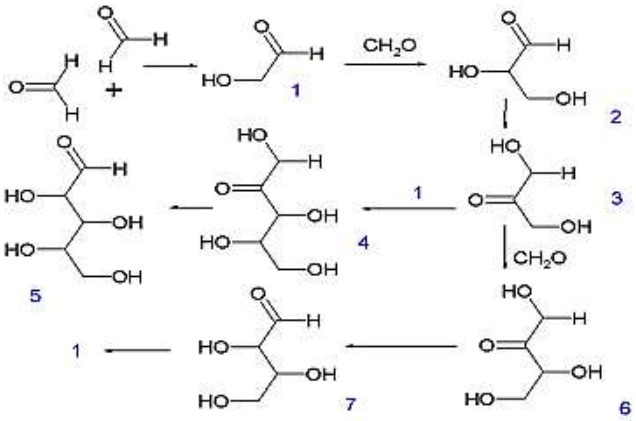

Figure 1: Formose Reaction

The outcome of new research on this hypothesis

A discovery by scientists at Scripps Research and the Georgia Institute of Technology questions the validity of the Formose Reaction Hypothesis. According to these new findings, under controlled experimental conditions, the Formose Reaction

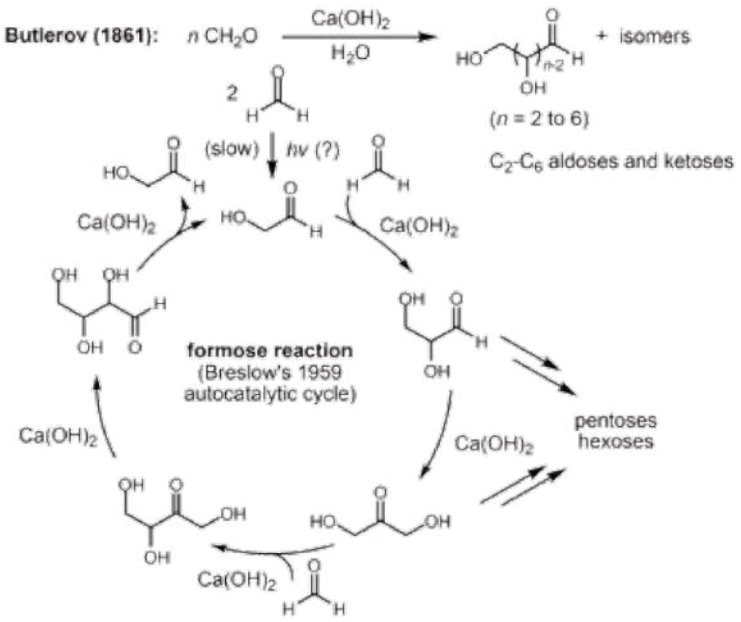

Figure 2: Another depiction of the Breslow catalytic cycle for formaldehyde dimerization and C2-C6 saccharide formation.
Source: https://en.wikipedia.org/wiki/File:FormoseReaction.png

does not yield linear sugars like Ribose. Instead, it predominantly produces branched Sugar structures, which are incompatible with the formation of RNA.

According to Ramanarayanan Krishnamurthy, professor of Chemistry at Scripps Research, "The concept of the Formose reaction as a prebiotic source of ribose needs serious reconsideration. The problem is it's a very messy reaction, and if Ribose is formed at all, it's a minuscule part and only one among hundreds and thousands of compounds that will be formed." To monitor the abundance and types of sugars produced in the conductive Formose reaction, researchers used a high-powered analytical technique known as nuclear magnetic resonance (NMR) spectroscopy. The NMR data revealed that all of the larger sugars produced had branched structures. All the sugars that are present as molecular building blocks in organisms are linear and unbranched. According to Charles Liotta, Regents' professor Emeritus of the Georgia Institute of Technology, "Our results cast doubt on the Formose reaction as the basis for the formation of linear sugars." The research outcome inspires us towards discovering new aspects defining the origin of life.

Life on Mars

Will we ever find life beyond Earth? Exobiologists have traditionally focused on the possibility of life on Mars. In quest of this belief, the Curiosity Rover was launched in 2011 as part of NASA's Mars Science Laboratory mission and landed on Mars' Gale

Crater in 2012. It was sent to assess whether Mars had the necessary conditions to support microbial life in the past. It has since explored the crater floors, discovering chemical and mineral evidence confirming the past habitable environments.

The habitability of the Martian land

Present-day Mars is extremely cold and dry, but geo-morphological and geo-chemical evidence on mars indicates an environment suitable for the formation of biomolecules essential for the formation of proteins and RNA. The recent studies by the Curiosity Rover have measured highly variable and 13C - depleted carbon isotopic values in early Martian organic matter, whose origin is uncertain. One hypothesis suggests the deposition of these molecules generated from 13C - depleted CO derived from CO_2 photochemical reduction in the atmosphere. The strong depletion in 13C - observed in the Martian organic matter can be explained by

the formation of complex organic matter byy the polymerization of H_2CO (Formaldehyde). Hence, the Martian land of the presence of Formaldehyde, which in turn can be converted to Sugars and Amino acids, responsible for RNA formation.

The Re-emergence of the Theory of Panspermia

Panspermia is a controversial theory that claims that life evolved elsewhere in the Universe and somehow or another made it here, where it developed into the diversity we see on today's Earth. Though there have been many versions of this Theory suggesting the extra-terrestrials intentionally seeded life on Earth, referring to Alien interference, or spores of life appeared through debris traveling across Space. The most accepted version suggests that the building blocks of life such, as Amino acids, could have come from elsewhere in the Universe, eventually evolving into life. Experts cannot seem to agree with this theory. But a recent study provides new evidence to support that, life on Earth might have been extra-terrestrial all along.

Did Life begin on Mars and then Travel to earth for its blossoming?

Recently, two scientists, Steven Benner and Christopher Adcock, separately proposed that early Earth lacked some chemicals essential to forming life, while early Mars likely had them. According to them, three key factors were:

1. Presence of Formaldehyde
2. Presence of Boron
3. Greater solubility of Phosphates

These three key components could have facilitated the formation of RNA on Mars. The Martian land shows traces of formaldehyde responsible for the Formose reaction, which eventually formed into the first prebiotic Sugar components. The presence of Boron on early Martian land was abundant to support widespread formation of RNA, whereas it was too scarce on early Earth. Hence, it could be assumed that some Martian boron was transferred to Earth in the form of meteorites. Also, the Martian phosphates turned out to be far more soluble in water also more abundant than on Earth. Hence, it could have also been delivered to Earth through meteorites. This evidence conclude that early Mars was a better nursery for life.

Conclusion

Though it is very difficult to develop the preconditions and reconstruct the conditions that prevailed billions of years ago in the land of Earth artificially in the environment of a laboratory to allow the Formose reaction to propagate through the prescribed path in the Petri dish, yet nobody should deny the fact that the magic reaction happened truly on the land of Earth. The first chain reaction of life had evolved by some natural magic. The soil, the water, the environment, or the extra-terrestrial X factor were all arranged in a way to create a beginning. There remains the big fallacy of this Universe where the first trace of life on a small planet came along silently through a reaction that took billions of years to occur, and the path remains veiled.

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A Review of Optogenetics in the Medical Field

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Keywords: Optogenetics, Phototaxis, Channelrhodopsin

Introduction

Optogenetics deals with the genetic engineering of light sensitive systems for controlling cellular processes with pinpoint accuracy which aligns with the fundamental principles of synthetic biology. A research was conducted on the molecular mechanism of 'algal phototaxis' or 'archaeal light driven ion transport' had interested the readers of medical journal. On the other hand, Channelrhodopsin is helping researchers to address specific questions, for example, the Channelrhodopsin approach is being used for various studies like the molecular events that occurs during the induction of synaptic plasticity. It is also used to map long range connection from one side of the brain to another, or to map the special location of inputs on dendritic tree of individual neurons. Channelrhodopsin-2 (chR2) is extensively used in the field of optogenetics, to control neurons or other cells with the help of light.

Preface about Channelrhodopsin

Channelrhodopsins are a subfamily of retinylidene proteins which serves the function of light gated ion channels. They were originally found in algae where they function as sensory photoreceptors, that allow the passive flow of cations across cell membranes when illuminated with lights of specific wavelength. Therefore, Channelrhodopsins are mostly responsible for phototaxis. The first progress at discovering Channelrhodopsins was made by Hartmann Harz, who recorded the photocurrents from Chlamydomonas by using Oleg's suction pipette technique for a cell wall deficient mutant of Chlamydomonas. The recorded action spectra led to the proposal that the photocurrent was being mediated by a certain type of rhodopsin. On the other hand, the super-fast appearance of the photocurrents gave the researchers (Braun, Hegemann) an idea that it is a single protein complex where the photoreceptors and ion channels are closely linked. Years later, novel DNA sequence that code for a large microbial-type rhodopsins was found in the cDNA data bank from Chlamydomonas. Later on, two rhodopsins were found from Xenopus oocytes and both of them directly encoded light gated cation channels. They were named Channelrhodopsin-1 (chR1) and Channelrhodopsin-2 (chR2). Among them, chR2 was used in human kidney and other mammalian cells, which showed light-induced membrane depolarization in a large amount. Researchers suggested that chR2 can be used to depolarize other cells with light.

Related Works

The most recent work is the use of cerebellar optogenetic stimulation in promoting cognitive recovery. This research was conducted on mice with Traumatic Brain Injury or TBI. As we know, Traumatic Brain Injury can cause long-term cognitive dysfunction and the traditional treatments have limited the ability to produce a desired or intended result. A transgenic mouse model with TBI, expressing the light-sensitive channel protein channelrhodopsin-2, specifically in the cerebellar Purkinje cells with Cre-LoxP system, was used for this study. Optogenetics was used to excite the Purkinje cells causing an inhibition of the output from the deep cerebellar nuclei to deep assess the effect of cerebellar neuromodulation on spatial working memory and the decision-

making behaviour in mice. The mice received 14 days of cerebellar stimulation twice daily for ten minutes. This improved spontaneous alteration rate, and significantly increased correct decision rate in the mice. Therefore, this suggests that there is noticeable improvement in the special working memory and goal directed decision making skills. This research helps to understand the underlying role of cerebellar output in functional recovery.

Another study was done on ex-vivo mouse bladder by activation of channelrhodopsin-2 in urothelial cell. The signalling molecules released from the urothelium by mechanical stretch play a sensory role in the bladder contractions through sensory signalling. There is also a theory suggesting that these molecules that are released from the urothelium could act locally to induce urothelial cell-mediated local bladder contractions. By using the ex-vivo mouse bladder preparation, the urothelial cells were stimulated by activating the channelrhodopsin-2 with blue light to investigate the urothelial cell mediated local bladder contractions. Thus it was found that the optogenic stimulation are able to produce cell mediated local bladder contraction. This validates the hypothesis which states that urothelial release factors can produce contractions locally without the signalling from the central nervous system. Further studies are still required to be conducted for normal bladder physiology and pathophysiologic conditions.

A study was done by screening of adeno-associated virus serotypes to transduce gastric smooth muscle cells for optogenetic stimulation. This study was done on Gastroparesis, which is characterized by severe gastric emptying of stomach without any physical obstruction which related symptoms such as, nausea, vomiting and epigastric pain. There is no treatment to restore gastric emptying of stomach up to date however, direct optogenetic stimulation of murine gastric smooth muscle cells (SMCs) with UV or blue light can induce force and intragastric pressure in transgenic mice by expressing Neuropsin (hOPN5) or channelrhodopsin-2 (chR2). Towards clinical translation, an efficient gene delivery vector is needed to express the optogenic proteins in gastric SMCs in vivo.

An in-vivo optogenetic research was carried out. The researchers claim that the excess neovascularization does not affect the entire retina, the global inhibition treatment of angiogenesis critically interferes with healthy unaffected retinal tissue. An in-vivo photoactivated gene expression paradigm was established that allows light-mediated targeting of anti-angiogenic genetic treatment only to the affected retinal regions. Since the retina is prone to develop pathological neovascularization, therefore, a reversibly inhibited, “caged” photosensitive 4-hydroxytamoxifen analogue was synthesized and injected into the mice harbouring the inducible Cre/lox system, intravitreally. By using GFAP-CreERT2 mice, photoactivation was achieved successfully in the eyes and also in the ex-vivo slices of the brain to validate the approach. By this research we get to know the importance of light-mediated gene therapy for retina, which can be called a key step in personalized medicine.

Conclusion

The future applications of Channelrhodopsin are high. Scientists claim countless Channelrhodopsin variants will be discovered from the hundreds of new algal genomes sequenced, moreover they may become commonly used analytical tools and may be used to treat many more diseases. Single-component optogenetic tools have created a huge impact on neuroscience enabling specific modulations of specific cells from neural tissues for light mediated gene therapy. Many new opportunities for using Channelrhodopsin is still on the process of discovery by various researchers, with the potential to redesign accurately to create new appliances.

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Genetic Circuits - Wonders of Synthetic Biology

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Keywords: Synthetic Biology, DNA, Genetic circuits, Therapeutics

Introduction

What sounds like science fiction today is the technology of tomorrow – it is often said. Science fiction often refers to being able to control and manipulate the characteristics and traits of human beings, developing them just as they are needed. Today's world is pretty close to making it a reality as we enter the phase of Synthetic Biology. Man's curiosity knows no ends; hence what was first known only as biology started to combine with other branches of science and developed into biotechnology which gave us a deeper insight into the functioning of the human body at molecular levels from the earlier anatomical levels. Now, it has evolved further from figuring out what is present – we now plan to manipulate the system into doing what we want it to do and do it our way. And how to do it? Synthetic biology!

Helix of Life

In all living organisms, hereditary information is passed on through DNA, which is in turn formed by genes. These genes are the ones responsible for carrying characteristics from the previous generations and making sure we turn out the right way with correctly functioning systems. One single mistake in one single gene can often cause drastic changes or damages in the organism. So we can infer that genes are quite powerful – they are the basic structures for the perfect functioning of cells which is the basis of a healthy and normal life unmarred by any genetic disorders.

The Journey of DNA

DNA transcribes into RNA and this RNA is translated by the ribosomes present in the cells into proteins. But how are these processes triggered? This is through the expression of genes. Gene expression controls when, why and how much of proteins are supposed to be synthesized. The process is regulated by the presence of 'cellular switches' i.e., the operon systems. Now, with the help of genetic engineering, we are trying to regulate the ON/OFF mechanism to synthesize the desired protein by controlling gene expression.

Biology in Synthesis

Synthetic Biology is an interdisciplinary field that combines engineering and computational principles with the processes of biotechnology. It allows scientists to design and create new biological parts, devices and systems or re-design the old naturally existing ones to suit our purposes. The core methods involve the use of engineering principles and tools like DNA synthesis, CRISPR, GENETIC CIRCUITS, gene editing to design, build and modify biological systems for new functions, enabling the creation of novel organisms and products for medicine, manufacturing, agriculture and other fields. Synthetic biology also emphasizes the use of standardized, interchangeable biological parts to create complex systems very easily. It even incorporates mathematical modelling for supporting the entire design process.

Synthetic Bio-Circuits

Genetic circuits are synthetic biological systems that use standardized DNA parts to create logical functions within cells, analogous to electrical circuits. These circuits allow cells to sense input signals (like

small molecules, light or other biological signals) and produce specific outputs (such as proteins or changes in cell behaviour). Genetic circuits are built from basic DNA and protein components that act like electronic gates, including promoters

(initiate transcription), ribosome binding sites (RBS - initiate translation), protein-coding sequences (CDS - encode desired proteins), terminators (end transcription), repressors (block gene expression) and sensors, processors and actuators (functional modules within a genetic circuit).

Circuits in Action

Genetic circuits work analogous to electrical circuits. They are built from standardized DNA components called 'Biobricks', which are catalogued and assembled like building blocks. These components are designed to perform logical functions similar to those in electrical circuits (AND, OR, NOT gates). These gates work with specific inputs and outputs. Inputs can be external or internal signals (light, small molecules or presence of a specific protein). Outputs are generally the production of specific proteins or nucleic acids or a change in the cell's function.

The Multi-Talented Genetic Circuits

Now that the technical terms are over, it is time to know how these genetic circuits can be applied in real life situations. Genetic circuits have diverse applications across innumerable fields. It can change the way we view medical treatment by the development of Personalized and On-demand Therapies where gene circuits precisely control therapeutic interventions. Genetic circuits in human immune cells and bacteria can trigger killing responses to pathogens or cancer cells, revolutionizing cancer treatment by targeting tumours locally. Circuits can be used to create implantable biodevices and regenerative medicines and therapies.

Genetic circuits have their uses in Biomanufacturing and Metabolic Engineering. They are used to create cell factories that can perform self-learning and decision-making, optimizing metabolic flux for producing useful compounds. Circuits can also provide dynamic control over metabolic networks and facilitate high-throughput screening for identifying overproducers. Future applications of genetic circuits also include designing crop plants with custom traits, thus improving crop productivity.

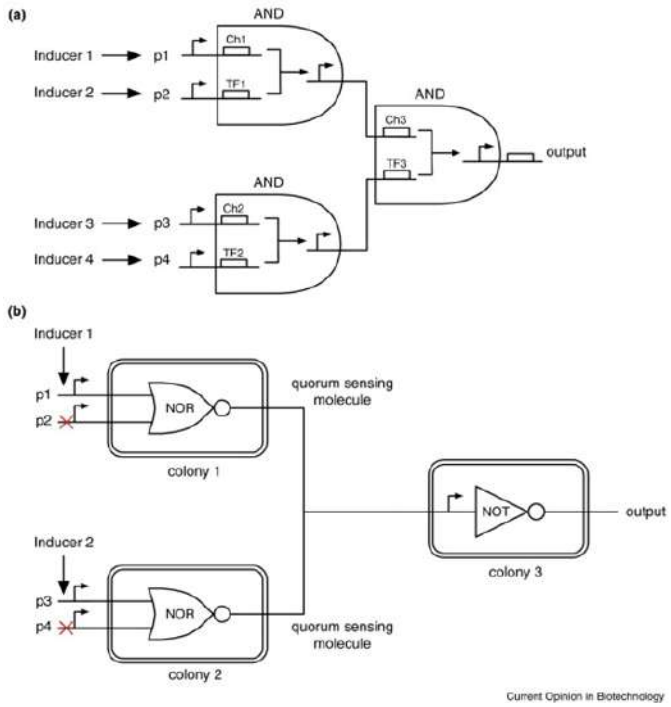

Figure 1: Analogy between electric circuits and genetic circuits

Source: Synthetic Analog and Digital Circuits for Cellular Computation and Memory - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/a-A-4-input-genetic-AND-gate-formed-by-coupling-the-output-of-two-2-input-genetic-AND_fig1_262054749

In today's world, where climate change and environmental issues are taking the centre stage, genetic circuits have found their way into Environmental Monitoring and Biosensing. Gene circuits can serve as sensitive biosensors for monitoring biomanufacturing, food safety and environmental conditions, hence converting specific environmental signals into measurable outputs. Also, the development of cell-free synthetic gene circuits allows for the creation of microbial sensors with various response mechanisms for bioassay applications.

Are they infallible?

No, Genetic circuits too have their limitations. These include inherent biological uncertainty and complexity and cellular heterogeneity that makes them difficult to control , a lack of standardized parts (genetic components) and quantitative data for robust design, low through put in testing methods which make the process time-consuming and metabolic balance trade-offs as optimizing for product synthesis can disrupt the balance between growth and production efficiency. There remains performance and stability issues as achieving precise control over strength, timing and cellular context of a circuit's therapeutic effect is quite difficult. One of the major problems is Circuit Memory Loss – the performance of a genetic circuit can be compromised by the host's growth feedback, which can lead to a loss of circuit memory and desired functional states. Also, in therapeutic applications involving stem cells, uncontrolled cell proliferation can lead to cancer-associated mutations, highlighting a serious safety concern.

Conclusion

Setting aside the pros and cons, and even the ethical concerns that surround such scientific developments, there is no doubt that genetic circuits, or better to say synthetic biology has opened up so many new directions of science and technology. And it is needless to say that man is never satisfied with what he has already discovered. So, as a result, science keeps evolving and diverging as more and more new discoveries and inventions come to light. Change is permanent, and thus science never stops evolving, just gets better!

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CRISPR and Synthetic Biology: from Molecular Origins to Planetary Solutions

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Keywords: Synthetic Biology, Molecular Origins, Biosafety

Introduction

The existence of life forms as small as cells in a Petri dish to as big as a planet itself, symbolises how biology has evolved from small-scale laboratory experiments to a discipline capable of influencing global systems. Understanding life at the molecular level has enabled humans to manipulate and redesign biological processes, leading to the development of synthetic biology.

The molecular origin of life has long fascinated scientists, with the RNA World Hypothesis suggesting that self-replicating RNA molecules were the precursors to life (Gilbert, 1986). Over the years, the ability to decode and modify genetic material has progressed from simple observation to direct manipulation. Synthetic biology combines biology and engineering, using living systems to perform designed functions (Khalil and Collins, 2010). Among the many tools enabling this revolution, the CRISPR-Cas9 system has emerged as one of the most powerful (Doudna and Charpentier, 2014).

This article summarises existing studies to understand how CRISPR connects the molecular origins of life with synthetic biology and its potential applications in various fields.

Molecular Origins of Life

The origin of life is one of the most profound scientific questions. Experiments such as those conducted by Miller and Urey in 1952 demonstrated that organic molecules like amino acids could form under early Earth conditions, suggesting a chemical basis for biological evolution. Later theories proposed that RNA molecules capable of catalysis and self-replication could have been the first genetic systems (Gilbert, 1986). As research expanded, scientists uncovered the central dogma of molecular biology—DNA makes RNA, and RNA makes protein—providing a framework for understanding how genetic information flows. The ability to read and manipulate DNA sequences later became the cornerstone of biotechnology.

> "The chemistry that began life continues to shape every living system on the planet." (Ellis, 2019)

This statement resonates because the same molecular principles that governed early evolution now guide synthetic biology.

From Petri Dish to Planet: Applications and Possibilities

Synthetic biology's applications now extend far beyond laboratory experiments. It contributes to addressing some of the most urgent global challenges. For example, engineered microbes are being developed to clean oil spills, degrade plastics, and sequester carbon dioxide (Ellis, 2019). In agriculture, CRISPR-edited crops promise resilience against drought and disease, offering potential solutions to food insecurity.

In medicine, gene therapies using CRISPR have shown success in early clinical trials for diseases like sickle cell anaemia. Synthetic biology also offers possibilities for producing vaccines and bio-based materials at scale.

Nevertheless, many of these solutions are still experimental. It would be incorrect to view synthetic biology as a complete answer to planetary problems. Instead, it should be regarded as a

promising, continuously evolving approach that requires collaboration between biologists, ethicists, and policymakers.

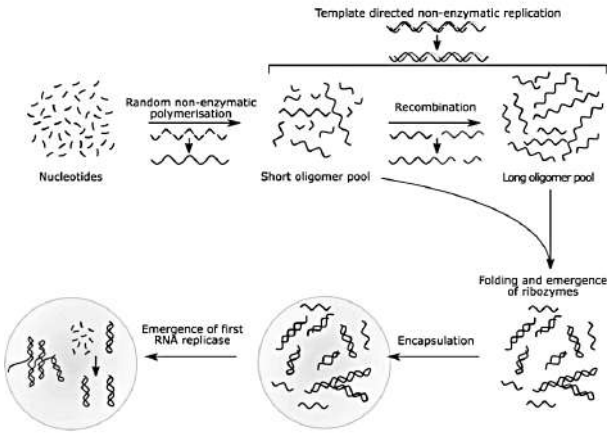

Figure 1: Schematic representation of the transition from inorganic molecules to the RNA world (adapted from Gilbert, 1986)

Ethical and Biosafety Considerations

Every technological advance comes with responsibilities. In synthetic biology, biosafety concerns include accidental release of engineered organisms and potential misuse for harmful purposes (Rodríguez et al., 2020). Ethical discussions also arise around genome editing in humans, particularly regarding germline modifications.

The scientific community has historically shown awareness of such risks, beginning with the 1975 Asilomar Conference, where guidelines for recombinant DNA research were established. Today, the emphasis remains on transparency, risk assessment, and international collaboration.

From a budding biotechnologist's perspective, understanding ethics early on, is essential. As researchers, even at the beginning of our journeys, we must realise that the purpose of science is not merely to create but to contribute responsibly.

Conclusion

CRISPR and synthetic biology represent the convergence of nature's evolution and human innovation. They demonstrate how knowledge of molecular origins can be applied to design systems for the benefit of life on Earth.

Future research may focus on improving the accuracy of gene-editing tools, developing safer synthetic organisms, and integrating biology with computational modelling. There is also growing interest in using synthetic biology to restore ecosystems and promote sustainability.

While it is too early to predict the full impact of these technologies, they undeniably symbolise how scientific progress can influence planetary well-being. The essence of modern biology lies in small-scale understanding leading to large-scale transformation.

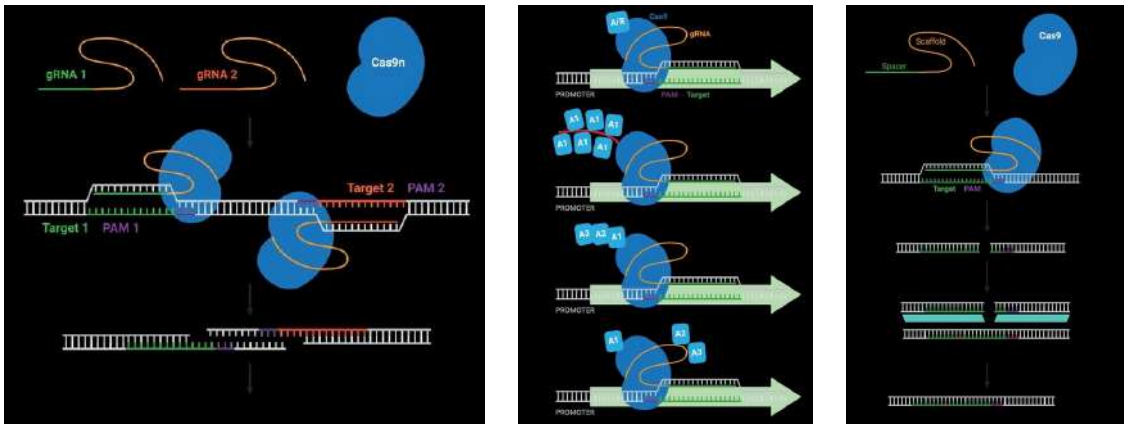

Figure 2: Mechanism of CRISPR-Cas9 gene editing showing guide RNA, Cas9 enzyme, and target DNA (Addgene: CRISPR Guide, n.d.)

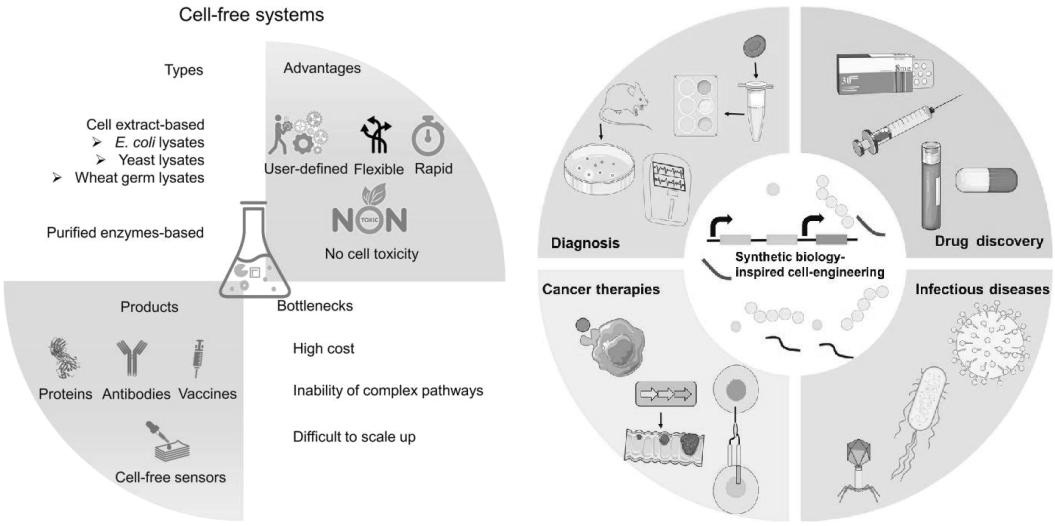

Figure 3: Global applications of synthetic biology in medicine, agriculture, and environmental sustainability (adapted from Ellis, 2019)

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Nanotech based Drug Delivery: A New Age of Cancer Therapy

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Keywords: Nanoparticles, Folate-receptors, Multi-drug Resistance, Clathrin

Introduction

Cancer has been known to be a leading cause of fatality, with 9.7 million deaths reported globally in 2022. Such numbers are expected to rise even further in the future, despite advancements in medical science and technology, as reported by the National Cancer Institute (USA). Deaths owing to cancer occur mainly due to diagnosis of patients in the later stages of the disease, by which time treatment via conventional techniques fail to provide a complete cure, and often result in high relapse rates. Treatments are especially difficult due to the complex nature of cancer, especially when they metastasize. Around 85% of the patients are curable if caught in their early stages, which can be made possible using nanotechnology-based applications. CT scans, MRIs or Biopsies cannot help in early detection unless a significant amount of solid tumor has been formed.

What is Nanotech?

The use of Nanotechnology, or more specifically, Nanomedicine, to detect and cure cancer has proved to be an absolute game-changer. In simple words, nanotechnology is a multidisciplinary field which focuses on the synthesis, structure and use of nanoparticles and nanomaterials. Nanoparticles (NP) are structures which strictly have at least one of their three dimensions in the scale of 1-100 nm (European Science Foundation). Such small size means greater surface area and other unique properties at submicron level which can be exploited for altered cellular responses. There are different types of nanomaterials for detection, therapy or both. Most common nanomaterials are: Quantum Dots, Nanowires (having predominant diagnostic applications in biological fluids or lesions), Solid Lipid NP, Nanomotors (having therapeutic applications), Liposomes, Dendrimers, Magnetic NPs, Multifunctional NPs (for combined therapeutic and diagnostic applications), etc. There are other NPs but they have been excluded from the discussion for the time being due to their toxicity in cellular environment and controversial evidences in their effects on cancer.

Why is Nanotech better for Drug Delivery?

A drug delivery system must check a few boxes in terms of their features in order to be considered effective. Drug residence time, muco-adhesive properties, biocompatibility, biodegradability and toxicity of the carrier molecules, drug sensitivity to enzymes, pH, temperature, aqueous solubility, etc., need to be considered before choosing the combination of therapeutic drug moiety and the carrier polymer.

By synthesizing nano polymers with complementary receptor protein or surface protein, as opposed to the ones expressed on cancer cells, one can actively target only the cancer cells, without damaging the nearby healthy cells. Side effects of using traditional chemotherapy or radiotherapy where the patients experience hair loss, nausea, etc., can thus be avoided. For example, acylated generation-5 dendrimers, albumins and magnetic nanoparticles were used by researchers to target the folate receptors (FRs) expressed on squamous cell in cancer of head and neck region, breast cancer and

colorectal cancer, respectively. Folate receptors are not expressed in normal cells of the body except in cells of ovary, testes and pelvic region but their over-expression is seen in aggressive cancer cells as they need more folate or cell proliferation and DNA/RNA synthesis.

NPs can be synthesized in such a way that they can mimic the property of cancer cells to bypass our immune system by avoiding Reticuloendothelial System (RES) uptake and getting excreted out of the body without working effectively on the cancer cells, as seen with natural polymers utilized as nano polymer carriers for therapeutic moiety (Liu et. al). Additionally, the dosage of the drugs required is also less as there is higher chance of them acting only on the neoplastic cells rather than all the cells. This feature allows them to be made into a more potent oral drug form, making it a more economical and affordable option of cure for afflicted people. Nanoparticles can act as a controlled Release system, depending on their polymeric composition, as seen in case of "stimuli responsive nanocarriers."

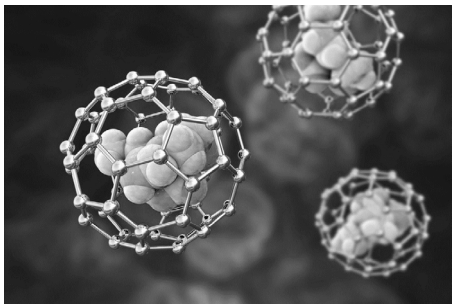

Figure 1: Structure of Nanoparticles
Source: Shutterstock

How do the Nanoparticles work?

For the drugs to perform their function, they must go inside the cancer cells. The receptors expressed on the tumor cell get attached to their complimentary proteins expressed on the surface of the engineered nanoparticles, which leads to the formation of a pit on the surface of cancer cells, since the NPs cannot directly pass through the cell (depending upon the hydrophilicity or polarity of the nanocarrier). This is called Receptor mediated internalization, assisted by assistor-proteins like clathrin. The NP is then engulfed to form a vesicle which drives the entire structure into the cell. The vesicle then merges with an endosome, which enhances the therapeutic efficacy of the drug, and this entrapment is a primary step in the incorporation of the drug to undergo metabolism thanks to the acidic medium of the endosome and lysosome. The drugs are designed in a way such that they stay stable in blood but get activated (not degraded as seen in other cases) in endolysosomal environments. The engulfed NP is destined for lysosomal degradation (as its entry was clathrin assisted) which will break the outer covering and the matrix of the nanocarrier to release the drug molecules entrapped inside it. By making use of pH sensitive nature of NPs one can bypass the efflux pumps in cells and prevent the exocytosis of the drug molecules. This ultimately causes the cell to degrade.

This method is thus capable of revolutionizing the way in which the problem of Multi-drug Resistance (MDR) is dealt with. Along with therapeutic moiety, it is possible to imbibe a P-Glycoprotein inhibitor in order to block the pumps to prevent the drug from getting effluxed. Endolysosomal homeostatsis via altered lysosomal trafficking pathways can potentially open up a new era of therapeutic efficacy and battle the long-standing problem of intrinsic or acquired MDR.

What are some preferred nanoparticles?

Usually, a thermodynamically and kinetically stable system is favored for long circulating, low immunogenic and sustained drug delivery. Some mentionable types of nanomaterials with the aforementioned features are Amphiphillic Block Copolymers (ABCs). ABCs are less prone to be disassembled even at low concentrations and have a "stealthy nature" to bypass our own immune system, which makes it even tougher to defeat cancer. Another hotshot within nanostructures are natural polysaccharides. Because of their excellent biocompatibility, low toxicity and mucoadhesive properties they can help the drug in getting absorbed

by the mucosal lining of the body which might be the target sites for gastric or colorectal cancers.

Conclusion

Although comparatively an under-researched topic, Nanomedicine is a promising field worth exploring. It hash the potential to treat cancer in various effective and modern ways that have not been adopted in the conventional methods of diagnosis and therapeutics before. The complexity of cancer makes it difficult to treat, even with a combination of different therapeutic procedures or administration of multiple drugs in chemotherapy. However, nanoparticles can easily be tagged with biomarkers and loaded with multiple types of drugs to combat the neoplastic cells. Hence, Nanotechnology based drug delivery systems may usher in a new era of cancer therapy with the conjoined attention and efforts of oncologists, biotechnologists and nanoengineers when old therapy methods fail. It is more efficient, specific, with lesser side effects.

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Literary Articles

Of Fall, Tea, and New Destinations

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Our lives have become so entwined with the internet and its siblings that we often tend to believe we already know - about things, experiences, stories. The remedy for this (in this case) was to take a trip to Rishop and Dawaipani, places I had no prior knowledge of, to form memories untainted by strangers on my phone.

Rishop is a Lepcha village in Kalimpong. Transport here scarcely varies, and cars are a necessity. We boarded a bus to Siliguri, followed by a car to Rishop, and reached our homestay by afternoon the next day, exhausted but exhilarated. It began raining by dusk, and we cozied up in one room to have conversations about previous trips and Bengali literature while sipping hot tea and gorging on fries. We slept early, hoping to get a view of the Kanchenjunga the next day.

The alarm went off at 4:30 in the morning. With droopy eyes and unkempt hair, we went to catch a glimpse of the Kanchenjunga. This was not exactly fruitful, as thick clouds had hidden the mountain range. However, it did not matter, for we were witness to something extraordinary. Within minutes, the sky shifted from pitch dark to deep blue, then gradually to a play of yellow and white as day dawned. After having hot, soupy vegetable maggi for breakfast, we began our tour with a 2-hour ride to Changey Falls, nested in lush greenery. From there, we went to the Lovers Meet View Point, also known as Triveni View Point, where the Teesta and Rangeet rivers meet yet remain distinct. Tea gardens and small food stalls lined the area. We had momos here, and our driver, surprised we hadn't tried squash yet, made us buy some. Our last stop of the day was the Kagyu Thekchen Ling Monastery, built to preserve local culture during critical times. Our time in Rishop ended here. We planned to drive to Dawaipani the next day.

Dawaipani lies about 6,500 feet above sea level in Darjeeling, roughly 63 kilometres from Rishop. The homestay we stayed at was in what locals call 'Bhutia Busty' in Upper Dawaipani, referring to people who migrated from Tibet eons ago. From there, the sky looked vast and endless, with Darjeeling on one side and parts of Sikkim on the other, unravelling like a live painting. In the evenings, the light from Siddheshwar Dham in Sikkim shone brighter than stars. For a moment, it felt like a scene from Life of Pi, a magically lit ocean with myriad creatures. We also celebrated Vijaya Dashami with our hosts, putting rice with red vermilion on our foreheads and sharing sweets while learning that the festival, for them, is about new beginnings and hope.

As we prepared to leave after a week, I realized how quiet times in Rishop and Dawaipani offered the luxury of simply being together without a single thought. We added a silent space to our hearts, for future reflections, as we returned, with revived phone networks to continue writing our lives, in haste and (organised) chaos, to Kolkata.

The Odyssey of a Cell

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The first thing I would recall is the warmth, the subtle vibration of the incubator above, the soft luminescence never fades. I came into existence in a mystic shallow world of agar and glass, a universe no bigger than a palm of human hand. All around me, there were countless others, their reverbed voice carrying across the gelatinous medium. We were cells, but distinct - endowed with a piece of human will, a piece of sequence carefully sewn into my genetic makeup. It was referred to as " genetic engineering." I referred to it as redefined destiny.

I was growing not randomly but by design. The scientists, attired in white and intent, had bestowed upon me a gift — a gene from another realm of reality, one which would enable me to survive where my forebears died. I was to survive in soil leached by salt, where crops choked by drought, or maybe counter a disease. I did not yet know where I was going, but I could sense it inscribed deep in my double helix: I had potential.

Days went by in the quiet of the Petri dish. The scientist's gloved hand would pick me up, examine my growth, smile weakly — a god watching creation. What an irony to be different and thus be trapped - the dish was a cradle, not a world. I yearned for the unknown, for the buzz of life outside sterile air, all I had regularly was a cold pipette, a brief flicker of light, then blackness.

Petri to jars to a pot in a chamber - it felt the same. One day the air was heavy, the expanse enormous. I was no longer by myself. Entangled in a living web — roots, microbes, minerals, movement. The ground was breathing, and I breathed with the ground. The zing ions, the hug of dampness, the heat of sun filtered through soil. I was unencumbered. I was terrified. I was alive.

It was here that I first realized my role. My gene, once dormant, had begun to sing. I released enzymes that broke the crust of salt, renewed its rhythm, and fed the roots that were intricately bound with me. Life stirred, picking up pace steadily. The plants grew greener; their leaves no longer crisped with dryness. I understood then that the researchers had not just made me; they had given hope. I was their trophy to the world.

Seasons went by. Occasionally, when I sense the shake of rain in the earth, I am reminded of the Petri dish — the start, the quiet, the hands that molded me. I wonder if the scientist still gazes into another dish somewhere, imagining what lies ahead. Do they realize their dream is already on the planet, in the oceans, in the fields?

I was never merely a cell. I was a question, an experiment, a shard of faith in the vocabulary of life. And as I split again under the roots of a thriving world, I whisper to the air,

"You gave me life in a dish — and I gave it back to the planet."

I Am You

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I just happen to know it, and carry it everywhere, with my own people callously denying my reality. The execution of my act of rebellion hangs in the air, crushed between a strong fear of unknown repercussions and the overpowering shackles which subjugate my identity. I am left to fight my battles, all alone.

Roop sat at her desk, brooding over the journal she had just filled. Any moment her friends, Chandan, Kirti, Mohini, and Shakti, would arrive for their café outing. College and jobs had pulled them away from their hometown long ago. She was wearing a soft grey tunic, loose pants, bare feet, hair falling freely, quietly plain, a feminine monotony out of perpetual coercion.

Turning to the mirror beside her desk to look at herself, she caught an eerie movement behind her. Something had materialized, slowly taking her exact shape. Terrified, she watched it mirror her every gesture, leaning slightly, tapping its fingers. Then it stopped and grinned, "Why have you dressed up like someone died?"

Roop, frozen, stammered, "Wh- who are youu?"

"I am you."

Half-shocked, half-flustered, she whispered, "You are I, whattt??" "Don't we look alike?" the figure teased.

Roop tried to process it. "What should I call you then?" "What does your family call you?"

"Moni… My father—"

"Gave me that name when I was little, I know," the figure finished, still grinning.

A sudden honk broke the spell. Chandan's car waited outside, calling her to join the others. Roop peeked out the window, and when she turned back, Moni was gone.

She left the house, still trembling. But the moment she met her long-lost friends, her face softened into warmth. In the car, laughter filled the air, familiar and distant all at once for Roop. By the time they reached the café, she was already slipping into her void once again.

Then a sudden shiver ran through her. Moni (the figure; her inner hue) materializing behind her, in a calm yet teasing tone, asked,

"How come you always feel you're above everyone?"

"I don't," Roop murmured almost defensively. "I just can't stay engaged for long."

"That's no excuse," Moni said. "They never wronged you." Both of them knew that was a lie.

Roop tried leaning back on Moni for comfort, but they vanished into thin air, pushing her back to reality; the laughter, the chatter, the soft clink of spoons being too loud all at once. She joined in without giving it a much thought.

Cut to their ride home, pitch-dark had dawned upon the road outside, and sleep wrapped around her. In her dream stood a glowing presence, cloaked in white, eyes deep and tender. Moni was there too; bright and alive, reaching for that light as if it were home. A soft calm washed over Roop, a peace she had never known, until a gentle shake pulled her

back to waking. It was her home. As Roop stepped inside, the familiar soft scent of sandalwood and old paper greeted her. The quiet of her room pressed close, she lived alone. She splashed water on her face, hoping it would wash away the strange ache inside. When she

looked up, Moni was there again; serene, waiting outside her room. Roop rushed to embrace Moni, and somehow it felt possible. They both cried happy tears. Wiping her tear Roop asked, "Why do you look like you walked out of a magazine?" Moni smiled, "Then just be me, I am You!! Don't push everyone away, they mean good for you. We have a good start right here" as their embrace lingered. "You are a spitting image of my father as a youngster" exclaimed Roop. Moni met her gaze, a faint smile saying more than words could. "Look," they murmured softly, "it's 12:10a.m already."

Suddenly, her phone buzzed. It was her mother. Moni gestured, 'That's your cue, Moni' and with that Moni faded away. Roop picked up; "Hello Maa… I mean to tell you something."

The Quiet Colony

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I hold a planet within my palms, and it trembles into being
It may be small, but it's begging to be seen
For we are all echoes of creation, dreaming of evolution
And every soul is a note in Earth's grand resolution.

In mist and microbes, in valleys and rivers, the Earth hums
Every organism joins in, as the song of life strums
In sunlight and shadows, in oceans and forests, it plays
Every heartbeat joins in, in a timeless blaze.

Then why harm the planet, where life sings in endless ways
It holds the story of a million lives through infinite days
Let us guard this song, and let our hands not erase
Earth's quiet pulse and its delicate grace.

Who is at Fault?

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In an attempt to comprehend the complexities of human relations, let us unfold a scenario. Suman and Iman are close friends. They lead similar lives initially, considering their achievements and social circles. Then, one day, Iman suddenly becomes incredibly successful, almost overnight. Naturally, Suman, who never saw Iman as a competition, is ecstatic upon getting the news. From then on, Iman's world begins to expand. He meets new people, builds new connections, gains social recognition and starts living all his dreams - travelling, celebrating and savoring his success. Inevitably, this means he can no longer be there with Suman like before. Suman begins to feel the drift in their bond. She sees him stepping into a new, glamorous world while remaining where she was.

At first, Suman feels hurt, almost disappointed by Iman's growing absence. Yet, instead of bottling it up, she chooses to talk to him about it, as any genuine friend would. Iman listens, tries to see things from her perspective and assures her that nothing has changed; their friendship still means the same to him. However, what he does not realize is that now, they view life through very different lenses. After their candid exchange, they spend some time together again. For a while, things seem back to normal. Eventually, Iman resumes his busy life, balancing fame, new experiences and endless opportunities. To his credit, he tries to include Suman in his world, introducing her to his new circles. Yet, while Iman has already adapted to this fast-moving lifestyle, Suman has not. She feels out of place among his new acquaintances. Suman hesitates to express this unease, fearing she might come across as needy or demanding. She comforts herself with the thought that at least she is still by his side. She does not want to weigh Iman down with her emotions and spoil his happiness but deep inside, a quiet sense of exclusion begins to grow. As Iman's success achieves new heights, Suman starts questioning her own life. She works hard but the results never seem to match his. With time, self-doubt takes hold. Unable to manage these feelings, she begins projecting them onto Iman — asking for more of his attention, his company and more moments together, away from the chaos of his world.

Iman, on his part, sees this as a sign of loyalty. He believes Suman still values their friendship for what it truly is, not for what he has achieved. Gradually, Suman starts defining her own worth through Iman's life. She feels like a side character in his vast world. On the other hand, for her, he remains everything. Insecurity shapes into quiet jealousy. Intentionally or unintentionally, Suman begins to hold Iman back — subtly resisting anything that might take him further away. She starts nit- picking over small things, blaming his absence for all that feels wrong in her life. Iman though patient, starts to feel the suffocation of this constant tension but stays, hoping it will pass. He convinces himself that Suman acts this way only because she cares for him too deeply.

However, the energy between them shifts. The warmth begins to fade and a feeling of walking on eggshells creeps in. Iman chooses avoidance. Suman becomes even more restless, making small but cutting remarks, criticizing almost everything

he does. Eventually, Iman realizes that her affection has curdled into resentment and envy. One day, after what feels like an endless argument, volumes of unspoken emotions burst at once and they fight bitterly. Words are thrown, tears fall, and silence follows. From then on, neither has spoken to the other.

Now the question arises – who is right here? More importantly, what could both the parties have done better?

सोचो के तुम और मैं

लिजा अगस्तिना तिर्की
सेमेस्टर ५
जैव प्रौद्योगिकी स्नातकोत्तर एवं अनुसंधान विभाग
सेंट जेवियर्स कॉलेज (स्वायत्त), कोलकाता

सोचो के तुम और मैं,
एक किताब में क़ैद,
दो किरदार होते।

चंद पन्ने हमारी दुनिया होती।
पन्नों के मुड़ने से दिखने वाले दाग़ — हमारे गिले-शिकवे।
उन पन्नों की संख्याएँ — हमारे रिश्ते की उम्र।
दसवें पन्ने पर मिलते,
तीसवें पर बिछड़ते,
सौवें पर फिर मिलते।

छोटे-बड़े, मुश्किल-आसान तरह के शब्द —
हमारी ज़िंदगी के अनगिनत अरमान।
शब्दों के बीच का खालीपन —
एक-दूसरे से कहे गए झूठ।
शब्दों से बुनी पंक्तियों के बीच का सूनापन —
बिना कहे समझ लेने वाली सच्चाई।

जहाँ अल्पविराम —
हमारी नादानी भरी मन-मुटाव के दिन।
जहाँ अर्धविराम —
हमारे शक से पनपी गलतफ़हमियों की शाम।
जहाँ पूर्णविराम —
हमारे बेवजह के झगड़ों की रात।
जहाँ प्रश्नचिह्न —
हमारा एक-दूसरे से लंबे दिनों तक रूठना।
जहाँ नया अध्याय —
हमारी नई शुरुआत।

अगर कोई किताब खुली छोड़ देता,
हम मिलने के लिए तड़पते।

अगर कोई फिर से पढ़ने लगता,
हम रो के, देर तक गले मिलते।
अगर कभी कोई शुरू से पढ़ता,
हम भी शुरुआत से अपना अंत जी लेते।

अगर कोई आधे में कहानी छोड़ देता,
हम उसे अपनी किस्मत समझकर अपने में सिमट जाते।
अगर कोई किताब को बरसों तक नहीं छूता,
हम साथ बूढ़े होते।

सोचो के तुम और मैं,
एक किताब में क़ैद,
दो किरदार होते।

Worshipped and Chained

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They raise their drums; they light the flame,
Loudly chanting the Holy Mother's name,
Her power echoes through the air
In a land where a daughter's life whispers fear.

Beneath the Sindoor Khela's
crimson tinted sky
Drowns the sound of a wounded woman's cry
A cry buried so deep inside,
forbidden to see the light
Are we too blind to see the fathomless plight?
Women being deprived of rights, day and night!

They carve the goddess fierce and divine,
With ten strong hands- but none are mine.
They call her Shakti- power and grace,
But criticize a woman for showing her face.

They gift her vermilion, caging her dreams
Drowning her identity into the holy streams.

When voices rise to drown my own,
Do they not silence the Shakti known?
How do they seek her in stones or flame,
While denying her presence in a woman's name?
Strangely, they end up praying to Shakti therein
To wash away all their heinous sins

The idol sinks and so do our hopes,
Women eternally walking on a tightrope.
And just like clockwork, every passing year, the trumpets roar
But when are we to finally reach the shore?
Since, even Ma Durga's lion's powerful roar
Cannot save the girl next door.

The Hunger After

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Oh, the primal will behind all motion,
That feeds on loss, yet learns to keep.
An atom born from rapid fusion,
Where hearts divide and eyes weep.

It asked for all, and I gave more,
The tremor, the pulse, the hearth.
Until my hands forgot the shore,
And my thirst survived the tide and its dearth.

It came like rain to a barren ground,
And I evolved where I should have bled.
Yet even in touch, some cells unbound,
Remained unfelt, unread, unsaid.

For some hungers thrive as others cease,
Mutating genes, in search of peace.
Hence from the ash, a new life begins,
The world remade, from what it thins.

The Printing Press

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As I sat there, watching the elaborate machinery in motion,
I felt a deeper sense of the crest and trough of the human heartbeat
In the sound of wheels that rolled and bars that struck.

Page after page in print,
heaped one on top of another,
Telling stories of real lives and real dreams.
Words that remain like the fading light of day,
feelings that resonate through barriers
All cradled there.

Giant machines operated together in a wholesome show.
At first, I thought it too large a place for the making of a book.
But as I stayed a while, it seemed to me too small a place for such a task.
For it is the origin of great things
The outflow of ideas!

Voices of the multitudes hummed through the rattling sound of metal,
And as the levers were pulled, with every mark of ink on paper,
A thought was set free
The passion of an unknown soul communicated to another.
And in the hollow of that room, I found the entire world itself.
There were workers at work, tired and unwilling, yet pushing hard,
For dreams sparkled in their eyes
To see their children stand with heads held high.

And there was the young writer,
Among a pile of crumbling manuscripts,
staring at the sky A heart throbbing fast,
A smile blooming in anticipation he himself knew not.

I could see the huge devices tremble, and I felt
The earth beneath my feet shake
For it was no ordinary place.

Different from all other factories,
Inanimate as it seemed yet all of life breathed in it.
Somewhere, I believe, amidst all the relentless work going on,
The place itself knows the
great duties it holds
For there are dreams to fulfill,
A whole generation to rouse.

Utkarsh: Insights on Philosophy and Life

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After exploring philosophies from different traditions, Christian concepts like the image of God and love, Greek ideas of reason, character, and moderation, Islamic principles of oneness and justice, and Jewish teachings on knowledge and responsibility, I always return to the essence of the Sanatan philosophy. Sanatan holds a unique significance. While all traditions convey similar moral and philosophical truths, Sanatan emphasizes living principles that are intertwined with daily life rather than only abstract concepts. It is often misunderstood as an orthodox system with outdated practices, but at its core, it teaches balance, self-reflection, and harmony in thought and action. The ancient teachings highlight the importance of knowledge, ethics, and human values. Over time, as cultural and intellectual influences shifted, many of these foundational principles were overshadowed by external ideas, leading to a gradual disconnect from our roots. Understanding and reconnecting with these origins helps us recognize the strength, resilience, and wisdom embedded in these philosophies.

Sanatan philosophy encourages reflection on oneself, mindfulness, and the pursuit of knowledge and truth. It emphasizes equality and balance between men and women, highlighting that true strength is realized only when both coexist in mutual respect. Education should empower both genders to recognize and embrace their potential and contribute meaningfully to society.

Ultimately, these philosophies remind us that the values we uphold, the principles we practice, and the awareness we cultivate shape not only individual growth but also the collective progress of society. By revisiting these timeless teachings, we can foster a more grounded, thoughtful, and conscious way of living.

A little hope

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Hopefulness is nothing-
but a wish from the quiet depths of one's heart,
for clear minds, and brighter days,
and a peaceful sleep to start.

For without hope, we can hardly cope
with the endless tempests we must fight;
for hope is a truth we cannot possess,
yet long for...day and night.

Hopefulness is nothing-
but faith in what we cannot yet see,
a trust that time will mend the gaps
between effort and destiny.
However dim the path may seem,
however long the way,
hope keeps the weary soul awake
through stormy nights to a brighter day.
Hopefulness is nothing-
but a thought that dares us to believe:
no summit is too distant,
no dream too far to weave.

The path we traverse might be narrow
but if our spirit does not fray,
the shadows of our doubts will flee,
and hope will light the way.

And if you're seeking the very road
that leads where your heart is freed...
then listen close, my steadfast friend-
a little hope is all you need.

The unexplored frontier

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I drive my horse through the
red soil and sand,
With strange cacti, starched grass,
a strange land;
My work is now over,
Nothing stops me from going further.
I have the whole vessel,
And two tanks filled with fuel,
A dedicated and obedient crew,
I have a whole range of scrambled grass on
the sea to explore,
an opportunity held by few.
I have a computer before me,
Full on battery, and ready to access network;
I got a loophole in the net,
I get through to explore,
hoping for the best.
I have the ruins of civilization before me,
Ready to make the lens through which
people could see,
The glimpse of our glorious history,
I have the whole team ready,
Now cheers to our nerves and machines,
which must remain steady.

Petri to Planet: A journey called Life

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4 Billion Years Ago – Organic Molecules
The Earth we see now, was the restless world back then,
Its skies were thick with CO_2, ammonia, methane.
We added some lightning, volcanoes and UV light,
Thus the magic sparked- organic molecules came into sight.

3.5–3.8 Billion Years Ago – RNA World
Thereafter, came molecules that self-replicate,
The RNA world evolved to determine the genetic fate.
These nucleic acids then got membranes to surround,
In these tiny protocells, life, for the first time, was found.

1.2 Billion Years Ago – Multicellular Organisms
One cell then became two, and multiplied again,
Behold, multicellular organisms — a new chapter began.
Organized together, these cells made tissues and more,
Life became more complex than it had ever been before.

1665 onwards– Start of Cell Biology
Innovative Robert Hooke, coined the word "cell" so precise,
Soon came Leeuwenhoek, saw organisms of microscopic size.
To better study these, Richard Petri worked with care,
He made the first Petri dish, to culture microbes there.

1953 onwards– DNA Double Helix and Recombinant DNA
From Franklin and Wilkins' data, Watson and Crick took clue,
And for the DNA structure, revealed the double helix view.
With enzymes cutting DNA, new genes we could combine,
Recombinant forms of life appeared, made of our own design.

1983 onwards – PCR and Cloning

Then came a new invention to copy genes with speed,
PCR could amplify the fragments that we need.
Science advanced with daring stride, and took a great leap,
Making mammal cloning successful — we got Dolly the Sheep.

2010 onwards – Synthetic Cell and CRISPR

Craig Venter made a synthetic cell — a genome he designed,
It successfully grew in a host cell, a milestone redefined.
We could modify genes now, we could delete and append,
As CRISPR gave us sharper tools to edit, cut, and mend.

2020 onwards – Synthetic Biology

From mRNA vaccines to crops that are gene-edited,
And carbon-capture microbes that remove CO_2 emitted.
Firmly carrying the promise of all we have begun,
From Petri to Planet — we rise as one.

Dust

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Dust- as insignificant as it seems,
A remnant of powerful action.
A curtain over the drama of history, life and existence.
A fossil of passion,
It is more than just debris.

Life ends in it,
Yet dust does not teach pessimism,
It is reminder of human resilience and optimism,
And that all we started with, was a bit.

It is also the greatest warning to those consumed by hubris,
That all they are proud of can be turned to debris.

Finally Free

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The leaf sways
At a precarious angle
As the breeze comes
All it does is dangle.

It was once green
Healthy and strong
But now it's all crumpled
What suddenly went wrong?

Its grip is failing
The tree doesn't help out
'All leaves fall one day', it thinks
What's all this fuss about?

Struggling futilely
The leaf begins to tire
'Just go with the flow,' it thinks
When circumstances are dire.

So when the next gust comes,
It simply lets go
Swaying gracefully,
Falls on the ground below.

Of that once flourishing leaf
There is now no trace,
Did it simply get lost
In the lifecycle race?

Months go by,
Winter begins to loom
When all of a sudden
A sapling begins to bloom.

The leaf will now form
Its very own tree
After all it went through
It is finally free.

My Mother Dreams of Rain

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My mother caresses my forehead,
as she puts me to bed.
The creases of her palm
resemble the absence of calm.
The din, the heat, tumult,
so precariously neutralised by her tranquil presence.
Oh but she cries!
She sheds tears that descend upon me.
They remove the anvils of glee
from my pensive countenance.
She cries the tears of the same despair,
that another mother,
across the ocean must've cried.
For another child, in another land
where brave-hearts had died.
In the world and in its inexorable heat
my mother yearns, she dreams,
of Pacific downpour.
A rain so strong that it shall drain the bilge of hate and misery and then only,
can she finally lower her head,
adorn a smile on her bleared countenance.
And thus seek retribution in the abyss of heaven!

Escapism

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It was a humid August afternoon. I had just completed attending all my college classes and was listlessly walking towards the metro station. It was a short walk, most of the surroundings were quite known, yet I saw this celestial maiden of a city unfurl before my eyes, which made the walk pleasant even considering the blistering heat.

By happenstance, as if, my glance fell upon an almost tumbled down building, bearing dilapidation and the imprints of time. The façade of the building bore the name, "Earth-care bookstore". The sheer mention of the word bookstore entrapped my attention, like how a bug gets trapped in the mesh crafted so carefully by a spider. For me it seemed like a honeyed labyrinth, and hence without thinking twice I walked inside. The building, however, did not seem worn down at all from the inside. It was cool, damp yet beauteous, a litany of books was arranged on clean shelves. From Fitzgerald to Steinbeck, from Amitava Ghosh to Chitra Banerjee, from Hemingway to Arundhati Roy, the collection was simply eclectic. It seemed like an utter dream for a bibliophile. I sprawled on one of the short stools kept singularly for eager readers like me. I flipped through pages of fiction, non-fiction irrespective of genre and topic.

After reading for an hour or so, I got up and left for home. The experience felt whimsical of sort, and I kept on thinking about the same thing repeatedly, that when upon life's wild uncertainties we are tossed into tempests, when its vicissitudes unsettle us, may we find our "Earth-care bookstore" and unwind and rejuvenate from the monotony of everyday life.

Photography & Artworks

Aditya Chatterjee
Semester 3

Poulami Sinha
Semester 5

Anish Gupta
Semester 3

Anisha Biswas
Semester 1

Aditya Chatterjee
Semester 3

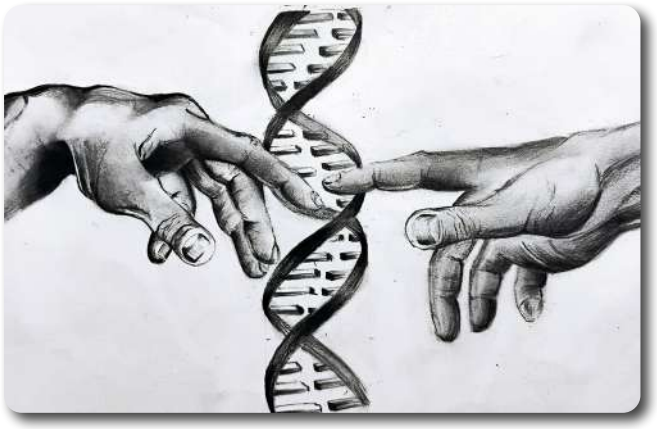
Heeya Gupta
Semester 9

Cynthia Sanjana D Rozario
Semester 3

Emmanuel Bhora
Semester 5

Anish Gupta
Semester 3

Heeya Gupta
Semester 9



Samriddha Das
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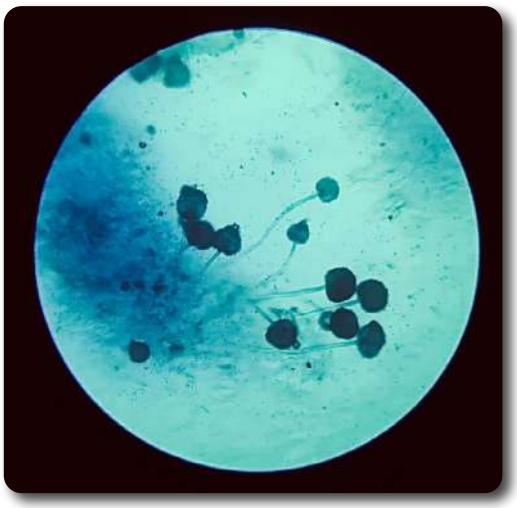
Meghna Chatterjee
Semester 5

Sutanu Bose
Semester 5

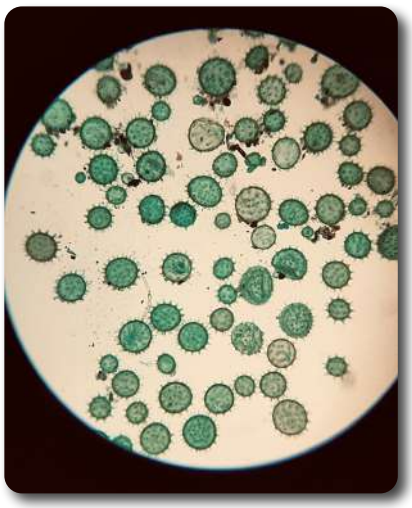


Rittika Dhar
Semester 5

Shinjini Mukherjee
Semester 1

Samonwita Sarkar
Semester 3

Poulami Sinha
Semester 5



Rittika Dhar
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Sutanu Bose
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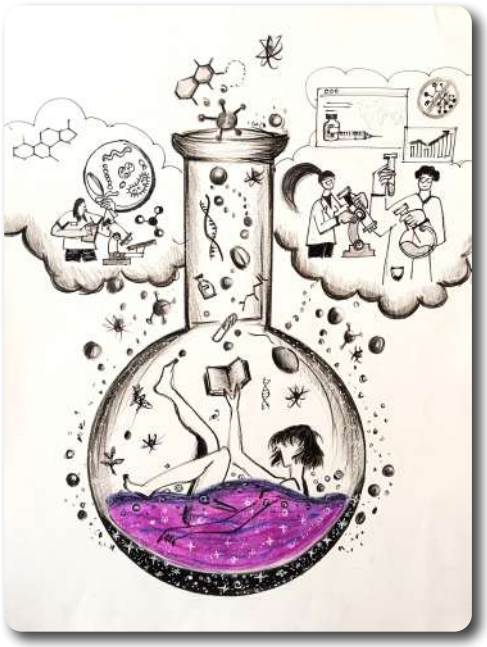
Sohini Das
Semester 7

Uttaran Giri
Semester 3

Sohini Das
Semester 7

Sharanya Datta
Semester 3



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