14th Young Investigators' Meeting 2022

ABSTRACT BOOK

IndiaBioscience

Acknowledgements

IndiaBioscience and the organisers of YIM 2022 are thankful for the support they received from:

- Student volunteers:
  - **Atchuta Srinivas Duddu** from the Indian Institute of Science, Bengaluru;
  - **Jyoti Kumari, Mahima Mohanto** and **Mohabbat Singh** from the Central University of Punjab, Bathinda; and
  - **Sania Kouser** from The University of Trans-Disciplinary Health Sciences and Technology, Bengaluru.

- Sponsors of YIM 2022:
  - Department of Biotechnology, Govt. of India and
  - CACTUS Communications Pvt. Ltd.

- The staff of the administration and purchase departments of NCBS and inStem, and

- Board members of IndiaBioscience

They also thank the Indian life science community for their engagement!

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Conference Code of Conduct

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Table of Contents

The Young Investigators' Meeting Series

Building a community of young Indian biologists

The YIM series aims to build a vibrant community of biologists by allowing young Indian scientists from different regions and institutions to establish friendships, initiate collaborations, and learn from peer-to-peer mentoring.

The annual Young Investigators' Meeting (YIM) brings together exceptional young and senior scientists, heads of institutes, and representatives from funding agencies for discussions and interactions focusing on science and careers in a broad range of disciplines of biology. Since its inception in 2009, the YIM has established its brand in the life-science fraternity. The meeting has created a vibrant atmosphere for exchanging ideas for improving science in India and catalysing friendships and collaborations between young Indian scientists.

Perhaps the greatest accomplishment of the YIM series is building a vibrant community of well connected biologists, allowing young Indian scientists from different regions and institutions to establish friendships, initiate collaborations, and learn from peer-to-peer mentoring. Every year the YIM is organised by a different committee, comprising young faculty members from institutions across the country. IndiaBioscience plays an administrative and advisory role in each year's YIM.

The Young Investigators' Meeting 2022 is themed on the idea of "community", the holistic ecosystem that nurtures and sustains scientific discovery. It will feature talks by Indian and international scientists, networking/breakout sessions, and panel discussions to address the importance of communities not just at the level of a PI's lab but also at the level of institutes, science, and the public. COVID-19 has sharply brought into focus our need to work collectively and early career scientists can explore the potential of collaboration and allyship. This will also bring to the forefront discussion on topics, including mentorship, setting up a research group, interdisciplinary research, open science, and funding opportunities. Established scientists will describe their scientific journeys, sharing inspirational and amusing anecdotes about their experiences with younger scientists who are establishing their careers.

YIM 2022 will be held in an online mode. Although it is not an in-person meeting, it has been designed in such a way that it will enable the participants to network and forge connections. It will also give them the opportunity to share their experiences and become a part of the larger scientific community, which the YIMs are already known to cater to.

YIM 2022 is supported by the Department of Biotechnology, Govt. of India and Cactus Communications Pvt. Ltd.

YIM 2022
Organisers

FELIX BAST

Central University of Punjab, Bathinda
Email: felix.bast@gmail.com

Felix Bast is an award-winning Indian Science Communicator and a public educator working currently as a Professor at Central University of Punjab, India. He founded Young Academy of India-YAI in the model of Die Junge Akademie of Germany. With over 16,000 members, YAI is one of the largest science academies in the world. He holds a PhD in Marine Biology from MEXT, Japan, and served as expedition scientist in Indian Antarctic Mission. Bast served as a resident intern with the President of India and received the "President's Inspired Teacher" recognition. He also won a teaching innovator award from the Indian Ministry of Education. Bast has discovered seven new plant species from India and Antarctica. Sustainability is a major focus of his works.

MEGHA

The University of Trans-disciplinary Health Sciences and Technology, Bengaluru
Email: megha@tdu.edu.in

Megha is a biochemist passionate about nutrition, dietetics, public policy and communication - not always in that order! After a traditional PhD and postdoc she worked for the India Alliance as a grants and programme manager. She returned to the bench to pursue developmental biology, an interest which evolved into the focus of her independent laboratory: early life malnutrition. Using TDU's expertise in traditional medicine and local health, she now leads the Ayurveda Dietetics program and co-leads India's first PG program to blend Ayurveda and contemporary biology. She is an Associate Professor at the Centre for Ayurveda Biology and Holistic Nutrition, TDU.

YIM 2022
Organisers

MOHIT KUMAR JOLLY

Indian Institute of Science, Bengaluru
Email: mkjolly@iisc.ac.in

Mohit Kumar Jolly is an Assistant Professor at Indian Institute of Science, Bangalore, where he leads Cancer Systems Biology Laboratory. His interdisciplinary research group is focused on understanding the emergent dynamics of regulatory networks underlying phenotypic plasticity and heterogeneity driving cancer metastasis and therapy resistance. His group integrates multi-scale mathematical models and single-cell multi-omics analysis, in close collaboration with experimental cancer biologists and clinical oncologists. He is passionate about effective science communication and outreach, and won the 2016 Young Scientist Seminar Series – a coveted award to communicate one's research to diverse audience.

SHANTALA HARI DASS

IndiaBioscience, Bengaluru
Email: shantala@indiabioscience.org

Shantala completed her PhD in behavioural neuroscience from Nanyang Technological University, Singapore following which she moved to McGill University, Canada for her postdoctoral studies. Across the continents and research questions, her interest in communicating science and facilitating the evolution of the scientific community has stayed strong. At IndiaBioscience, she is keen to see their network grow, expand their activities bringing greater national and international visibility to the Indian life science community and think of creative and bilateral modes of engagement with the community.

About IndiaBioscience

IndiaBioscience

IndiaBioscience is an organization that fills a unique niche in the ecosystem of the life sciences in India, by being a catalyst to promote changes that affect the culture and practice of the field, through engagement with academia, government and industry at various levels. IndiaBioscience aims to increase the visibility of science in society, by being a hub for policy discussions, science communication, and as an aggregator of information.

IndiaBioscience plays an administrative and advisory role in each year's YIM, but its engagement with the participants extends beyond the meeting. IndiaBioscience sets out to forge a long-standing bond with the YIM alumni to promote the development of their career and aid the flourishing of their research groups. Through this sustained ripple effect, it hopes to create a meaningful and lasting impact on the research ecosystem in the life sciences in India

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About IndiaBioscience

IndiaBioscience

Engage with us

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Schedule of the Meeting

- The details of the invited guests, the dates and the times of the various sessions can be found in the following pages of the abstract book.
- The speakers of a session are given in the order of their appearance in the meeting.
- All the times are in IST.
- The timings may have changed after this book was published. Please visit the website for the most updated programme.

Special Talks

Keynote Talk

K VIJAYRAGHAVAN

Emeritus Professor, National Centre for Biological Sciences.
Former Principal Scientific Advisor
Email: vijay@ncbs.res.in
Title: To be decided
Date | 4 May 2022, Time | 17:45- 18:05

Special Talk 1

RAJESH GOKHALE

Secretary, Department of Biotechnology, Govt. of India
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Title: To be decided
Date | 4 May 2022, Time | 17:30-17:45

Special Talk 2

PRANAY LAL

Public health advocate and natural history writer
Email: invisible.empire@tutanota.com
Title: Why I study natural history (and so should you)
Date | 6 May 2022, Time | 18:45-19:15

Special Talk 3

HARINI CALAMUR

Head, Impact Science, CACTUS Communications
Email: harini.calamur@cactusglobal.com
Title: The need for making research more accessible
Date | 9 May 2022, Time | 17:45-18:00

Mentors

VISHWESHA GUTTAL

Indian Institute of Science, Bengaluru
Email: guttal@iisc.ac.in
Talk Title: Random walk from physics to biology.
Date | 4 May 2022, Time | 18:05-18:35

SWATI PATANKAR

Indian Institute of Technology Bombay, Mumbai
Email: patankar@iitb.ac.in
Talk Title: Reaching your destination: Organelles of apicomplexan parasites (and also in professional life)
Date | 5 May 2022, Time | 18:05-18:35

MANOJ PRASAD

National Institute of Plant Genome Research, Delhi
Email: manoj_prasad@nipgr.ac.in
Talk Title: Climbing the career ladder: Roles of mentor and mentee
Date | 6 May 2022, Time | 17:05-17:35

HARMIT S MALIK

Fred Hutchinson Cancer Research Center, USA
Email: hsmalik@fredhutch.org
Talk Title: Navigating an academic career with a little bit of help
Date | 4 May 2022, Time | 17:00 - 17:30

Mentors

VASUDHARANI DEVANATHAN

Indian Institute of Science Education and Research Tirupati, Tirupati
Email: vasudharani@iisertirupati.ac.in
Talk Title: Journey to a YI
Date | 10 May 2022, Time | 17:40- 17:57

IMROZE KHAN

Ashoka University, Sonepat
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Talk Title: Journey to a YI
Date | 11 May 2022, Time | 17:40- 17:57

KARISHMA KAUSHIK

Savitribai Phule Pune University, Pune
Email: karishmaskaushik@gmail.com
Talk Title: Journey to a YI: Settling in and Branching out
Date | 12 May 2022, Time | 17:40-17:57

Breakout Sessions

Getting Started
5 May 2022 (19:45 - 20:45)

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Breakout Sessions

Addressing Diversity and Inclusivity in Research Groups /Institutions
6 May 2022 (17:40-18:40)

ABHIJIT MAJUMDER

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Establishing and Nurturing Interdisciplinary Research Ecosystems

Panel Discussion 1
4 May 2022 (18:40-19:40)
Moderator
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Funding Opportunities for Early Career Scientists

Panel Discussion 2
5 May 2022 (17:05-18:05)
Moderator
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Building and Sustaining a Research Group

Panel Discussion 3
5 May 2022 (18:40-19:40)
Moderator
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Science Communication and Society

Panel Discussion 4
6 May 2022 (19:15-20:15)
Moderator
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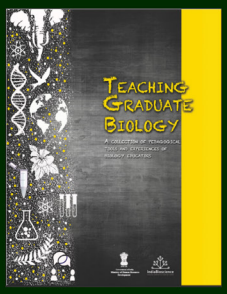

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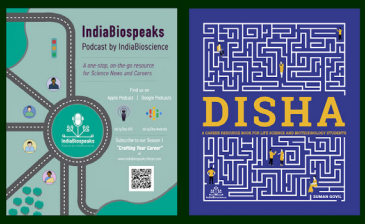
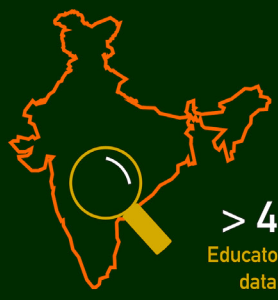


Podcasts, workshops, articles, webinars, videos and booklets to provide information on science careers in India

NETWORK



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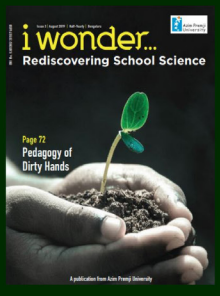

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Videos, events, jobs and other resources for young investigators

To know more, visit www.indiabioscience.org

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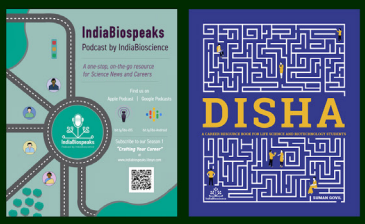

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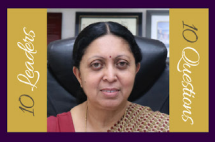

"10 Leaders, 10 Questions" - interviews on leadership skills

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"10 Women, 10 Questions" and other articles based on interviews with women scientists

BE INSPIRED

"Spoorthi" - An e-booklet featuring articles based on conversations with trailblazing women, and other resources for women in science

BE SEEN

"Wikipedia edit-a- thon" - a public event to increase the visibility of Indian women scientists on Wikipedia

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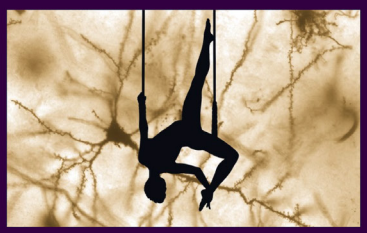

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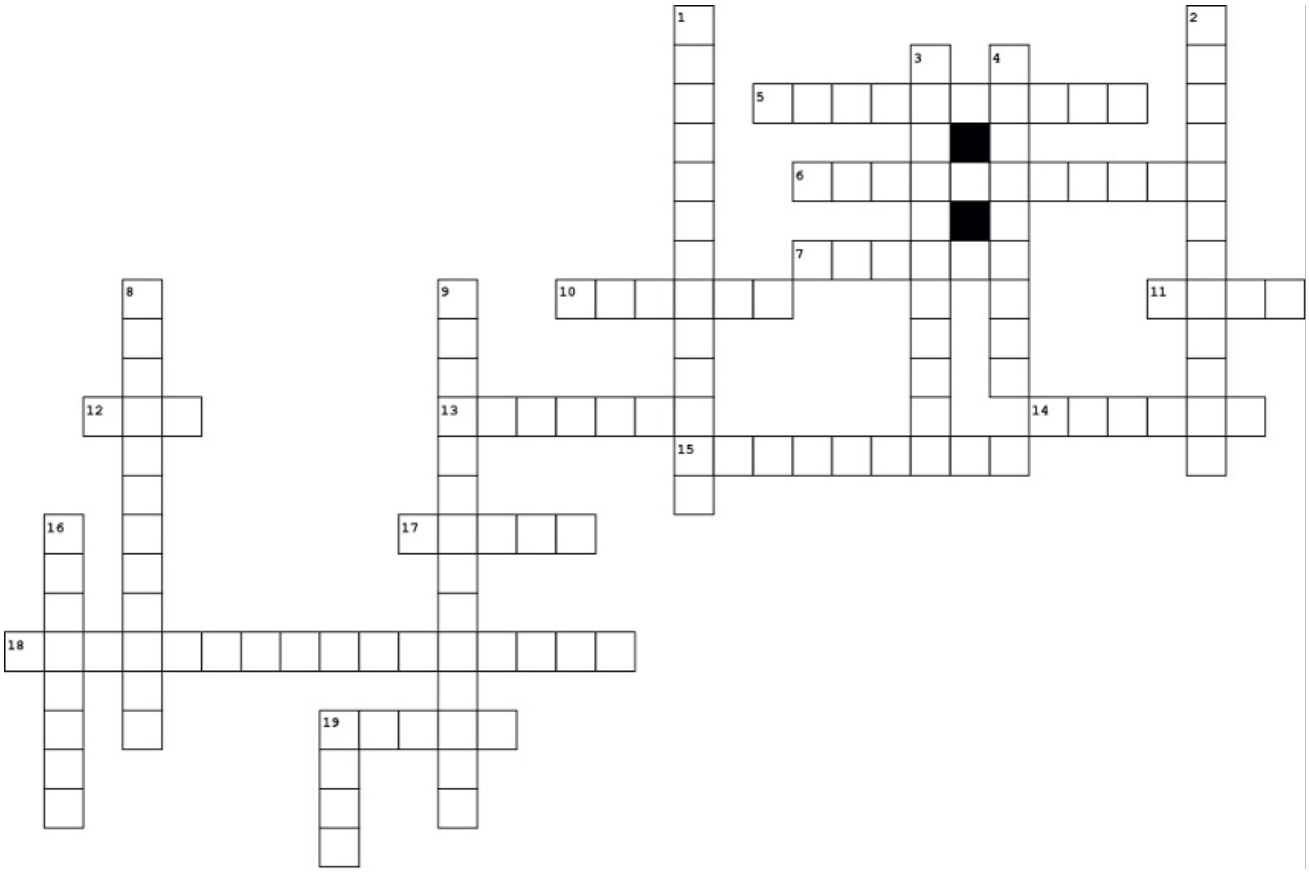
YIM 2022
Crosswords

By **Sania Kouser**, YIM 2022 volunteer, TDU, Bengaluru

Here's a fun way to explore the abstracts shared by your fellow participants. Enjoy!

YI Crossword

Based on YI abstracts. Only first names serve as answers for clues.
Play online here: https://crosswordlabs.com/view/yim2022



YIM 2022
Crosswords

Across

5. YI who is working on an approach to delay sprout initiation

6. YI from Andhra Pradesh who is interested in conserving fossil fuels

7. YI from Bhubaneswar has found that this protein has an important function in bone health

10. YI interested in chemo-immunotherapy resistant tumors

11. This micronutrient is of special interest to the YI from Presidency University

12. This receptor is involved in inflammation in Alzheimer's according to the YI from Visakhapatnam

13. YI who is interested in understanding the impact of variation in plant diet on survival of herbivores

14. An IIT based YI has found this particle to be more efficient in drug delivery

15. YI from Mysuru who has identified TPH1 inhibitors

17. YI who aims to understand immune modulation in lower urinary tract

18. Knowledge centre named after a famous Indian king

19. YI who is amused by how amino acids can tune spectroscopic properties

Down

1. Delhi based YI is interested in the inhibition of this enzyme

2. An MHRD institute at which a fluorescence-based DNA origami sensor is being worked on

3. YI from Kanpur prepared nanofibre using this naturally occurring polymer

4. YI whose work has shown that glycylation is present on primary cilia

8. This repressor protein is of special interest to the YI from Gandhinagar

9. Work on nanoemulsified garlic oil blend was conducted in this institute

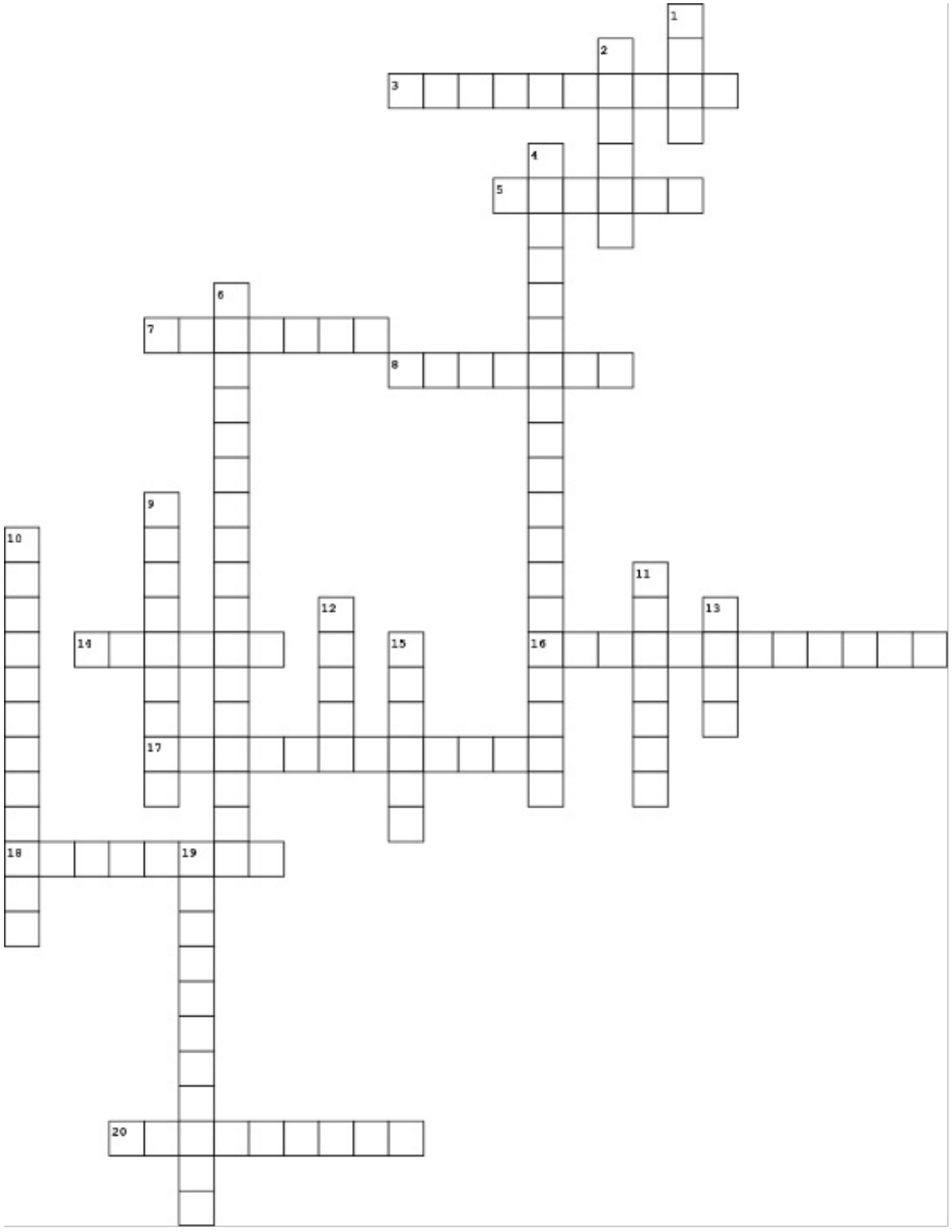
16. YI who constructed a novel antibody library

19. YI from Hyderabad is fascinated by this enzyme

YIM 2022
Crosswords

PDF Crossword

Based on PDF abstracts. Only first names serve as answers for clues.
Play online here: https://crosswordlabs.com/view/yim2022-pdf-crossword



YIM 2022
Crosswords

Across

3. A parasite in digital form being studied by PDF from Belgium

5. PDF using nematodes to understand immune response to infection

7. PDF who is amused by the evolution of cooperation

8. PDF working on using the size and shape of oligomers as diagnostic markers in neurodegenerative disorders

14. PDF developing fluorogenic dyes

16. Disease being studied by a PDF in zebrafish embryo

17. PDF developing affordable blood test to detect lung cancer

18. A German university where the PDF is working on sustainable cropping systems

20. PDF using flies to understand growth and development

Down

1. PDF fascinated by antimicrobial resistance

2. PDF from Seattle studying the diversity of lateral organs in plantae

4. A societal problem being addressed by PDF from Mumbai

6. Animal behaviour to understand sensorimotor dynamics by a PDF in Seattle.

9. Model organism of choice for PDF studying stress resilience

10. Glycosylation of this protein fascinates a PDF from France

11. A PDF who is studying the hangry phenomenon

12. PDF optimizing a gene therapy tool for scalability and cost effectiveness

13. An institute (acronym) in India, where a PDF is interested in DAG metabolism

15. PDF fascinated by how the brain recalls memories

19. Plant being studied by PDF from Assam for drought

Young Investigators' Abstracts

The contents in the abstracts (except references) have been printed exactly as submitted by the participants. The organisers of YIM 2022 are not responsible for any errors in them. In some cases, a few references were removed due to shortage of space.

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YI 15 KIRTIKUMAR KONDHARE
Utilizing genome editing tools to delay storage root sprouting in sweet potato - one of the major, yet neglected staple crops in the world

YI 16 MAMONI DASH
Mucins: Potential proteins for bone tissue engineering

YI 17 MANU SINGH
Nanomedicine for treatment of ovarian cancer

YI 18 NALINI E
Immunomodulation of gut by Lactobacillus sp.

YI 19 NEERAJ JAIN
Targetable novel oncogenes for chemo-sensitization in B-cell lymphoma

YI 20 PRAMOD YADAV
Structural enzymology of mammalian hydrogen sulfide metabolism & signaling

YI 21 PRITI JAIN
Design and development of tri-substituted pyrimidine derivative as BACE-1 inhibitors for treatment of Alzheimer's disease

YI 22 PRIYANKA BAJAJ
Identification and characterization of a novel P450 enzyme RufO from Rufomycin biosynthetic pathway: A green way to synthesize regiospecific nitroaromatic compounds

YI 23 RAJIV KAR
Molecular informatics-based design of optogenetic tool using LOV-protein

YI 24 RAMENDRA PATI PANDEY
The translational prospective of secretory proteins of Mycobacterium tuberculosis encapsulated in bio-polymeric nanoparticles: An interplay of immune response and oxidative stress

YI 25 ROHAN KHADILKAR
Understanding molecular regulators of stem cell homeostasis and modelling human diseases using Drosophila as a model organism.

YI 26 SARAN KUMAR
How blood vessels shape tumor stemness in glioblastoma?

YI 27 SARAVANAN P
Discovery of tryptophan hydroxylase 1 inhibitors for obesity

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YI 01

ADITYA PAREKH

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Keywords: sustainable agriculture, soil, climate change, industrial agriculture, human health.

Promoting sustainable agriculture through scientific evidences, education and community outreach.

Conventional or chemical-intensive agriculture is not sustainable, as stated by FAO-UN, because of its negative impacts on the environment and humans. Currently, the agriculture sector is also responsible for producing about 1/3rd of the total greenhouse gases, thus contributing significantly to global warming. It also reduces soil fertility, risks the life of many land and aquatic animals, and have been correlated with deleterious human diseases like Alzheimer, Cancer amongst others. Alternate sustainable methods in agriculture including regenerative agriculture, organic farming, and others promise to have a positive impact on the environment, mitigate climate change, provide safe food. Although alternate methods have been practically demonstrated, scientific evidence are scattered and not enough to support the shift from industrial farming. Adoption of alternate agriculture practices is also challenging because it requires good understanding of ecology. Furthermore, yields from alternate farming are questionable.

We believe that extensive research and validations, education to students and the wider public, alongside favorable government policies can accelerate the adoption of sustainable agriculture practices. Our work is based on three pillars, a) scientific experiments with different alternate farming techniques to demonstrate data and support validations, b) making a model sustainable farm for education, and c) community outreach. Experiments are currently being carried out using Zero Budget Natural Farming for measuring impact on soil quality, and yield. The sustainable model farm has components like efficient management of natural resources, preparation of natural fertilizers and pesticides, growing of local, indigenous, and medicinal plants, adoption of multi-layer farming. Community outreach involves volunteering activities, screening of educational documentaries, growing your own food amongst a few others.

Although these initiatives are at initial stages and we don't have enough data to validate, we believe that the above-mentioned pillars are crucial for sustainable agriculture practices to scale.

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3. https://www.mdpi.com/2071-1050/7/6/7833
4. https://www.nature.com/articles/s43016-021-00225-9

YI 02

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Keywords: cancer stem cells, miRNA, computational biology, and metabolism.

Cancer stem cells specific MicroRNA assisted gene regulation in Breast cancer

Stem cells play a pivotal role in tissue remodelling and differentiation during normal growth and repair when injury occurs as well. In malignancy, these cells become more aggressive and proliferate in an uncontrolled manner called cancer stem cells. miRNA works in two different ways as" oncomiRs" in cancer and tumor suppressor in normal tissue. During altered genetic conditions these oncomiRs bind with oncogenes and promote their expression, leading to cancer progression. Moreover, tissue specific miRNA regulates mRNA transcription activities upon binding to the target site. Furthermore, experimental studies have raised hope to understand functionality of miRNAs- mRNA target sites using numerous software based high-throughput computational biology prediction approaches. Their role in oncology can serve as prognostic and predictive factors and can be used as a diagnostic tool for cancer treatment therapy.

The study aimed to predict the mechanism of gene regulation mediated through stem cells specific microRNAs involved in breast cancer progression using the in-silico approach. Since the discovery of microRNA, several studies have reported their involvement in a variety of physiological and pathological processes and mutations affecting their normal expression which may be critical to their role in the development of human diseases.

References:

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YI 03

ANTARA DAS

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Keywords: epilepsy, ion channel, CRISPR, thermosensation

Interneuron dysfunction in a new knock-in mouse model of SCN1A associated epilepsy

Epilepsy is a common neurological disorder that affects 1% of the world population. Advanced genome sequencing has identified over 1300 mutations in the human SCN1A, a gene that encodes the alpha subunit of a sodium ion channel Nav1.1. About 20% of SCN1A missense mutations result in an epilepsy disorder-Genetic Epilepsy with Febrile Seizures Plus (GEFS+). GEFS+ is a childhood onset disorder, characterized by febrile (or fever associated) seizures, which can persist beyond 6-7 years of age. A fundamental challenge in understanding the etiology and developing treatments for genetic epilepsies is the heterogeneity of the phenotypes. To examine the behavioral and cellular effects of this mutation in mammalian circuits, we introduced the equivalent KT mutation into the mouse Scn1a gene using CRISPR/Cas9. Mutant mouse lines were generated in two widely used genetic backgrounds: C57BL/6NJ and 129X1/SvJ. In both backgrounds, mice homozygous for the KT mutation had spontaneous seizures and died by postnatal day 23. Heterozygous mutants exhibited heat-induced seizures at ~42ºC, a temperature that did not induce seizures in wild-type littermates. In acute brain slices at permissive temperatures, current-clamp recordings revealed a significantly depolarized shift in action potential threshold and reduced action potential amplitude in hippocampal parvalbumin-expressing inhibitory interneurons in heterozygous mice. In contrast, there was no change in the firing properties of excitatory CA1 pyramidal neurons. Thus, GEFS+ causing K1270T mutation leads to decrease in inhibitory interneuron excitability contributes to the seizure phenotype in the mouse model. These results are concurrent with impaired GABAergic firing in K1270T knock-in model of Drosophila and human iPSC stem cells, lending support to the 'Interneuron disinhibition' hypothesis for seizure generation. The SCN1A KT mouse model represents an important tool for identifying mechanisms of seizure generation in relation to other epilepsy models, and for development of mutation-specific therapies.

References:

1. Das, Antara*, Martin A. Smith, and Diane K. O'Dowd*. A Behavioral Screen for Heat-Induced Seizures in Mouse Models of Epilepsy. (2021). Journal of Visualized Experiments, no. 173 (July 12, 2021): 62846. * co-corresponding authors.
2. Antara Das, Bingyao Zhu, Yunyao Xie, Lisha Zeng, An Pham, Olga Safrina, Daniel Benavides, Jonathan C. Neumann, Soleil Schutte, Grant R. MacGregor, Robert F. Hunt and Diane K. O'Dowd (2021). Interneuron dysfunction in a new knock-in mouse model of SCN1A GEFS+. eNeuro 2021

YI 03

ANTARA DAS

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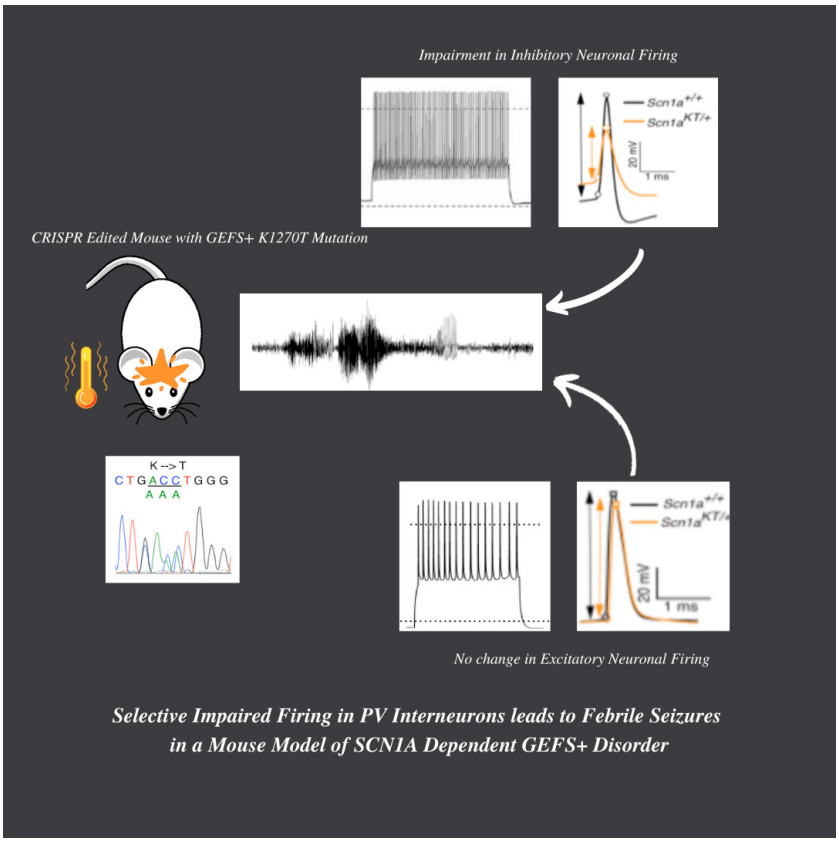

Credits: Sai Snigdha Kodali (2nd yr BSc student, Azim Premji University)

YI 04

ARCHANA KUMARI

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Keywords: plant-insect interaction, defense, jasmonic acid, long-distance signaling, metabolites

Understanding the early defense signaling against the herbivorous insects.

Plant and insects have co-evolved for millions of years, leading to their large numbers inhabiting earth today. Being sessile, the plant responded to the herbivores' attack through the precise perception of aggressors followed by signal transduction which leads to transcriptional reprogramming and synthesis of defense compound, whereas the lipid-derived phytohormone Jasmonic acid plays a crucial role. Early signaling components to the herbivores' attack include calcium flux, plasma membrane potential variation, reactive oxygen species production, and phosphorylation cascades. This can further lead to systemic signaling affecting parts of the plant distant from the damaged tissue. Here, systemic defense responses are one of the central mechanisms to minimize added herbivore challenges after an initial attack. Efficient plant defense imposes pressure on herbivores, which develops a way to interfere with defense mechanisms or adapt to the detrimental effect of plant toxins. In this context, relevant questions are: How are long-distance herbivore/wound signals generated, propagated, and decoded to activate Jasmonate synthesis and further defense responses? Similarly, from the herbivores' perspective, the possible questions are: How do herbivores with different feeding styles exploit the same resources. Does variation in plant diet may impact herbivores' performance and survival. Here, it is also essential to know whether plants respond similarly to different types of leaf damage and feeding style. Possibly, in the process of crop domestication, we have lost some of the defense traits, which may be a precious tool for insect/ pest control. Understanding the early signaling components regulating plant and insect interaction will allow us to design future crops with enhanced defense against herbivores.

YI 05

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Keywords: milk exosomes, antimicrobial resistance, cancer, bacteriophage, nanoparticles

Milk-derived exosomes for oral delivery of paclitaxel

In this report milk-derived exosomes have been investigated for oral delivery of the chemotherapeutic drug paclitaxel (PAC) as an alternative to conventional i.v. therapy for improved efficacy and reduced toxicity. PAC-loaded exosomes (ExoPAC) were found to have a particle size of ~108 nm, a narrow particle size distribution (PDI ~0.190), zeta potential (~ −7 mV) and a practical loading efficiency of ~8%. Exosomes and ExoPAC exhibited excellent stability in the presence of simulated-gastrointestinal fluids, and during the storage at −80 °C. A sustained release of PAC was also observed up to 48 h in vitro using PBS (pH 6.8). Importantly, ExoPAC delivered orally showed significant tumor growth inhibition (60%; P b 0.001) against human lung tumor xenografts in nude mice. Treatment with i.p. PAC at the same dose as ExoPAC, however, showed modest but statistically insignificant inhibition (31%). Moreover, ExoPAC demonstrated remarkably lower systemic and immunologic toxicities as compared to i.v. PAC.

References:

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YI 06

ASHUTOSH SRIVASTAVA

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Keywords: computational biology, network biology, circadian biology, integrative modeling, molecular dynamics simulations

Molecular insights into the regulation of mammalian circadian clock

The physiology and behavior of almost all living organisms on earth is synchronized to a 24-hour solar cycle by a well-regulated molecular clock mechanism. In mammals, this mechanism comprises transcription-translation feedback loop involving complex interactions between transcription factors, clock proteins, cryptochromes, kinases, phosphatases and several other associated proteins. Cryptochromes (CRY) are repressor proteins that bind to the transcription factors CLOCK and BMAL1 and stop the transcription of their own as well as other clock genes. There are two isoforms of CRY in mammals with high sequence and structural similarity in the conserved Photolyase Homology Region (PHR) but show crucial functional differences. Using integrative structural biology approach involving X-ray crystallography, Cryo-electron microscopy, mutational studies, molecular dynamics simulations and computational docking, we have deciphered the structural and dynamical basis of functional divergence between the two isoforms of CRY. We identified two regions in cryptochrome that show conformational variation between the two isoforms and affect function as well as selectivity of certain small molecules that bind to the FAD binding pocket of cryptochromes. Further, the long, disordered region at the C-terminus of cryptochromes shows considerable variation in terms of sequence across different species as well as isoforms. We are currently trying to understand the conformational landscape of this region in context of its interaction with the structured domain.

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YI 07

AVIJIT BANIK

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Keywords: Credits: Prostaglandin receptor EP2 inhibitor ameliorates neuroinflammation in two-hit AD brains.

Prostaglandin EP2 receptor – A potential anti-inflammatory target in Alzheimer's disease brain.

Prostaglandin receptors modulate many physiological activities in mammalian cells including the gastrointestinal, endocrine, respiratory, cardiovascular, CNS and immune systems. Out of ten different prostaglandin receptors, EP2 plays a key inflammatory role in many neurodegenerative disorders including Alzheimer's disease (AD) brain. In this study, we examined whether EP2 receptor antagonist can ameliorate neuroinflammation in AD brains. A transgenic mouse model of AD (5xFAD) was subjected to a secondary inflammatory stimulus (Lipopolysaccharide, LPS, two-hit) to induce additional level of peripheral and brain inflammation. Mice were treated with a potent and selective EP2 antagonist in drinking water. Blood and brains were harvested for further analysis. Complete blood count (CBC) analysis revealed an anemia like inflammation by LPS, which could not be altered by the EP2 antagonist. There was an elevation in brain inflammation by LPS and brain tissue analysis revealed that the EP2 antagonist could selectively ameliorate the neuroinflammation in these mice associated with significant reduction in glial activity. There was no change in the amyloid pathology by the drug treatment. Overall, our findings suggest a therapeutic effect of EP2 antagonism in ameliorating chronic neuroinflammation in AD brain. Further investigations are underway to elucidate the effect of this anti-inflammatory property in cognitive performance.

Acknowledgement: This work was supported by National Institutes of Health grants: NIA, U01 AG052460 (T.G.), and, NINDS, R21/R33 NS10167 (T.G.).

References:

Banik A, Amaradhi R, Lee D, Sau M, Wang W, Dingledine R, Ganesh T. 2021. Prostaglandin EP2 receptor antagonist ameliorates neuroinflammation in a two-hit mouse model of Alzheimer's disease. J Neuroinflammation. 18(1): 1-21.

YI 07

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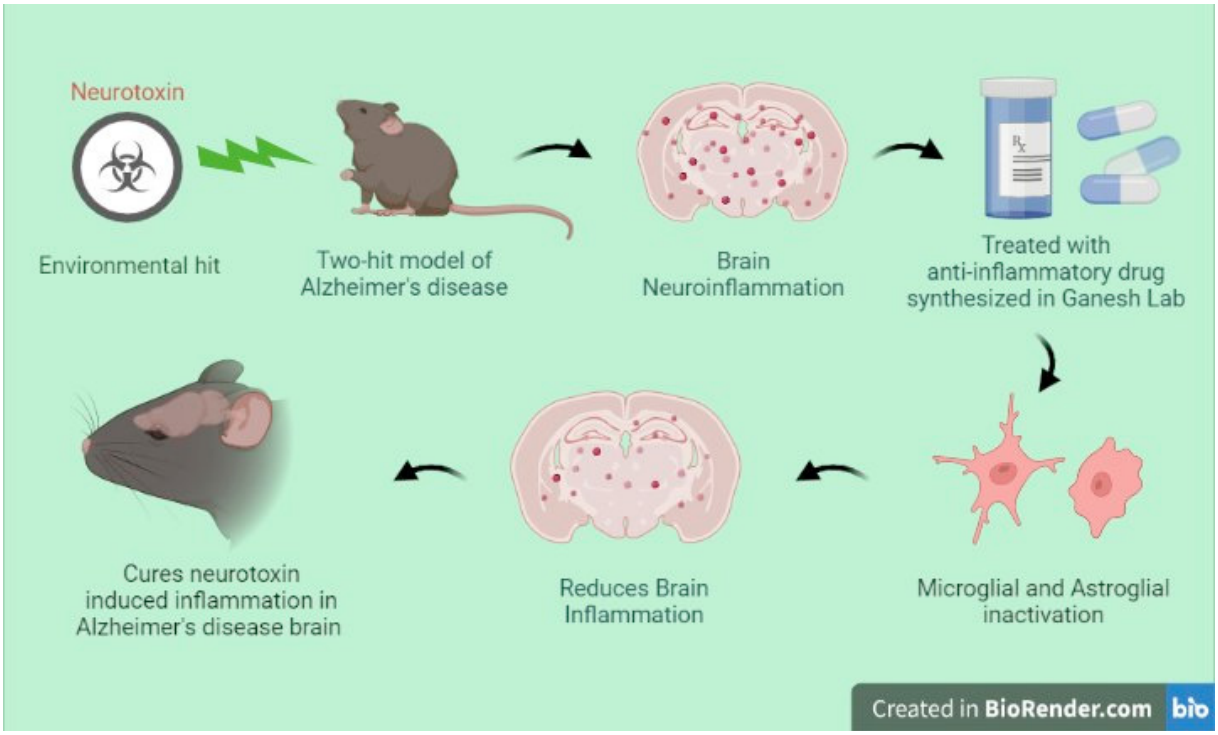

Credits: Prostaglandin receptor EP2 inhibitor ameliorates neuroinflammation in two-hit AD brains.

YI 08

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Keywords: glycobiology, plant-microbe interactions, plant cell wall, synthetic biology, chemical biology

Fungi hijack a plant apoplastic endoglucanase to release a ROS scavenging β-glucan decasaccharide to subvert immune responses

Plant pathogenic and beneficial fungi have evolved several strategies to evade immunity and cope with host-derived hydrolytic enzymes and oxidative stress in the apoplast, the extracellular space of plant tissues. Fungal hyphae are surrounded by an inner, insoluble cell wall (CW) layer and an outer, soluble extracellular polysaccharide (EPS) matrix. Here we show by proteomics and glycomics that these two layers have distinct protein and carbohydrate signatures, implicating different biological functions. The barley (Hordeum vulgare) β-1,3-endoglucanase HvBGLUII, which belongs to the widely distributed apoplastic glycoside hydrolase 17 family (GH17), releases a conserved β-1,3;1,6-glucan decasaccharide (β-GD) from the EPS matrices of fungi with different lifestyles and taxonomic positions. This low molecular weight β-GD does not activate plant immunity, is resilient to further enzymatic hydrolysis by β-1,3-endoglucanases due to the presence of three β-1,6-linked glucose branches and can scavenge reactive oxygen species. Additionally, exogenous application of β-GD leads to enhanced fungal colonization in barley. Our data highlights the hitherto undescribed capacity of this often overseen fungal EPS layer to act as an outer protective barrier important for fungal accommodation within the hostile environment at the apoplastic plant-microbe interface.

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YI 09

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Keywords: anaerobic digestion, microbial fuel cell, microbial electrolysis cell, biogas, biohydrogen

Bioenergy: sustainable renewable energy

India is one of the fastest-growing economies in the world and its energy consumption is expected to grow rapidly. The Ministry of Petroleum and Natural Gas estimates that India has a total of 763 million tonnes of crude oil and 1.488 billion cubic meters of natural gas reserves. The country currently imports about 77% of its crude oil needs and 50% of its natural gas needs. Moreover, the government has decided to increase renewable energy capacity up to 500MW by 2030 and net-zero emissions control by 2070. Even worldwide, the over-exploitation of fossil fuel to fulfil the global energy demands may lead to its depletion by the next 50 years. In addition, fossil fuel utilization causes severe environmental pollution harmful to human health. However, the world and India have predominated waste sources like biomass resources such as organic waste and agricultural residues, animal manure, sugar cane sludge, solid municipal waste and wastewater. In this context, I am focusing on the generation of bioenergy, biogas, renewable natural gas, biohydrogen by different technologies like anaerobic digestion, Microbial fuel cells, Microbial electrolysis cells and combination of these technologies.

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3. Microbial electrochemical electrodes (US patent-2021; Publication number: WO2021/038576).

YI 09

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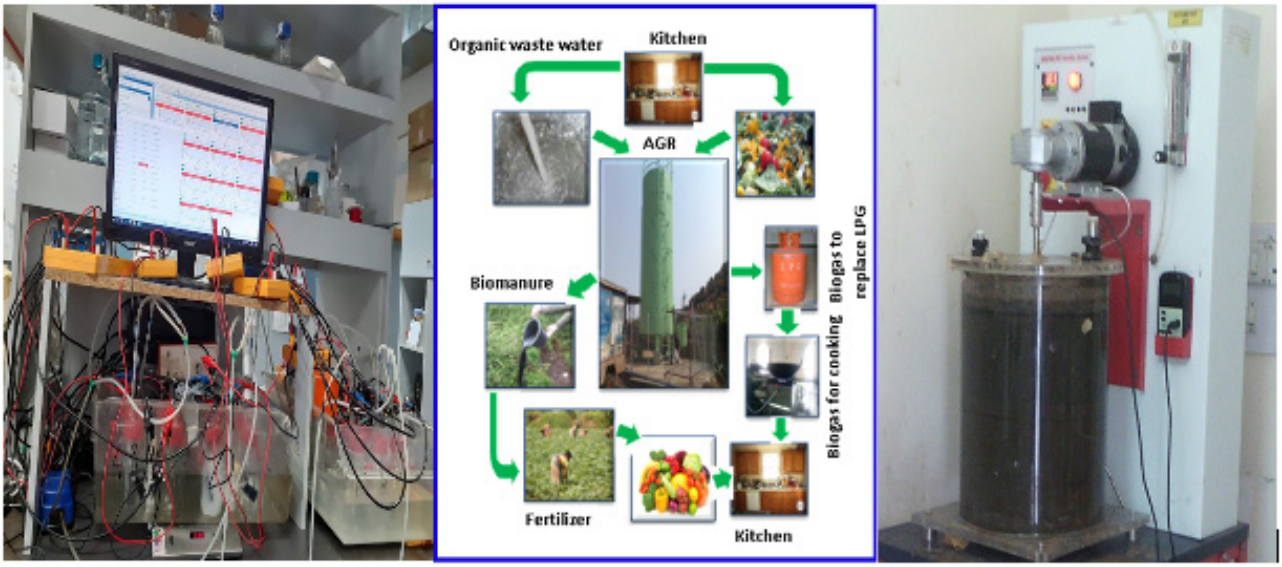

Bioreactors

YI 10

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Keywords: multi drug resistance, antibiotics, Plasmodium falciparum, P. berghei, antimalarial drug resistance

Synthesis and biological assessment of N-sulfonylpiperidine dispiro-1,2,4,5-tetraoxanes as new antimalarial candidates.

Malaria, a mosquito-borne infectious disease of humans, is synonymous with devastation in the tropics. The evolution of parasite resistance to most existing medications, including semi-synthetic artemisinin derivatives or an ACT, is a major source of global concern. High cost, lack of public understanding about combination therapy (CT) concept and ACT in particular, inappropriate drug use, lack of adequate drug formulations, and unviable commercial synthesis of artemisinin make ACTs inaccessible and expensive for the poor in developing nations. As a result of these circumstances, researchers have been working to develop novel synthetic peroxides as antimalarial medicines. 1,2,4,5-tetraoxanes are another class of cyclic peroxide has drawn an exponentially increasing interest due to their artemisinin like antimalarial activity. They are more benign as they are entirely synthetic and synthesized from readily available and low-cost raw materials. In addition, there are few reports on the cytotoxicity and the antiproliferative activity are also limited. The investigated, dispiro-1,2,4,5-tetraoxanes analogs emerged as potent anti-malarial candidates with negligible toxicity to mammalian cells, has potent nanomolar inhibitory activity against intra-erythrocytic asexual stages of chloroquine-resistant and chloroquine-sensitive strains of P. falciparum in vitro and efficacious against P. berghei in in vivo rodent models, produces parasite reduction ratios equivalent to artesunate.

References:

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YI 11

DIVYA M S

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Keywords: stem cells, disease modeling, neurodegenerative disorders, LncRNAs, CRISPR

In vitro modelling of temporal aging in hiPSC-derived neural cells and organoids to elucidate the molecular pathology of α-synucleinopathy

Being a relatively late onset disorder with an uneventful pre-symptomatic phase, early detection of Parkinson's disorder (PD) and other -synucleinopathies is difficult, until the symptoms appear at an advanced age. While, genetic variations in -synuclein (SNCA) gene has been attributed to the risk of PD and pathogenic neuronal aggregates known as Lewy bodies, the delayed onset should need additional risk factors. Although postmortem brain studies have provided insights into the pathogenesis of PD, they depict pathological endpoints, rather than disease progression. Rodent models of pathogenic SNCA mutations observed in patients have been hindered by the absence of pathogenic phenotypes. Furthermore, cell-specific expression and functionality of α-synuclein limits testing in non-neuronal cell lines. This demand, an alternative model accounted for disease progression that can be probed longitudinally to discern the molecular events during the pathogenic course. Genomic manipulation and lineage-specific differentiation of human-induced pluripotent stem cells (hiPSC) into neural cells and organoids enables to study recapitulation of molecular and cellular aspects of disease pathogenesis in a near-physiological condition. Since aging is one of the major risk factors for -synucleinopathies, inducing temporal aging in this model is worth testing. I hypothesize that inducing temporal aging through advanced glycation end products (AGE) build-up in -synuclein mutation model could faithfully recapitulate the pathological events of α-synucleinopathy progression. To this end, I plan to develop and characterize hiPSC-derived neural cell and organoid models for PD, by generating SNCA mutation resulting in protein misfolding. Next, I will incorporate the aging factor by temporally inducing carbonyl stress endogenously, resulting in AGE build-up via; knocking down glyoxalase I (GLO1), a critical enzyme for AGE clearance. Collectively, this model may recapitulate the pathogenesis, and progression of pathological events in PD and other -synucleinopathies, thus offering a prospect for biomarker discovery and therapeutic targets, upon longitudinal evaluation and also for drug screening.

YI 12

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Keywords: bladder, urethra, infection, inflammation, epithelial homeostasis

Regulation of immune defenses and homeostasis at the urethral barrier

Epithelial linings of organs that interface with the environment employ innate immune defenses to protect against environmental exposures and pathogens. Understanding the role of specific immune modulating genes will improve our ability to design targeted therapies to prevent chronic inflammation and tissue damage following infection. The lower urinary tract, comprised of the bladder and urethra, acts as a barrier against urine components and urinary pathogens originating from the gut. Recent advances in single cell transcriptomics have enabled us to resolve cell type-specific gene expression in the urethra and bladder, revealing the plethora of immune modulating and defense genes expressed by these epithelial barriers [1,2]. Although most research has focused on the bladder, a key gap in knowledge is the role of the urethra during urinary tract infections. Urinary pathogens, usually originating in the gut, have to ascend the length of the urethra to infect bladder cells. My postdoctoral work identified that urethral cells are not passive onlookers and express antimicrobial peptides, microbial recognition receptors and chemokines [1,2]. As an independent investigator, I want to understand how immune defenses in the urethra are regulated which can potentially allow us to limit infections before they spread to the bladder. My long-term goal is to understand the regulation of immune modulators and defense genes in the lower urinary tract and harness this knowledge to develop novel therapeutic strategies to treat urinary tract infections that do not rely on antibiotics. I will work towards achieving this in my research program by addressing the following immediate questions:

1. How are immune defenses in the lower urinary tract shaped by establishment of the urinary microbiome after birth?

2. What are the molecular mechanisms that determine the antimicrobial functions of urethral epithelial cells?

3. What is the contribution of hormonal regulation to sex-specific differences in urethral defences?

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YI 13

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Keywords: climate change, plant adaptation, photosynthesis, transcriptome, gene editing

Insights on plant responses to global climate change at multiple organizational levels

Global climate change involves multiple environmental factors such as rising atmospheric CO2, extreme temperature events, and drought episodes. These factors increasingly threaten plant growth, productivity, and quality. However, the combinatorial effects of global climate change factors remain largely unexplored from genes to species levels. I will provide mechanistic insights on climate change impact on various species viz. Arabidopsis thaliana, grasslands (legumes and grasses), C3 and C4 (maize and barley) and birch tree. The key findings include 1) high CO2 mitigates the impact of combined high temperature and drought stress on growth and photosynthesis, 2) short- and long-term exposure to climate extremes impact primary metabolism differentially, 3) nutrient quality losses are less prominent in grasses than legumes under climate change conditions, 4) grasses and legumes opt unique proline accumulation strategies to cope climatic stress, and 5) crops belonging to different photosynthetic functional groups (C3 and C4) respond differently to stresses under high CO2 and 6) epigenetics (DNA methylation) plays a crucial role in stress adaptation. Overall, multi-scale analyses provide a clearer picture of global climate change on plants.

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YI 14

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Keywords: multiscale modelling and simulations, DNA nanotechnology, lipid-DN, interactions, nanopores, artificial water channels

DNA origami Voltage Sensor

A change in the electrical potential across a plasma membrane enables signal transmission among neurons. Measuring such electrical potential change with high spatial resolution remains an outstanding technical challenge. In collaboration with the Tinnefeld lab (LMU, Germany), we developed a fluorescence-based DNA origami sensor of transmembrane potential. As a sensing unit, we used a pair of dyes embedded within a DNA origami plate which was attached to a lipid membrane via cholesterol anchors. Experiment had shown that a change of the transmembranevoltageproducesmeasurable change of fluorescence resonance energy transfer (FRET) between the dyes. All-atom MD simulations showed that binding of the DNA origami construct to the membrane increases the distance between the dyes as one of them gets incorporated within the membrane, however, the location of the dye within the membrane is insensitive to the transmembrane voltage. We deciphered the mechanism of transmembrane voltage sensing by constructing a double-membrane system to measure a change in the free energy of a DNA duplex upon transfer of ions from one compartment to the other. Our free energy calculations showed that a small difference in ion concentration across the membrane (causing the transmembrane bias) is sufficient to change the location of the DNA relative to the membrane and hence the distance between the dyes, explaining the modulation of the FRET signal.

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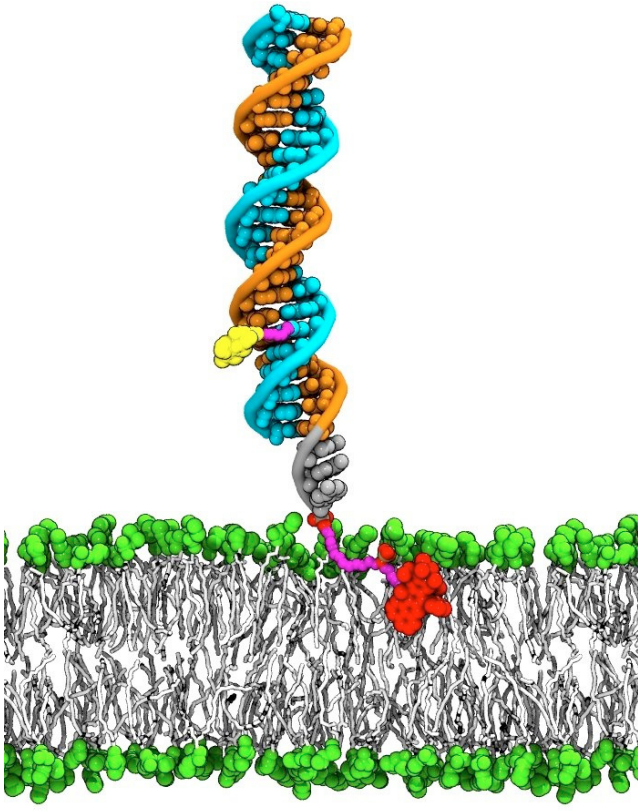

All-atom model of dye-conjugated ds-DNA embedded in DOPC lipid bilayer membrane

YI 15

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Keywords: tuber and storage root development, plant tissue culture, plant developmental biology, role of phytohormones, wheat grain development

Utilizing genome editing tools to delay storage root sprouting in sweet potato - one of the major, yet neglected staple crops in the world

Tuber and storage root crops serve as the most important staple food after cereals. However, potato tubers and storage roots of sweet potato if stored and transported at room temperature, sprouting is observed. Sprouting is a phenomenon wherein dormant tubers/storage roots lose their dormancy due to various environmental, physiological, and molecular changes, leading to bud break and sprout initiation. At the onset of sprouting, tubers turn into a source organ supporting growth of developing sprouts. Starch and protein degradation is initiated and soluble sugars and amino acids are formed. The short shelf-life of sweet potato storage roots after harvest (2-3 weeks) makes them susceptible to sprouting and causes ~20-45% income loss to farmers. Moreover, sprouted sweet potatoes are not suitable for human consumption and are often considered animal feed. Although storage at lower temperatures prevents sprouting, it can lead to cold-induced sweetening. This is a physiological disorder caused by increased levels of reducing sugars (glucose and fructose) that interact with free amino acids in tubers affecting the taste and color of processed products or can lead to acrylamide formation (a potential carcinogen). The molecular mechanism of sprouting is widely studied in potato, but no information is available in sweet potato. To design biotechnological and advanced genome editing approaches for agricultural benefits, it is imperative to understand the molecular mechanism governing sweet potato sprout initiation. In this work, we identified candidate genes with a potential role in sprout initiation and we plan to use CRISPR/Cas9 and cis-genic approaches to delay the sprout initiation process, thereby increasing the shelf-life of edible storage roots of sweet potato for the farmers' benefit.

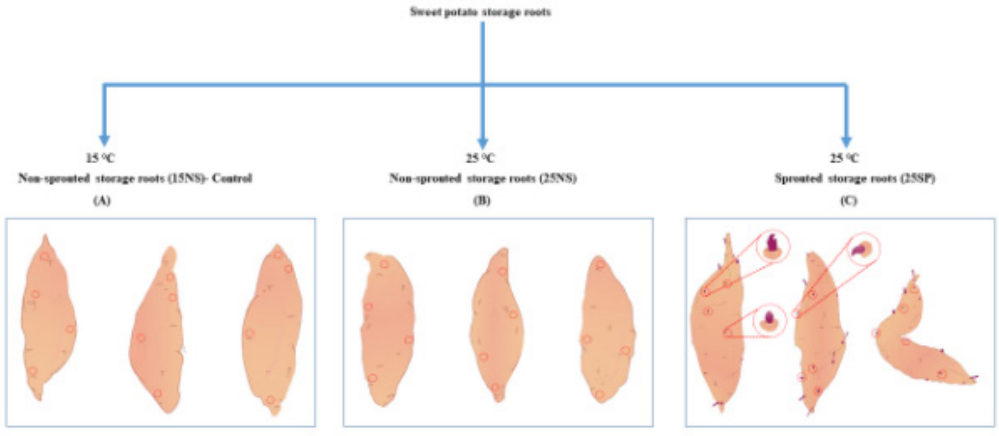

Fig 1. Schematic of experimental design and storage root samples harvested for RNA-sequencing analysis. After the harvest, sweet potato storage roots were hardened for 1 week at room temperature and incubated in a growth chamber under dark conditions at 15 or 25 °C. After 2 weeks of incubations, storage roots that were incubated at 15 °C **(A)** showed no sign of the sprout initiation (referred as 15NS), whereas those incubated at 25 °C showed two types of phenotypes: **(B)** non-sprouted (referred as 25NS), and **(C)** sprout initiated (referred as 25SP). At the onset of a visible sprout initiation, storage root samples from three different treatments (15NS, 25S and 25SP) were harvested in liquid nitrogen. The scooped samples containing the sprout initials with the base of sprouts from the 25SP treatment or the random regions of the non-sprouted storage roots from the 15NS or 25NS treatment (highlighted by dotted red circles) depict the sample taken for RNA-seq analysis.

YI 16

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Keywords: polymers, biomaterials, tissue engineering, drug delivery, exosomes

Mucins: Potential Proteins for Bone Tissue Engineering

Bone disorders caused by illness or trauma significantly compromises patient quality of life. Although bone is one of the organs that has tremendous self regeneration potential, there are still complications wherein regeneration is delayed or hampered and needs to be stimulated. The existing practices are autologous, allogenic or xenogenic bone grafts which encounter limitations. This is where tissue engineering can play a crucial role in introducing approaches and solutions. One of the approaches of tissue engineering relies on the use of biomaterials to mimick the bone microenvironment and to stimulate bone formation. One of the approaches of tissue engineering relies on the use of biomaterials to mimick the bone microenvironment and to stimulate bone formation. Furtherdown, tissue engineering strategies work on the traid of scaffolds, cells and signaling cues. A scaffold serves as a temporary extracellular matrix (ECM) to promote 3D bone tissue formation or regeneration. A temporary scaffold must provide a suitable microenvironment for cells in order to attach, proliferate and differentiate to form new tissue. It is imperative that the scaffold should mimick the ECM as closely as possible. In this context, we are exploring the role of Mucins as a potential material for bone tissue engineering. Our results so far have proven Mucins to have osteogenic potential thereby promoting bone healing.

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YI 17

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Keywords: nanomedicine, cancer, gene delivery, drug delivery, 3D tumor model

Nanomedicine for treatment of Ovarian Cancer

Ovarian cancer is a lethal form of gynecological malignancy. 70% cases are diagnosed in stage 3-4 with a 5-year survival of less than 30%. In my previous work I have developed in vitro and in vivo model of ovarian cancer to represent clinically relevant advanced stage ovarian cancer. My future work will include developing nanomedicine- drug/gene-based for the treatment of ovarian cancer.

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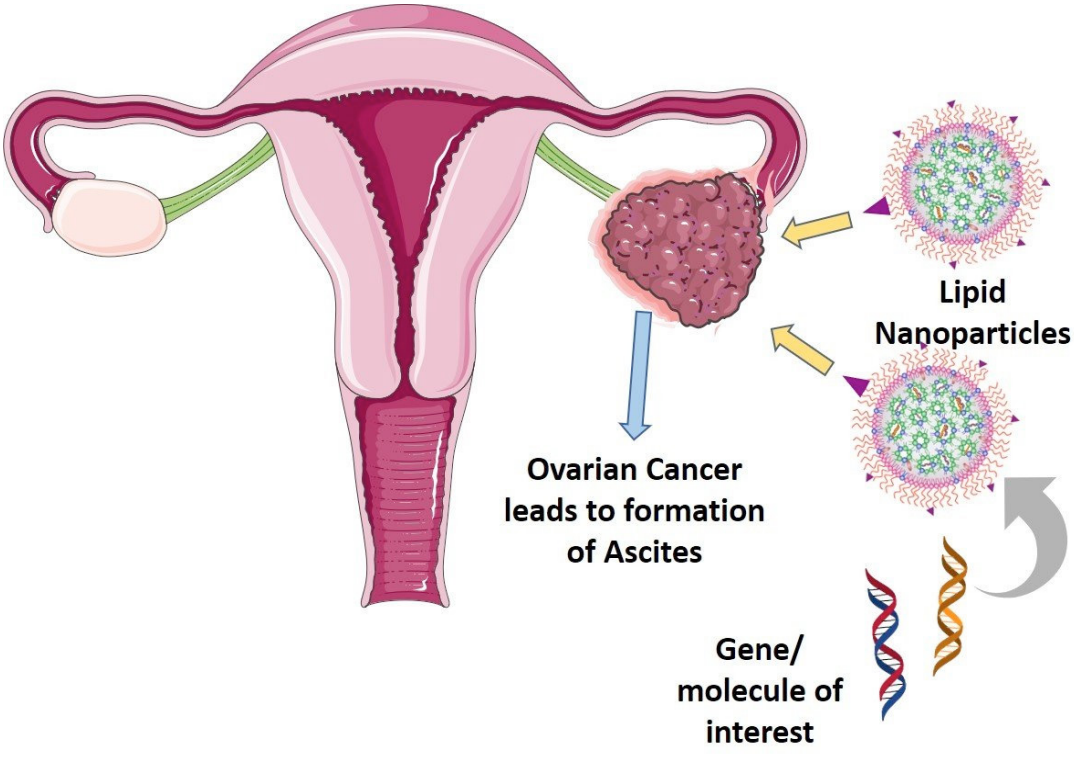

Nanomedicine for treatment of Ovarian Cancer

YI 18

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Keywords: gut microbiome homeostasis, quorum sensing & biofilm formation, immunomodulation, inflammation & dysbiosis, prophylaxis

Immunomodulation of gut by Lactobacillus sp

Helicobacter pylori induced ulcer is a major illness which can be treated with Lactobacillus probiotics. As commensal/ probiotic has the ability to immunomodulate gut epithelial and immune cells, it is possible to treat or reduce disease symptoms and can also provide immunity to future infections. This would greatly reduce usage of antibiotics thus could curtail development of antibiotic resistant strains. Lactobacillus species use quorum sensing and biofilm formation to prevent establishment of pathogen in the gut. Intercellular signal transmission of gut commensal coordinately function to compete with the pathogen for space and nutrients, thereby provides gut homeostasis.

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YI 19

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Keywords: cancer stem cells, neoantigens, B-cell lymphoma, tumor immune microenvironment, epigenetic modulation

Targetable novel oncogenes for chemo-sensitization in B-cell lymphoma

Chemo-immunotherapy resistance in tumors can be developed by multiple mechanisms including the selection of pre-existing drug-resistant tumor cells, un-touched tumor initiating cells, genetic aberrations, and oncogenic signaling associated with altered cancer cell surface receptors what we referred as "NEO-ANTIGENS". The last six years of my research in B-cell lymphoma have contributed towards mining several of such molecular targets associated with chemo-immunotherapy resistance development. Our current lab focus is to understand the majority of these parameters primarily those associated with tumor initiating cells, microenvironment and NEO-ANTIGENS mediated chemo-immunotherapy resistance development. We believe, chemo-resistant tumors have a unique expression of NEO-ANTIGENS compared to the chemo-sensitive tumors and B-cells from healthy donors. Using high-throughput next-generation multi-omics approach, CRISPR screening, therapeutic drugs screening, and syngeneic animal model of lymphoma to we are deciphering the molecular features of B-cell lymphoma subsets. While in search of NEO-ANTIGENS, we have research focus dissect the functions of RNA-binding & cancer cell-surface specific protein nucleolin in architecting tumor microenvironment through epigenetically regulation of immune-checkpoint proteins (PDL1, CD47, CTLA4). Nucleolin is a nucleolus-specific protein in normal cells; its unique expression on cancer cell surface makes it important as it can be selectively targetable.

Beside NEO-ANTIGENS, our another focus is towards screening tumor initiating cells those represents less than 1% of the total tumor population, have stem cell-like characteristics, resistant to chemotherapeutic agents and few as 100 of these can develop heterogeneous tumor in immunocompromised mice. Our lab focus is to characterize lymphoma-specific tumor initiating cells particularly non-coding RNA and identify key targets to kill these stem cells population. Knowledge from these studies will direct us to develop new therapeutic tools such as monoclonal antibodies, and DNA-based aptamers against selected oncogenic targets.

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YI 20

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Keywords: molecular enzymology, protein biochemistry, mammalian H2S metabolism & signalling, single particle cryoelectron microscopy

Structural Enzymology of Mammalian Hydrogen Sulfide Metabolism & Signaling

Cystathionine β-synthase (CBS) and cystathionine γ-lyase(CSE) and mercaptopyruvate sulfurtransferase (MST) are the three enzymes that produces Hydrogen Sulfide (H2S) in primary human organs (like; the liver, kidney and brain). CBS and CSE generate H2S by various reactions using cysteine and/or homocysteine as substrate. MST generates H2S from 3-merceptopyruvate in the presence of a reductant. H2S plays an essential role in cell signaling and shown to have multiple physiological functions and is suggested to be involved in oxidative stress defense and GSH production by increasing cysteine concentration in the cell. On the other hand, at elevated concentrations since H2S is toxic, cells are equipped to clear H2S. The mitochondrial sulfide oxidation pathway primarily clears H2S and converts it to thiosulfate and sulfate; both are the primary oxidation products of H2S. The H2S oxidation pathway begins with sulfide quinone oxidoreductase (SQR) and includes a sulfur dioxygenase (known as ETHE1), rhodanese, and sulfite oxidase. Human SQR is a flavoprotein that is tethered to the inner mitochondrial membrane. SQR catalyzes the first step in mitochondrial H2S oxidation and forms persulfide upon reacting with H2S. My research has been focused on understanding the mechanism of the enzymatic, molecular, structural and cellular basis of the regulation of H2S metabolism under normal and pathophysiological conditions.

YI 21

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Keywords: computational chemistry, synthesis, analytical development and validation, AD, HIV, cancer

Design and development of tri-substituted pyrimidine derivative as BACE-1 inhibitors for

Alzheimer's disease (AD) is the most common and severe neurodegenerative disorder. As per "Amyloid Cascade hypothesis", it has been noticed that BACE-1 (β-secretase), an aspartyl protease enzyme is involved in cleavage of amyloid precursor protein (APP), and considered to be responsible for development of AD. Thus, its inhibition is thought to be viable therapeutic approach to treat AD. Here, we report design and synthesis of low molecular weight tri-substituted pyrimidine derivatives as BACE-1 inhibitors. Based on our previous designed series, we tried modifications and exploited rigidity of chemical structure to allow proper occupancy of the two major active sites. This led us design pyrimidines having aromatic rings at position 4 and 6 and amino at position 2. The structure docked well with protein displaying all the desired interactions. A series of compounds with varying substituents was synthesized and tested for BACE-1 inhibition using FRET assay. One of the best active compounds displayed 78% inhibition at 10μM concentration with IC50 of 6.9 μM.

References:

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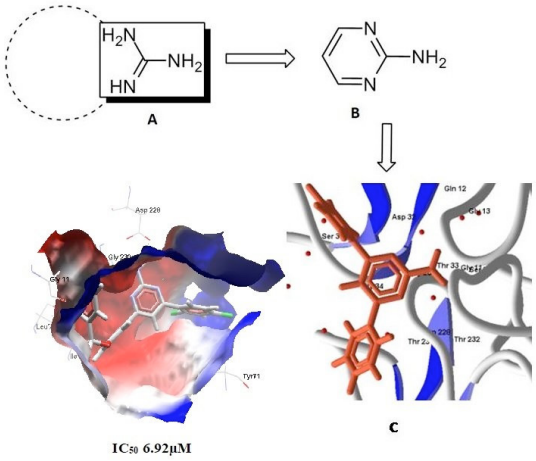

YI 22

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Keywords: biocatalysis, enzymology, protein biochemistry, enzyme mechanistic studies, green process development

Identification and characterization of a novel P450 enzyme RufO from Rufomycin biosynthetic pathway: A green way to synthesize regiospecific nitroaromatic compounds

Aromatic Nitration with high regio and chemoselectivity is the most soughtout reaction in chemistry, pharmaceuticals and other fine chemical industry. There are plethora of drug molecules, explosives, dyes and other fine chemicals such as pesticides, insecticides and many others who have aromatic ring structure containing Nitro group as functional group. However, these reactions are very tedious to carry out at industrial scale due to involvement of very harsh acids like Nitric and Sulphuric acid and also many unstable compounds. Thus, a green biocatatylic process which can give access to this functionality at high regio and chemoselectivity and good yield will be a boon for these industries.

Recently, a new enzyme called RufO has been discovered from the rufomycin biosynthetic pathway which has been shown to catalyze regio and chemoselective nitration on tyrosine (a phenol containing amino acid) to generate 3-Nitrotyrosine. However, this enzyme has not been studied in detail beyond the one report of its discovery because of poor activity of the enzyme. Given the importance of phenol ring as a template for direct nitrations, my research group picked up this interesting enzyme for further exploration. Interestingly, in our lab, we managed to study and characterize this enzyme by optimizing the assays for its production, increasing its native activity by optimizing multiple parameters with various redox factors, coenzymes, time, pH, temperature optimization and several fine tuning techniques to up to 50-60% conversion with tyrosine and also developed a colorimetric method for measuring its activity (earlier, the activity has been measured using LC-MS). We are also studying its primary and secondary coordination sphere by computational guided site directed mutagenesis. Thus, here, I will discuss about this marvelous enzyme and its capabilities and potential for industrial applications

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YI 22

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YI 23

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Keywords: quantum mechanics, spectroscopy, molecular dynamics, machine learning, optogenetic

Molecular informatics-based design of optogenetic tool using LOV-protein

Precise control of cellular machinery through light-activation can control biological functioning and gain spatiotemporal resolution. Light-oxygen-voltage (LOV) domain proteins are appropriate candidates that respond to blue light for activation and achieve domain-wise conformational changes to cascade biological functioning. LOV domain is a flavin-based photoreceptor (1), activated by blue light and forms a photocycle intermediate. Light energy triggers the electron transfer, leading to a covalent adduct between flavin and a conserved cysteine residue. More importantly, photochemistry also involves the formation of a short-lived flavin radical species, which is challenging to capture through conventional spectroscopic measurements. It marks the LOV domain's reversible light-activated state, which mediates allosteric conformational changes to propagate biological functioning.

Interestingly, the core network of amino acids around the chromophore tunes the half-life of light and dark forms of LOV-based proteins. Our research work aims to understand the role of amino acids in tuning the spectroscopic properties to gain control of light activation and its kinetics. The factors that are liable to manipulate dark/light-adapted state include changes in polarizabilities, solvent interaction, conformational restraint, to name a few. Using the quantum (bio)chemical calculations (2) and experimentally measured electronic spectra, we aim to understand the trend of transition energies and the kinetics involved. Our previous studies in the flavin-based (3,4) and retinal-based (5) optogenetic candidates have benchmarked accurate quantum mechanics and the hybrid variant quantum mechanics/molecular mechanics capable of capturing trends observed in experimental measurements. The chemical information is relevant to generating protein mutants with desirable properties. The long-term objective of our research is to design photoreceptor mutants and translate this technology to develop biosensors and optogenetic tools.

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YI 24

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Keywords: immunology, infectious diseases, drug discovery, nanotechnology, antimicrobial resistance

The Translational Prospective of secretory proteins of Mycobacterium tuberculosis encapsulated in Bio-polymeric nanoparticles: An Interplay of Immune Response and Oxidative stress

Mycobacterium tuberculosis (M.tb.) resides within macrophages of the host and completely evades the immune surveillance by secreting proteins that are immunogenic and provoke protective immunity. The study aims at developing nanoparticles carrying two secretory proteins of M. tb - CFP-10 and CFP-21 and evaluating their potential to invoke an immune response coupled with the oxidative stress when encapsulated in chitosan nanoparticles. Chitosan nanoparticles were prepared in the size range of ~250 to ~300nm. The cytokine levels of IFN-γ, TNF-α, IL-12, IL-17, IL-2, IL-10 and IL-4 was observed to be significantly increased for CHNP CFP-10 and CHNP CFP-21. CFP-10 and CFP-21 per se primed cells demonstrated a Th1 biased T cell response in an ex vivo assay. To further analyze the potential of the nanoparticles to cause oxidative stress, various biochemical assays were determined in the mice treated with CFP-10, CFP21, void CHNP, CHNP CFP-10, and CHNP CFP-21 in the liver, lung, and spleen post 7 days and 21 days of injection. The GST levels were lowered indicating oxidative stress in all the organs on Day 7. But post Day 21 of injections, enhanced GST levels indicated reduced or no oxidative stress in the tissues. The enhanced levels of IFN-γ and IL-12 clearly indicate a Th1 response coupled with low levels of GSH. Therefore, the interplay of the immune response, ROS, and RNS created by secretory proteins of M.tb. encapsulated in nanoparticles indicated interesting results which warrant detailed evaluation on the signaling pathways to ascertain the extent of interdependence.

References:

1. DOI: 10.1016/j.lfs.2020.117961

YI 24

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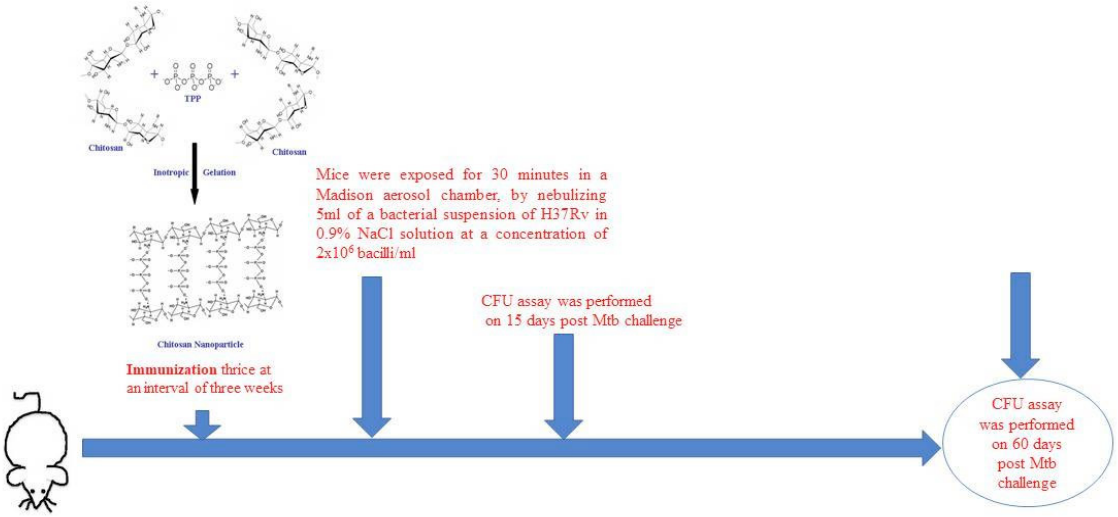
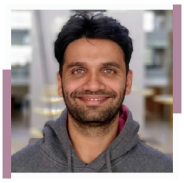


Fig. The chitosan nanoparticles were prepared by Inotropic gelation method. The desired ratio of Chitosan:TPP was 1:2. CFPs were encapsulated into the nanoparticles. Female Balb/c mice were divided into six groups and then immunized with Group I- Chitosan nanoparticles, Group II- CFP-10 *per se* , Group III- CFP-21 *per se*, Group IV-CFP- 10 encapsulated nanoparticles, Group V- CFP-21 encapsulated chitosan nanoparticles and Group VI- PBS *via* intraperitoneal routes thrice at an interval of three weeks. Mice were exposed for 30 minutes in a Madison aerosol chamber, by nebulizing 5ml of a bacterial suspension of H37Rv in 0.9% NaCl solution at a concentration of $2x10^6$ bacilli/ml. Mice were sacrificed 10 and 60 days post infection and Colony Forming Unit Assay was performed.



YI 25

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Keywords: stem cell-niche interactions, cellular signalling, systemic signalling, drosophila developmental genetics, hematopoieisis and immunity

Understanding molecular regulators of stem cell homeostasis and modelling human diseases using Drosophila as a model organism.

Our laboratory is trying to understand conserved molecular regulators of stem cell homeostasis using the intestinal stem cell and hematopoietic system in Drosophila. We are currently trying to elucidate the effects of genetic modulation of ageing in the stem cells to understand cellular signalling components that govern stem cell and tissue homeostasis. Our laboratory is also currently employing the Drosophila system to model human diseases like cancer, cancer induced cachexia. We intend to utilize flies to understand the molecular circuitry underlying cancer onset and progression. This will also help in using this model for screening and testing drug modalities.

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YI 26

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Keywords: vascular biology, tumor metabolism, cancer heterogeneity, anti-angiogenesis, cell plasticity

How blood vessels shape tumor stemness in glioblastoma?

Cell plasticity is a major challenge in treating cancers including glioblastoma. The existence of a perivascular niche for tumor-initiating cells in glioblastoma was reported more than a couple of decades ago. However, what are the vascular cue that are important in maintaining this stemness are underexplored. Vasculature can impact cancer stemness through both perfusion-dependent and endothelial cell-mediated cues. In this study, we isolated perivascular cancer stem cells from intracranially implanted human glioblastoma cell lines in immunocompromised mice and did transcriptomic profiling to identify novel markers. In order to dissect the importance of endothelial cell-mediated signaling important for cancer stemness, we harnessed in vitro co-culture of endothelial cells with human glioblastoma cells. The results will be presented and discussed in the meeting.

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YI 27

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Keywords: protein, bioinformatics, computer-aided drug discovery, molecular dynamics, miscibility

Discovery of Tryptophan Hydroxylase 1 Inhibitors for Obesity

Tryptophan hydroxylase 1 (TPH1) has been recently suggested as a promising therapeutic target for treating obesity and fatty liver disease. A new series of 1,2,4-oxadiazolylphenyl alanine derivatives were identified as TPH1 inhibitors. Among them, compound 23a was the most active in vitro, with an IC50 (half-maximal inhibitory concentration) value of 42 nM, showed good liver microsomal stability, and showed no significant inhibition of CYP and hERG. Compound 23a inhibited TPH1 in the peripheral tissue with limited BBB penetration. In high-fat diet-fed mice, 23a reduced body weight gain, body fat, and hepatic lipid accumulation. Also, 23a improved glucose intolerance and energy expenditure. Taken together, compound 23a shows promise as a therapeutic agent for the treatment of obesity and fatty liver diseases.

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YI 28

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Keywords: virulence regulation, anti-virulence targeting, microbial genomics, metagenomics, human gut microbiome

Emergence of colistin resistance in a strain of Klebsiella pneumoniae causing ICU-associated infections: Insights from genomic surveillance

Classical strains of Klebsiella pneumoniae (Kpn) commonly cause hospital-associated infections in immunocompromised individuals. These infections are usually difficult to treat as these strains carry multiple drug resistance determinants. We obtained two highly drug-resistant clinical isolates of Kpn, causing urinary tract infection (U23) and blood stream infection (BC16) from the ICU of a tertiary hospital in Jodhpur, India. While U23 was susceptible to colistin, BC16 tested as intermediate in an antimicrobial susceptibility assay. Phenotyping the strains and sequencing the genomes of U23 and BC16 on an Oxford Nanopore device provided insights into the resistome and virulome of these strains. Analysis of the profiles revealed near identical phenotypic and genomic characteristics suggesting that U23 and BC16 were the same strain of Kpn causing recurrent infections in the ICU. Comparative genomic analysis revealed the genetic basis of the emergence of colistin resistance in BC16 compared to U23, the ancestral strain. Our work shows that strains U23 and BC16 are single locus variants of the sequence type 16 (ST16), which is an emerging high risk sequence type that does not belong to major globally disseminated clonal complexes. The emergence of colistin resistance in these variants raises concerns on dissemination and transmission of resistance determinants. This study also highlights the importance and requirement of genomic surveillance approaches in ICU settings.

References:

Unpublished

YI 29

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Keywords: tumor-microenvironment, cancer-associated fibroblast, tumor-stroma

Role of Cancer-Associated Fibroblasts in Tumour-microenvironment

Cancer was considered a genetic disease for a long time, and researchers majorly focused on how different gene mutations contribute to cancer progression and disease. Recent studies have provided compelling evidence that the bidirectional interaction between the cancer cells and the surrounding microenvironment eventually determines cancer progression and metastasis. Our mechanistic understanding of how the tumour microenvironment (TME) regulates tumour growth is still incomplete. The TME comprises various stromal cells, such as fibroblasts, endothelial cells, pericytes, macrophages, lymphocytes, other immune cells, and the extracellular matrix (ECM) and soluble factors. Cancer-associated fibroblasts (CAFs) are one of the abundant stromal cells surrounding the tumour cells. They are a significant component of the TME in many cancers, including lung, breast and pancreatic cancer. In TME, CAFs play a substantial role in supporting tumour cell growth, extracellular matrix remodelling, and facilitating invasion and metastasis. Our lab focused on understanding the molecular mechanisms of CAF and tumour cell reciprocal cross-talks and their outcome on tumorigenesis. It has been reported that CAF secreted CXCL12 and TGF-beta binds to cognate receptors present and directly stimulate tumour cell proliferation and metastasis. We are in the process of identifying CAF secreted factors and their impact on tumour cell proliferation and migration properties. We use co-culture of patient-derived fibroblast and tumour cell, 3D organoid models and Xenograft mice models.

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YI 30

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Keywords: nanobiotechnology; biomaterials; drug / nutraceuticals / gene delivery; toxicology; and in-vivo cancer models

Curcumin loaded polycaprolactone-/polyvinyl alcohol-silk fibroin based electrospun nanofibrous mat for rapid healing of diabetic wound: An in-vitro and in-vivo studies

Electrospinning is emerging as a versatile technique nanofibers fabrication because due to their unique properties such as large surface area to volume ratio, porosity and maintaining moist wound environment, the nanofibers are able to deliver sustained drug release and oxygen to the wound for rapid healing of diabetic wound. The present work was aimed to prepare and evaluate silk fibroin-curcumin based nanofiber in combination with polycaprolactone (PCL) and polyvinyl alcohol (PVA) which helped to strengthen the wound healing properties of nanofiber. Silk fibroin is a naturally occurring polymer was selected one polymer for making nanofibrous mat due to its unique properties such as biodegradability, permeability, oxygen supply and maintain moisture content in the wound. SEM results showed diameters of fibers varied in the range between 200 and 350 nm and their tensile strength ranged from 12.41 to 16.80 MP. The nanofibers were causing sustained release of curcumin for many hours. The in-vivo wound healing studies in streptozotocin-induced diabetic mice showed rapid wound healing efficacy as compared to conventional formulations. Furthermore, the histopathological studies evidenced its ability to restore the normal skin structure and histological conditions of tissues. The silk fibroin-based nanofiber wound dressing, therefore appears to be an ideal preparation, in combination with curcumin, because it blends the anti-oxidant, anti-inflammatory properties of curcumin. Therefore, it was concluded that the silk fibroin-based nanofiber loaded with curcumin has great healing potential in diabetic wound.

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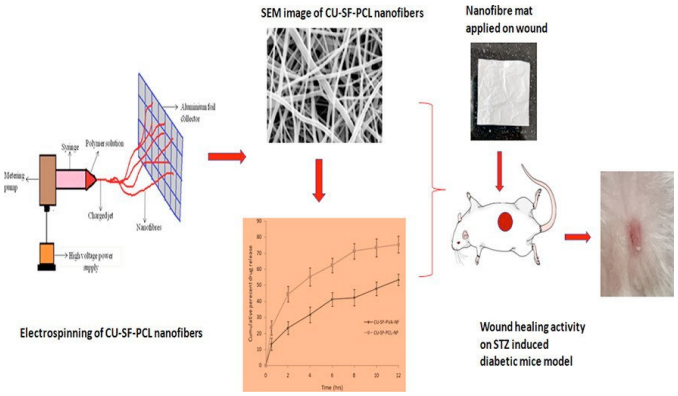

Curcumin nanofibrous formulation enhances the diabetic wound healing activity

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YI 31

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Keywords: experimental evolution, molecular evolution, novel traits, antibiotic resistance

Multiple Novel Traits without Immediate Benefits Originate in Bacteria Evolving on Single Antibiotics

How new traits originate in evolution is a fundamental question of evolutionary biology. When such traits arise, they can either be immediately beneficial in their environment of origin, or they may become beneficial only in a future environment. Compared to immediately beneficial novel traits, novel traits without immediate benefits remain poorly studied. Here we use experimental evolution to study novel traits that are not immediately beneficial but that allow bacteria to survive in new environments. Specifically, we evolved multiple E. coli populations in five antibiotics with different mechanisms of action, and then determined their ability to grow in more than 200 environments that are different from the environment in which they evolved. Our populations evolved viability in multiple environments that contain not just clinically relevant antibiotics, but a broad range of antimicrobial molecules, such as surfactants, organic and inorganic salts, nucleotide analogues and pyridine derivatives. Genome sequencing of multiple evolved clones shows that pleiotropic mutations are important for the origin of these novel traits. Our experiments, which lasted fewer than 250 generations, demonstrate that evolution can readily create an enormous reservoir of latent traits in microbial populations. These traits can facilitate adaptive evolution in a changing world.

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YI 32

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Keywords: nanopharmacology, nanomedicine, nano-drug delivery, nanotoxicology, nanotherapeutics

Hematinic effects and toxicological profile of Zinc Oxide Nanoparticles after oral administration in Wistar rats.

The applications of the nano bioscience for human use is likely to become yet another source for human exposure to engineered nanoparticles. But all the biological effects of nanoparticles may not be harmful. The present study is aimed at evaluating the pharmacological and toxicological and effects of zinc oxide nanoparticles (less than 50 nm) administered orally for 28 days. Wistar rats of either sex were treated with nanoparticle saline suspension at a dose of 100 mg/ 10 ml orally for 28 days. Random allocation of animals; 8 rats (4 Males and 4 Females) in the Test group and 4 rats (2 Males and 2 Females) in the Control group was done. There were no statistically significant changes in haematological and biochemical parameters except the rise in haemoglobin, red cell count and haematocrit. Histopathology of major organs was not associated with significant changes. In the present preclinical study, possible pharmacological effects of zinc oxide nanoparticles of fixed size (< 50 nm size) have been studied at a fixed dose (100 mg/kg). It was concluded that ZnONP if administered orally at this dose has no clinically observable adverse effects in animals. The hematinic effects, that are shown by zinc oxide nanoparticles, such as improved haemoglobin, red cell count and haematocrit require further research to establish the mechanism of action.

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YI 33

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Keywords: bioinformatics, human genetics, genomics, transcriptomics, gene regulation

A multi-layer functional genomic analysis to understand noncoding genetic variation in lipids

A major challenge of genome-wide association studies (GWAS) is to translate phenotypic associations into biological insights. Here, we integrate a large GWAS on blood lipids involving 1.6 million individuals from five ancestries with a wide array of functional genomic datasets to discover regulatory mechanisms underlying lipid associations. We first prioritize lipid-associated genes with expression quantitative trait locus (eQTL) colocalizations, and then add chromatin interaction data to narrow the search for functional genes. Polygenic enrichment analysis across 697 annotations from a host of tissues and cell types confirms the central role of the liver in lipid levels, and highlights the selective enrichment of adipose-specific chromatin marks in high-density lipoprotein cholesterol and triglycerides. Overlapping transcription factor (TF) binding sites with lipid-associated loci identifies TFs relevant in lipid biology. In addition, we present an integrative framework to prioritize causal variants at GWAS loci, producing a comprehensive list of candidate causal genes and variants with multiple layers of functional evidence. Two prioritized genes, CREBRF and RRBP1, show convergent evidence across functional datasets supporting their roles in lipid biology.

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YI 34

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Keywords: snails, conservation, shell composition, phylogeny, snail as model

Study on extant species of fresh water amphibious genera Pila using morphometric features and gene markers to reconstruct their phylogenetic affinities

Gastropods under the phylum Mollusca encompass slugs, limpet, and snails. The species collected for the entire study were from six families The morphometric parameters viz., body weight (g), height of the shell (H), breadth of the shell (B), length of the operculum (LO), breadth of the operculum (BO), were measured from different snails belonging to various taxonomic families collected from a varied areas so as to evaluate the species as well as geographic location specific variation among the chosen gastropods. Correlation coefficient, regression, ANOVA analysis was performed for different Pila species as well as between the intra and inter species. The morphometric analysis among molluscs, (2nd largest assemblage) could be used as the efficient models in prediction of shell size and shape heterogeneity. Gastropods were studied to determine strong intra and inter population affinities among the genera. The study of gastropods based on morphometric analysis seems to be incomplete thus further molecular based approach supports the systematic taxonomical classification. Samples were further studied using nuclear and molecular gene markers 18S, Cytochrome b and COI. Multigene analyses study with a variety of gastropods was used to generate a reliable robust result in metazoans. The methodology of my research included review of literature, collection of sample from different location, identification of the sample from Zoological Survey of India, DNA extraction, PCR, bidirectional sequencing, alignment, annotation, sequence submission to NCBI, and the reconstruction of the phylogenetic tree. As, the interpretation of the geographic diversification and evolutionary history can only be traced by phylogenetic studies. Hence, the systematic studies of gastropods were found desirable within India. Thus, exploring these gastropods representative conspecifics from different regions and their relationships across different families will invariably provide a deeper input into the taxonomic studies of geological interests and their habitat ecology.

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YI 34

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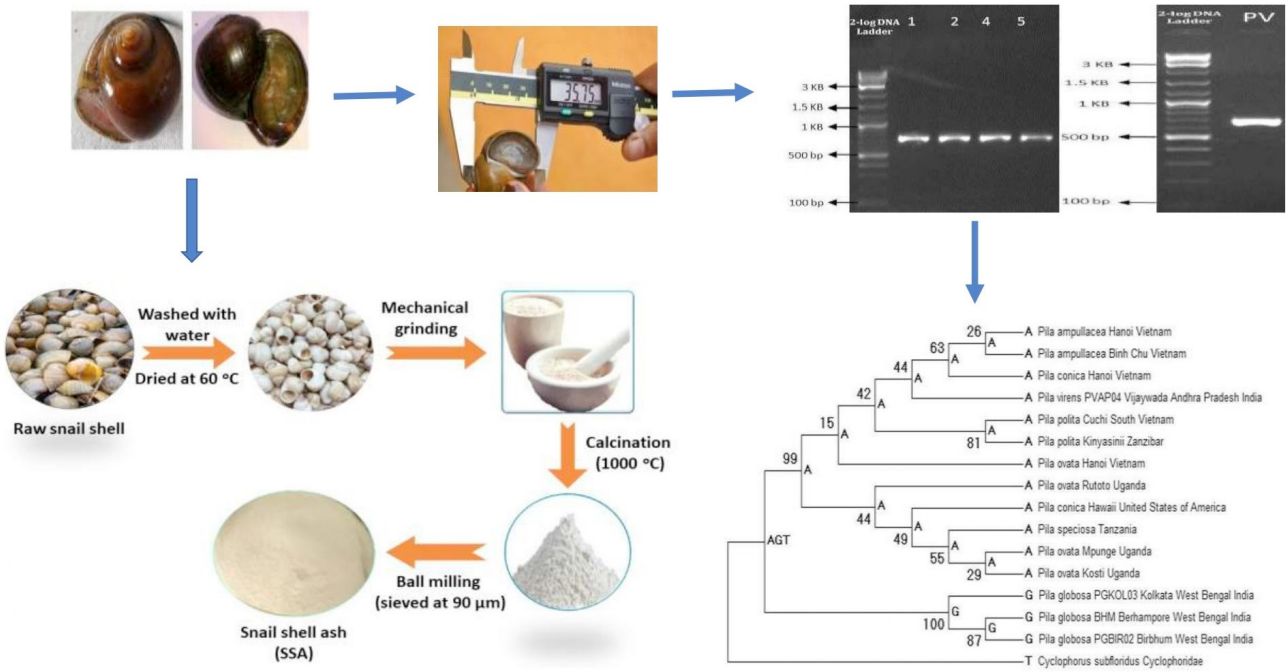

Snail as a model to study for morphology, phylogeny and application of shell powder
Credits: Dr. Silpi Sarkar

YI 35

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Keywords: clinical chemistry, diagnostics, immunology, host-virus interaction, clinical lipidology

Method-specific variation in the pooled average selenium levels in healthy adult Indian population

Selenium and selenoproteins are essential for the normal functioning of cellular, metabolic, and immune systems. The soil selenium levels differ in different countries and determine the vulnerability of the population for selenium deficiency. This meta-analysis aims to determine determine the average levels of the Selenium in the Indian population based on the geographic region and assessed whether the different methods for estimation of Selenium have any effect on the pooled values from different regions.

We searched relevant articles from PubMed databases. The literature search was done using the following terms: "Blood Selenium Levels" AND "INDIA". Studies that examined Blood Selenium Levels in various groups in India, which included healthy human adults and provided the sample size and Mean Blood Selenium levels with Standard deviation for the healthy control groups, were included in the meta-analysis.

Fourteen eligible articles were included in this meta-analysis. The pooled average level of Selenium in control subjects from the Indian population was found to be 101.53 µg/L (70.23-132.83 µg/L). A subgroup analysis demonstrated low selenium levels in Eastern parts of India. Further, a method-wise comparison of a pooled analysis of Selenium Levels yielded higher levels in Atomic absorption spectroscopy (AAS). However, the difference in estimation methods resulted in varying selenium levels, which prevented effective comparison between India's various geographical regions. This points towards as imminent need for harmonization between the different methods.

The region-specific variation observed in pooled average selenium levels in the Indian population, especially in the Eastern parts of India, signifies an inherent vulnerability to selenium deficiency associated diseases. However, the method-specific variation in the pooled average selenium levels highlights the prerequisite need for harmonization between different methods while estimating selenium levels on different platforms.

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YI 36

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Keywords: hearing loss, tinnitus, electrophysiology, translational studies, neuroscience

How higher structures regulate lower structures in the brain hierarchy and help us hear?

Hearing deficits lead to the use of cognitive resources both in the young and the elderly. Previous research implicated that this increases attention towards a given sound and helps better detect sound stimuli. Corticothalamic projections are shown to outnumber the thalamic projections. These projections are implicated in bringing the cognitive inputs, including attentional and mnemonic resources, to the thalamus to better sound stimuli processing. In our study, we hypothesized that blocking the corticothalamic resources to the auditory thalamus will disable this function. To model challenging stimuli, we decreased the temporal clarity of the sound stimuli. In this study, young rats were injected with an inhibitory opsin Archaerhodopsin (ArchT) in layer 5/6 of the auditory cortex. Optetrodes that carry both the electrodes and an optical fiber for optical stimulation were implanted post expression of these viral vectors. We examined the thalamic coding with and without optogenetic blockade of the corticothalamic projections. There was no adaptation to repeating stimuli in control trials, as we found in our previous study suggesting the usage of cortical resources with temporally less clear stimuli. However, we found that optical inhibition of the corticothalamic projections to the thalamus led to an adaptation. These data suggest an active role of cortical circuits in regulating thalamic activity. These data also support the active use of predictive coding mechanisms in the auditory modality.

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YI 37

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Keywords: rice, priming, iron-pulsing, nitrogen metabolism, photosynthesis

Iron pulsing: A novel rice seed invigoration technique to enhance yield by enhancing nitrogen and carbon assimilation

Rice is one of the major staple food for majority of the world's population. To meet up with this increasing food demand, augmenting rice yield especially through sustainable means appears to be the need of the moment. Iron is one of the most essential micronutrient. Iron (Fe) deficiency is a common nutritional problem faced by many crops, and it is the availability not the abundance that needs to be addressed. Moreover, Fe is susceptible to a series of reactions that alters its mobility, solubility thus sequential availability of it. We have implemented a novel seed invigoration technique termed as iron pulsing, that obliterates the difficulties associated with the present techniques of micronutrient application, yet delivers optimum results in terms of improving growth and yield attributes of treated rice plants. Rice seeds were treated with different concentrations (2.5, 5 & 10 mM) of iron salts (FeCl3 and FeSO4) for 72h and grown till maturity[1]. This treatment improved germination rates, relative water uptake and length of radical and plumule with increased iron content. Increased nitrogen assimilation and photosynthetic efficiency of the 14 dayy old seedlings was evident from higher protein and sugar contents[1]. The treated plants also accumulated higher amount of iron in its vegetative parts and also the grains. This treatment did not cause any toxicity, rather improved the functioning of the antioxidant enzymes as iron serves as a cofactor for them as well. All the data were statistically significant and a PCA analysis revealed that the best dose for treatment was 5 mM of both FeCl3 and FeSO4. Enhanced plant growth and vigour ultimately enhanced the agro-morphological traits and yield of the treated plants[2] making "Iron pulsing" as a promising tool in modern agriculture.

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YI 38

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Keywords: cilia and flagella, microtubules, ciliary signalling, homeostasis, tubulin posttranslational modifications

Understanding how tubulin posttranslational modifications regulate primary cilia, thus mammalian organ functions and homeostasis

Axonemes, the core microtubule-based structures of cilia and flagella, are a hub of various tubulin posttranslational modifications (PTMs) – a key component of the 'tubulin code' that emerges as a regulator of microtubule properties and functions. Cilia are enriched in two key tubulin PTMs, glutamylation and glycylation. My work has established that glycylation is also present on primary cilia and is stabilizing them like motile cilia. Using a mouse model knocked out for two glycylases, I established that male mice lacking glycylation are sub-fertile with sperm cells defective in flagellar beat and overall motility. Most sperm swim in a circular pattern leading to a loss in progressive swimming, thus providing the first molecular evidence for the role of glycylation in mammalian cilia and flagella.

Understanding the role of tubulin PTMs in cilia has predominantly come from studies on motile cilia with little or no understanding of regulating primary cilia functions. Primary cilia are a hub of signalling pathways, which are regulated by trafficking the signalling molecules through cilia via intraflagellar transport (IFT). Disrupting primary cilia and/or its function leads to several clinical disorders, collectively termed ciliopathies. Recent studies show that primary cilia are also key for regulating tissue homeostasis, regeneration and repair, which requires an intricate network of signalling pathways within primary cilia. However, the underlying molecular mechanisms and the involvement of microtubules and their PTMs are barely understood.

My lab will study the crosstalk between primary cilia on different cells that regulate tissue homeostasis, repair post injury/infections. A major focus will be to understand how tubulin PTMs modulate ciliary trafficking and primary cilia function in regulating organ functions. We will also study the underlying molecular mechanisms of clinical ciliopathies due to defects in tubulin PTMs, thus establishing tubulin PTMs as a key regulator of organ function and tissue homeostasis.

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YI 39

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Keywords: microbiology, metabolic engineering, synthetic biology, antimicrobial resistance, biofuel

Finding a needle in a haystack: A search for the right microlalgal model strain to produce biofuel

Microalgae-based biofuel production as an alternative to conventional fossil fuels has received considerable attention, in the wake of the uprising global energy crisis. Superior physiological properties such as high lipid content, tolerance to extreme environmental conditions and rapid biomass accumulation are some of the advantageous features that make microalgal strains potential candidates as biofuel feedstocks. Today, strategies in microalgal biotechnology towards large-scale production of biofuel primarily focus on (i) enhancing their photosynthetic efficiency for improved oil yield and enhanced rate of carbon sequestration in mass cultures, (ii) driving the carbon flux towards energy-rich compounds, useful as a biofuel source and (iii) developing robust and committed microalgal strains that can sustain low-cost, large-scale cultivation resulting in lower operational costs. Microalgal strains exhibit great phylogenetic diversity and vary widely in terms of growth rate, productivity, nutrient and light requirement, ability to accumulate different desirable compounds and adapt to adverse conditions. The foremost step in the mass cultivation of microalgae is, therefore, to screen or engineer the right species and strains for optimal biofuel production. A large number of native and engineered microalgal strains in this context has already been reported in the literature. Complete or near-complete genome sequences for many of them have already been solved. Also, strategies for genetic engineering and metabolic modelling are being explored. In the present work, typical microalgal strains- Chlamydomonas reinhardtii, Dunaliella salina, Botryococcus braunii, various Chlorella species, and many more model strains have been compared for various parameters of their growth physiology, metabolite production, robustness and amenability for genetic manipulation from the data of the existing literature. Such a comprehensive and comparative understanding of different strains will be useful for their future metabolic engineering to generate biofuels.

YI 40

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Keywords: antibody engineering, phage display, immunodiagnostics, anti-microbial resistance, antibody library

ImPACT: Immunization-free Phage-based Antibody Cloning Technology

Authors: Vaishali Verma, Amita Gupta, Vijay K. Chaudhary

Phage-displayed human antibody libraries have been successfully employed for the isolation of FDA approved therapeutic human antibodies. The naïve human antibody libraries contain antibody gene repertoire encoded by un-immunized individuals. Being "Universal", such libraries provide an excellent opportunity to explore the natural human antibody repertoire. Typically, the construction of such libraries involves several rounds of PCR-based amplification of the variable antibody genes followed by their assembly in desired format and cloning into appropriate phage display vector. However, the PCR-based amplification process is prone to chimerization events between the highly similar antibody sequences leading to generation of a significant fraction of spurious sequences, which are likely to be off-frame and can be seen as a smear on the agarose gel. The overall poor insert quality also negatively affects the ligation efficiencies making the construction of large libraries a difficult task. To overcome the existing bottlenecks, we have employed a novel combination of recombinant DNA technologies for the construction of phage-displayed naive human antibody library of much superior quality. We have employed emulsion-based SOE-PCR (SOE-ePCR) for the assembly for variable antibody genes to produce high quality scFv fragments that have been cloned seamlessly into a highly optimized phage display vector using a restriction enzyme-free cloning strategy integrated with protocols for achieving very high ligation efficiencies to obtain a naive human scFv library comprising of 10 billion independent clones. The performance of library has been demonstrated by selection of large number of different yet highly specific scFv binders against six mycobacterial proteins including isolation of exclusive or common binders against two very similar proteins (>80 % identity at amino acid level). This well-balanced and highly diverse library is expected to find use in isolation of specific binders against targets of therapeutic interest.

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YI 41

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Keywords: neuro-oncology, neurodegeneration, immunology, protein quality control system, natural molecules

Understanding cellular and molecular regulations of cancer and neurodegeneration and their modulation by natural molecules

Complex diseases like cancer and neurodegeneration are associated with multiple changes at the cellular and molecular level. A detailed mechanistic approach to understand these alterations provides a detailed understanding of disease pathology and help in finding new therapeutic solutions. The cellular protein quality control system, which includes molecular chaperones, the ubiquitin-proteasome system (UPS) and autophagy, plays a significant role in regulating the turnover of different proteins involved in cancer and neurodegeneration. The UPS employs few selective E3 ubiquitin ligases for the intracellular degradation of cyclin-dependent kinase inhibitor 1B (p27Kip1) that tightly controls cell cycle progression and may function as biomarkers in various cancers. However, the complex interplay between E3 ubiquitin ligases is required for the functional regulation and expression of p27. We demonstrated that cell surface glycoprotein Gp78, a putative E3 ubiquitin ligase, is involved in stabilizing steady-state levels of p27.

Molecular chaperones and E3 ubiquitin ligases are explored for their therapeutic potential against many neurodegenerative diseases as well. We recently identified novel small molecules that can modulate the activities and effectiveness of many crucial E3 ligases and chaperones that help cells clearing the proteotoxic load of misfolded proteins from the cells. We have further explored molecular alterations to understand the disease mechanisms and associated pathways.

Currently, we are working to explore immunomodulatory properties of natural molecules for glioblastoma therapeutic benefits.

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1. Polyphenolic flavonoid (Myricetin) upregulated proteasomal degradation mechanisms: Eliminates neurodegenerative proteins aggregation Vibhuti Joshi, Ribhav Mishra, Arun Upadhyay, Ayeman Amanullah, Krishna Mohan Poluri, Sarika Singh, Amit Kumar, Amit Mishra Journal of Cellular Physiology 2019
2. Gp78 Involvement In Cellular Proliferation: Can Act As A Promising Modulator For Cell Cycle Regulatory Proteins? Vibhuti Joshi, Arun Upadhyay, Deepak Chhangani, Rajesh N Sharan Amit Mishra Journal of Cellular Physiology 2018

YI 42

VISHNU SREEKUMAR

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Keywords: human memory, cognitive neuroscience, dynamical systems, EEG/iEEG, lifelogging

Neurocognitive studies of human memory

Human memory has been typically studied in the laboratory using random lists of words stripped of the rich contextual structures that usually accompany our normal everyday experiences. Neisser (1976) argued that cognitive psychology had failed to address everyday human behavior due to its overreliance on artificial laboratory-based experiments. While it was not clear at that time how one would develop an ecologically valid memory science, today we are able to rigorously capture human experience using wearable devices and smartphones. At the Memory And NeuroDynAmics (MANDA) lab at IIITH, we use smartphone-based lifelogging and extended reality technologies to capture and quantify human experience as it happens in the real world (Sreekumar et al., 2014) and use this information to design memory, learning, and decision-making tasks which are administered both in the laboratory and during the course of people's everyday experience, with or without concurrent brain recordings (EEG/fMRI; e.g. Nielsen et al., 2015). Complementing these naturalistic memory studies, we also perform more controlled laboratory studies with a focus on understanding the role of different dimensions of context in memory. Using such a multi-pronged approach, we will provide critical real-world tests of theories of memory and event cognition that were developed in highly contrived laboratory studies. In a related but separate line of research, we work with open datasets of hard-to-obtain neural recordings such as intracranial EEG to understand the neural dynamics underlying human learning and memory. Finally, we also study the influence of language and culture on memory using natural language processing methods applied on corpora in multiple languages combined with cross-cultural behavioral experiments.

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YI 43

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Keywords: early biomarker discovery, drug formulation, pre-clinical trials, disease management, proteomic studies

Potential application of nanoemulsified garlic oil blend in mitigating the progression of type 2 diabetes-mediated nephropathy in Wistar rats

The renoprotective potential of nanoemulsified garlic oil blend (GNE) in alleviating the progressive stages of hyperlipidemia-mediated diabetic nephropathy was examined. The study was carried out in high fat-fed, streptozotocin-induced type 2 diabetic Wistar rats for five months. The diabetic rats showed a significant increase of area under the curve in OGTT ($p < 0.01$) and IPITT ($p < 0.01$), increased urinary albumin ($p < 0.01$), urinary microprotein ($p < 0.001$), total cholesterol ($p < 0.01$), triglycerides ($p < 0.001$) and LDL cholesterol ($p < 0.001$), with decreased serum albumin ($p < 0.01$), serum protein ($p < 0.001$) and HDL-cholesterol levels ($p < 0.05$) than the control rats. The histopathological analysis evidenced mesangial expansion and hypercellularity at the end of the first and third month, and glomerulosclerosis and tubular atrophy at the end of the fifth month in diabetic rats. Moreover, on disease progression, increase in urinary podocalyxin, NGAL and CD36 was observed, and the renal mRNA and protein expression of podocalyxin decreased significantly with a concomitant increase in NGAL and CD36 expression from first till fifth month end. The treatment with GNE (20 mg/kg) significantly ameliorated the serum albumin ($p < 0.001$) and urine albumin ($p < 0.01$) from the end of the third month with significant attenuation in the lipid profile than GO (20 mg/kg) or Ator (8 mg/kg). Moreover, GNE reverted the histopathological alterations and attenuated the aberrant mRNA, protein expression and urinary excretion level of renal CD36, podocalyxin and NGAL in diabetic rats from an early stage of disease till the end of the study period. This study demonstrated the enhanced efficacy of GO in nanoemulsified form in mitigating the progression of nephropathy in type 2 diabetic rats.

References:

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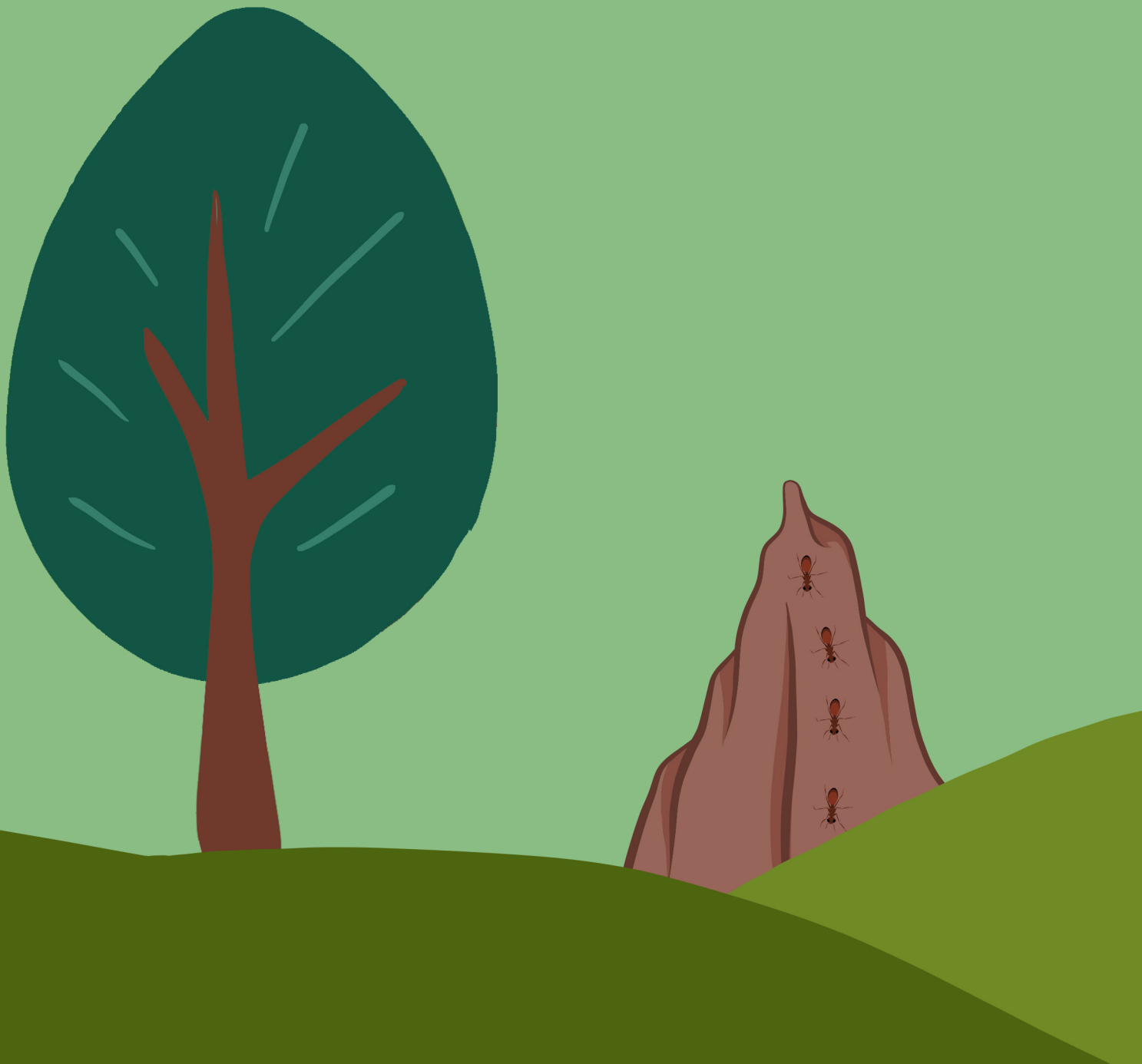

PDF
Abstracts

The contents in the abstracts (except references) have been printed exactly as submitted by the participants. The organisers of YIM 2022 are not responsible for any errors in them. In some cases, a few references were removed due to shortage of space.

PDF 01 AARAT KALRA
All wired up: Cytoskeletal filaments as hotspots for electromagnetic signalling

PDF 02 ABHISHEK SUBRAMANIAN
Building virtual cell models to understand biological mechanisms

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Energy dissipation in cell cortices leads to tough cell-cell junctions

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Functional ecology of plant roots and their surroundings to achieve food security in the 21st century

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Combinatorial antibiotic therapy; a boon to tackle the current scenario of antimicrobial resistance

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Finetuning the immune system to be more resilient to stress.

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microbial fuel cell, bioremediation, Bioremediation of low level uranium (VI) waste including denitrification using microbial fuel cell

PDF 09 ANUPAM SINGH
Mechanism and energetic cost of accurate DNA replication

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Decoding biases, hypotheses & regulation in big genomic datasets

PDF 12 BHUVANESHWARI SAMPATH
Pharmacophore modelling and atom based 3D QSAR for CRAC channel inhibitors

PDF 13 DHANAWANTARI L SINGHA
Development of rapid in vitro root regeneration of Withania somnifera (L) Dunal and identification of active antiviral compound

PDF 14 DIPANWITA MUKHERJEE
Delineating the fibroblast and ganglioside interplay in regulation of tumour microenvironment

PDF 15 HARDIK P GALA
Development of lateral organ in plants : proliferating to diverse fates

PDF 16 JITEN DOSHI
A synthetic biology approach towards the engineering of molecular determinants of adeno-associated viruses for its efficient manufacturing

PDF Abstracts

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PDF 17 KARTHIK KRISHNAMURTHY
Targeting aberrant protein aggregation in neurodegenerative diseases

PDF 18 KETAKI BELSARE
Soluble TREM2 inhibits secondary nucleation of Aβ fibrillization and enhances cellular uptake of fibrillar Aβ

PDF 19 MADHULIKA RAI
Lactate and glycerol-3-phosphate metabolism cooperatively regulate larval growth in a tissue nonautonomous manner

PDF 20 MADHUNITA BAKSHI
WRKY6 restricts Piriformospora indica-stimulated root development in Arabidopsis under phosphate limitation

PDF 21 MANISH GROVER
Neuronal C-type lectins mediate recognition of oomycete pathogens in C. elegans

PDF 22 MEETALI SINGH
Argonaute navigating the balance between protein translation and small RNA synthesis.

PDF 23 MEHRAB MODI
One engram, two ways to read it

PDF 24 PALANIVELU SENGOTTAIYAN
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PDF 25 PALLAVI SABHARWAL
Plant virus like particles – vehicle for intracellular antibody delivery

PDF 26 PRABHAT TIWARI
Mechanics of Drosophila ventral nerve cord condensation

PDF 27 PRATIK KUMAR
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PDF 28 PRAVESH GUPTA
Immunophenotyping of human brain tumors identifies Triggering Receptor Expressed on Myeloid cells 2 (Trem2) anti-glioma axis

PDF 29 PREETISH KADUR L MURTHY
Human distal lung maps and lineage hierarchies reveal a bipotent progenitor

PDF 30 PRIYADARSHAN KINATUKARA
Recruiting coenzyme-A independent fatty acid activation mechanism in eukaryotes for regulating diacylglycerol pools

PDF 31 PRIYADHARISHINI V
Role of presynaptic CaV2 channels in regulating synaptic vesicle release

PDF
Abstracts

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PDF 32 RAJAS M RAO
How do glycosylations influence glycoprotein dynamics & functioning?

PDF 33 RAJKUMAR KALRA
Cell transformation to epithelial-mesenchymal transition and metastases: Finding key pathways, novel signaling-axis and targets for antibody-mediated inhibition

PDF 34 RAKESH MAJHI
Harnessing the therapeutic potential of ion channels

PDF 35 RASHMI RAY
Immune responses in the settings of infections and vaccines

PDF 36 RATAN MURTY
Reverse-engineering human vision

PDF 37 RITWIK DATTA
Integrin-mediated regulation of intestinal lipid metabolism

PDF 38 RUKMINI MUKHERJEE
Phosphoribose linked serine ubiquitination of syntaxin17 regulates formation of bacterial vesicles which escape lysosomal degradation.

PDF 39 SAKET CHOUDHARY
Unraveling the role of sequence and chromatin state on the evolution of transcriptional regulation using single-cell data

PDF 40 SANDEEP BASU
Molecular dissection and chemical intervention of cardiovascular diseases in zebrafish

PDF 41 SANTOSH KUMAR C M
Chaperonins and tuberculosis; exploring the connection.

PDF 42 SANTOSH SATHE
How do microorganisms avoid exploitation?

PDF 43 SATYANARAYAN RAO
Using cell-free DNA to improve cancer survival

PDF 44 SAURABH AWASTHI
Single-particle characterization of protein aggregation

PDF 45 SHEETAL POTDAR
Hangry flies: Neuromodulation of protein hunger-induced aggressive behavior in Drosophila melanogaster

PDF 46 SHIRISH MISHRA
CG3860, a lipid transfer protein, potential regulator of phototransduction.

PDF 47 SHREYA SENGUPTA
Mycobacteriophage induced modifications in mycobacterial RNA polymerase

PDF
Abstracts

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PDF 48 SHWETHA SHIVAPRASAD
Dengue RNA-protein interactions that modulate infection in the mosquito host

PDF 49 SOUNAK SAHU
Self-organization of embryonic stem cells into mammary organoids: novel approaches to modeling disease and development

PDF 50 SREE RAMA CHAITANYA
Transcription dynamics prevent RNA-mediated genomic instability

PDF 51 SRIJIT DAS
Understanding the mechanisms of neuronal regulation of stress response and inheritance of epigenetic memory of stress in C. elegans

PDF 52 SUMIT KUMAR
Targeting pancreatic cancer by TAK-981: a SUMOylation inhibitor that activates the immune system and blocks cancer cell cycle progression in a preclinical model

PDF 53 SUSHMITA CHATTERJEE
CKAP5 as a potential therapeutic target in Ovarian Cancer

PDF 54 TAMISRA PAL
When two worlds meet: Interactions at the interface of chemical and biological systems

PDF 55 TANVI DEORA
Insect feeding and plant pollination: mechanics and neural control in natural contexts

PDF 56 VIJAY JAYARAMAN
A counter enzyme complex in B. subtilis glutamate metabolism

PDF 57 WASIM SAYYAD
Mechanism of formation of nodes, membrane-less organelles in fission yeast

PDF 58 ZARKA SARWAR
Polyoma Small T antigen promotes DBC1 protein degradation to antagonize AKT signaling via activation of LKB1.

PDF 01

AARAT KALRA

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LIGHTNING TALK

Keywords: microtubules, biophysics, actin filaments, fluorescence, bioelectricity

All Wired Up: Cytoskeletal Filaments as Hotspots for Electromagnetic Signalling

The brain consumes about 20 W of power to operate, but this input results in all sensory experience. Does such a high efficiency result from processing only biochemical stimulus, or do brain cells also process light and electricity? My group will address this question by investigating how intracellular protein polymers respond to such nonchemical stimuli. We will start by performing experiments on slender, tubelike microtubules, which act as 'fencing posts' for the cell, and flexible, wirelike actin filaments, that act as a cell's 'wiring'. Together, microtubules and actin filaments play a variety of well researched roles: they maintain cell shape and rigidity, orchestrate cell division and are crucial for cell movement. My group will understand if, in addition to these roles, microtubules and actin filaments can direct photonic and electrical energy to different parts of a cell. Previous work has shown that microtubules respond nontrivially to electric fields, perhaps allowing them to play intracellular electrical signaling roles (1). Devices using electrical stimuli for medical applications have also been modeled to target microtubules and actin filaments (2). My own work as a graduate student started experimental work in this direction, showing that microtubules dramatically lower local pH values by electrostatically attracting protons to their outer surface (3). In addition to electrical stimuli, light has been shown to cause changes in intracellular biochemistry (4). My postdoctoral work shows that the fluorescence properties of microtubules change upon interacting with biochemical agents. Such behaviour indicates that these polymers may not act simply as rudiments of the cell's skeleton, but rather as channels for signaling using electricity and light. My group's work on microtubules and actin filaments will illustrate the relevance of nonchemical information processing within cells, and in so doing, provide mechanistic insight into how the brain works.

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PDF 02

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LIGHTNING TALK

Keywords: computational systems biology, metabolism, mathematical and statistical, modeling, bioinformatics, machine learning

Building virtual cell models to understand biological mechanisms

Biological function is an outcome of the integrated behavior of simultaneously functioning components. Computational systems biology approaches provide a birds-eye perspective into these integrated components.

My PhD revolved around two fundamental questions - a) how does the Leishmania parasite developmental stages metabolically adapt to changes in its two host environments (sandfly and human)? b) what are the factors driving evolutionary changes in parasite genes? Genome-scale metabolic models (GEMs), an organized framework of whole-cell metabolism can predict metabolic pathways (fluxes) optimal for various cellular purposes. Thus, I manually assembled GEMs anew, for a species causing visceral leishmaniasis [1, 2]. These models predicted stage-specific metabolic behaviour, pathways essential for survival and dependence of parasite stages on unique environmental resources. Integrating sequence, expression, pathway information into statistical models, specific features could predict evolutionary rates in metabolic genes across Leishmania species. The ability of a metabolic gene to couple with other genes and codon usage bias were the most important factors driving evolutionary adaptations in parasite genes [3, 4].

My postdoctoral work involved building models of a more complex system: human endothelial cells (ECs). Upon a growth factor trigger, ECs rapidly proliferate/migrate to form blood vessels (angiogenesis) in pathophysiological situations like cancer [5]. To identify proliferation-specific metabolic changes, I developed whole-EC metabolic models and tailored them with transcriptomics data (single-cell, bulk RNA sequencing). These models could successfully recapitulate known metabolic pathways used by proliferating ECs with high precision. Interestingly, new anti-angiogenic metabolic enzymes were prioritized from the models and functionally validated in a pre-clinical mouse model of angiogenesis[6]. Currently, other novel targets / essential pathways are being experimentally tested in in vitro/in vivo models.

With this experience from both human and parasite perspectives, I would like to pioneer a new research area to explore systems-level metabolic co-associations between parasitic microeukaryotes and human host cells.

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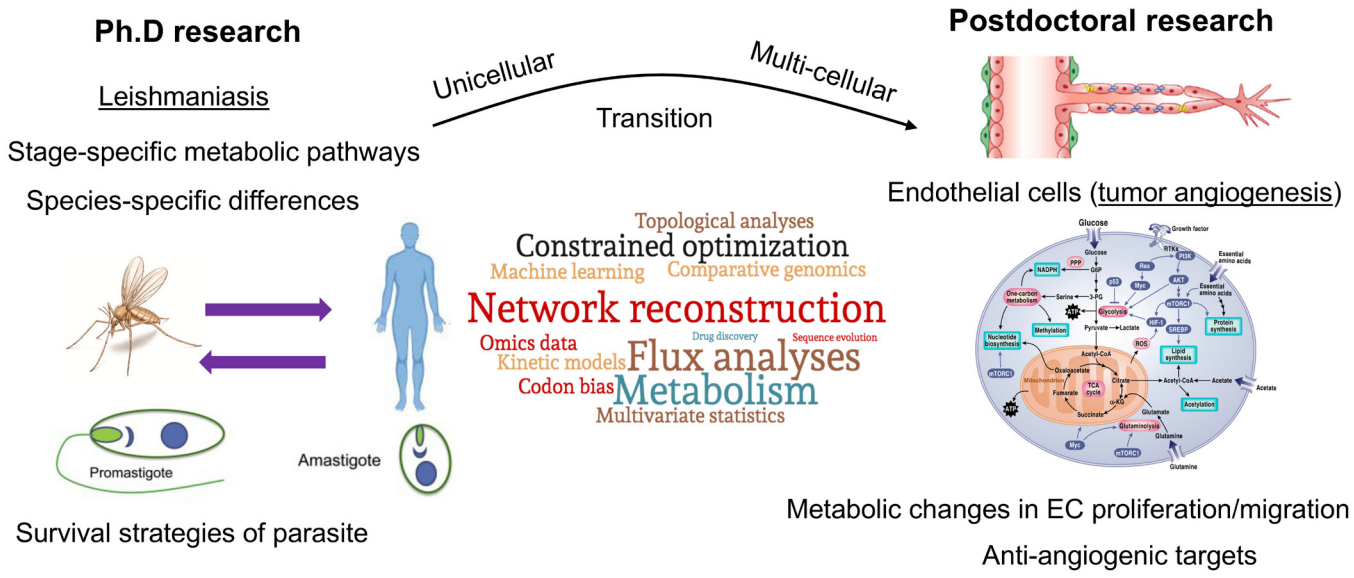

Figure showing the summary of my research career

PDF 03

ADITYA ARORA

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LIGHTNING TALK

Keywords: cadherin, cell and tissue mechanics, growth factor signalling, tissue engineering, tissue self-assembly

Energy dissipation in cell cortices leads to tough cell-cell junctions

Cell-cell adhesions form basis of organization of cells into tissues in multicellular organisms. Current understanding on mechanics of adhesion is limited to affinity between adhesion receptors and tension in the acto-myosin cortex. This work elucidates the role of cortex beyond the bounds of tension or contractility in cell-adhesion mechanics. To decouple cell adhesion and cortex remodelling through signalling from cadherins, we developed a DNA based cadherin (DNA cad) system where ectodomain of cadherin has been replaced with ssDNA strands and base pairing between complementary strands enables cell-cell junction formation. The DNA cad can form bonafide adherens like junctions between cells with stereotypical E cadherin like organization, however, they lack the biochemical signalling and biophysical modulation typical of E cad. Using this system, we demonstrate that adhesion receptor number, and not molecular affinity, has an important influence on the strength of cell junctions. We show that while upregulation of contractility non-monotonically increases separation force, this alone does not strengthen cell-cell adhesion in terms of fracture toughness. In contrast, actin polymerization which promotes a dissipative cortex significantly upregulates junction strength, wherein, branched actin (N WASP) promotes higher deformability while maintaining separation forces and linear actin (mDia1) promotes ability to bear larger forces through cell junctions. We show, biophysical modulation of cortex by E Cad maintains dissipation and deformability independent of contractile activity and this ensures junctions with high fracture toughness even at high contractility. Overall, our work demonstrates that junction mechanics is largely determined by energy dissipation in cell cortices which in turn can be regulated by the biochemical signalling from cadherins.

PDF 04

AMIT KUMAR

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LIGHTNING TALK

Keywords: rhizosphere biogeochemistry, microbiome structure and function, sustainable agroecosystems, global climate change

Functional ecology of plant roots and their surroundings to achieve food security in the 21st century

Roots constitute the interface between plants and soil and play a central role in numerous ecosystem processes and delivering multiple ecosystem services. Roots also release various organic and inorganic constituents in soil, a phenomenon called root exudation. The root exudates act as an energy source as well as signaling molecules that alter the composition and functioning of soil microorganisms making the rhizosphere (small soil volumes around roots) a hotspot with much faster process rates and much more intensive inter and intra-kingdom interactions as compared to average soil conditions. A holistic understanding and maximizing the potential of roots and rhizosphere processes, therefore, holds a tremendous potential that can be harnessed and utilized in making our crop production more sustainable through ecological intensification that can be adapted to farming practices and cropping systems. In the longer term, my research would be particularly beneficial in testing and designing novel cropping systems that are better resilient to environmental perturbations.

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PDF 05

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LIGHTNING TALK

Keywords: antibiotic bi-therapy, bacterial genetics, synthetic biology, reverse genetics, phage therapy

Combinatorial antibiotic Therapy; a boon to tackle the current scenario of antimicrobial resistance

By discovering ampicillin, Alexander Fleming opened the emporium of biological weapons for prolonged life of human beings. Universal tree of life evolves strategies to survive in changing environment, similarly bacteria become resistant to used antibiotics with time, in literature regarded as antimicrobial resistant (AMR). The ongoing menace of COVID19 pandemic is the result of AMR variants of SARS-CoV-2. AMR is estimated to cause 10 million deaths in an year by 2050 (Dixit et al., 2021) and Staphylococcus aureus is a serious contributor to this number. S. aureus, an opportunistic pathogen, is present in ~30% of the human population as a nasal carriage. Methicillin-resistant S. aureus (MRSA) is resistant to β-lactam antibiotics and is the main factor for blood poisoning (septicaemia/sepsis), which may cause death in immunocompromised patients. To evade bacterial infections, enzymes of essential pathways are targeted, provided the used drugs do not target the host pathway. Enzymes of Fatty Acid Synthesis II (FASII) fit this criterion.

During treatments with inhibitors of fatty acid synthesis II (FASII) in presence of host factors like serum, S. aureus remains inactive for a time interval (dormancy) and thereafter started growing actively (adaptation) (Kénanian et al., 2019). Recently, our group has shown that stringent response metabolite-(p)ppGpp inhibits synthesis of FASII inducer malonyl-CoA which also serves as a FASII metabolite. High (p)ppGpp and low malonyl-CoA in dormancy, and low (p)ppGpp and high malonyl-CoA in adaptation (Pathania et al., 2021) are one of the main factors for this growth phenotype. Using this knowledge during in vitro conditions, we showed that a combinatorial treatment, using a FASII inhibitor and mupirocin, a (p)ppGpp inducer, is more effective in inhibiting S. aureus growth (Pathania et al., 2021) and Figure attached.

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PDF 05

AMIT PATHANIA

Institute for Integrative Biology of the Cell (I2BC), France
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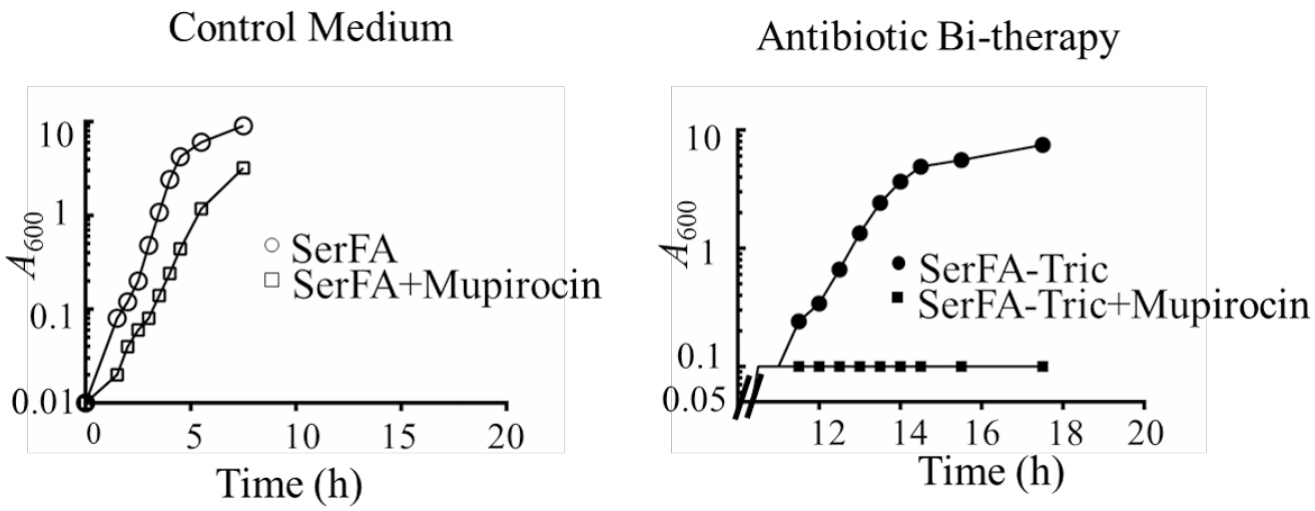
Malonyl-CoA Modulate Staphylococcus aureus Adaptation to FASII Antibiotics and Provide a Basis for Synergistic Bi-Therapy . MBio, 12(1), 1–15. https://doi.org/10.1128/mbio.03193-20



In control medium, left panel, (No FASII inhibitor; SerFA-Serum+Fatty Acids) S. aureus grows comparable in presence and absence of mupirocin. In presence of FASII inhibitor, right panel, (Triclosan; Tric), S. aureus starts to grow after 10 h but when mupirocin is added along with Tric, S. aureus does not grow up to ~20 h (Pathania et al., 2021).
Credits: Dr Amit Pathania and Dr. Alexandra Gruss

PDF 06

AMRUTHA SWAMINATHAN

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LIGHTNING TALK

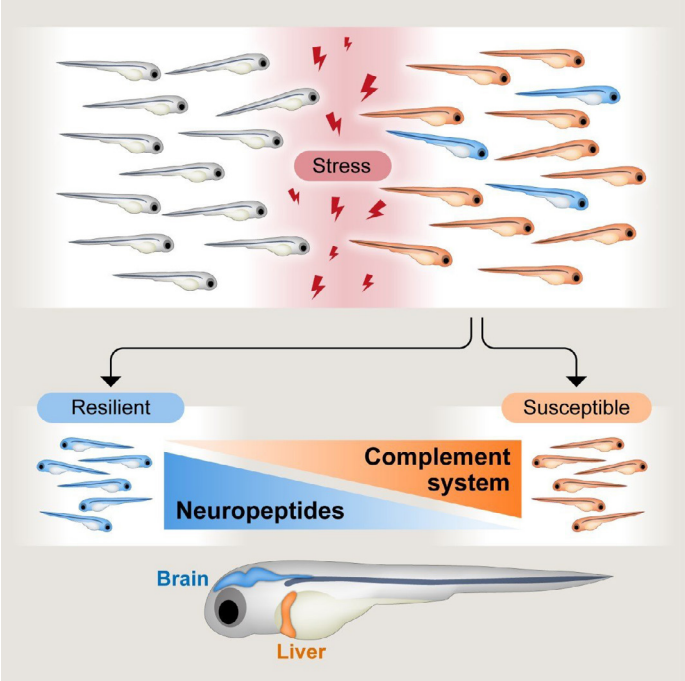
Keywords: behaviour, neurological disease, molecular mechanisms, development, small molecule modulators

Finetuning the immune system to be more resilient to stress.

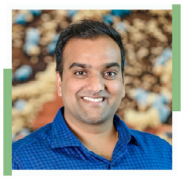
Stress is a systemic physiological and behavioral response to what an organism perceives as threat. Individuals in a population respond differently to stressful situations. While resilient individuals recover efficiently, others are susceptible to the same stressors. Though recent research has implicated molecular and environmental factors as being involved in stress resilience, it remains challenging to identify resilience in mammalian embryos to determine if stress resilience is established as a trait during development or acquired later in life. Using a new behavioural paradigm in zebrafish larvae, we show that resilience is a trait that is determined and exhibited early in life. Resilient and susceptible individuals retained these traits throughout life and passed them on to the next generation. Resilient larvae showed higher expression of resilience-associated genes and larvae lacking neuropeptide Y and miR218 were significantly under-represented in the resilient population. Unbiased transcriptome analysis revealed that resilient individuals show active response to stressful events by turning on a transcriptional program and multiple factors of the innate immune complement cascade were downregulated in resilient larvae in response to stressors. Pharmacological inhibition and genetic knockouts of critical complement factors led to an increase in resilience. We conclude that resilience is established early during development as a stable trait, and that neuropeptides and the complement pathway play positive and negative roles in determining resilience respectively.

References:

1. https://www.biorxiv.org/content/10.1101/2022.01.31.478444v1



Resilience to stress is established during zebrafish development; it is augmented by brain-derived neuropeptides and attenuated by innate immune complement factors specifically expressed in the liver.
Credits: Genia Brodsky



PDF 07

ANANT JAIN

Max Planck Florida Institute of Neuroscience, USA
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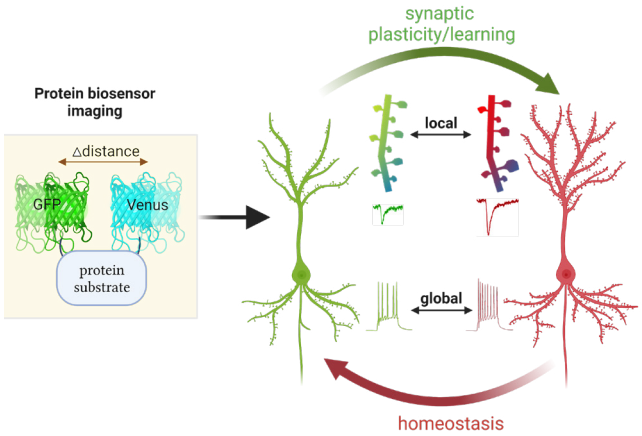
LIGHTNING TALK

Keywords: synapses, sex difference, learning, memory, brain plasticity

Understanding the role of homeostatic plasticity in epileptic seizures

One of the evolutionarily conserved phenomena across different species is that neuronal connections in the brain change their strength with experience throughout one's lifespan. These changes can last anywhere from a few seconds to several days and perform specific functions such as information processing, learning, and memory. However, if not kept under control, these electrical changes can make the brain network unstable. To prevent this, homeostatic mechanisms actively compensate for changes in neuronal activity to maintain electrical stability. Diverse mechanisms such as release of neuromodulators or patterns of electrical activity can induce changes in synaptic strength. Thus, to compensate for such electrical perturbations, several local and global homeostatic mechanisms exist that contribute to stabilization of altered neuronal activity. Although homeostatic mechanisms have been studied in isolation, how behavioral learning or underlying plasticity mechanisms activate these homeostatic processes is unknown. Thus, my first goal is to link homeostatic signaling with plasticity mechanisms that are relevant for learning. I will address this using novel biosensors and electrophysiological approaches in both in vitro slice culture and rodent models.

Understanding these mechanisms is also particularly relevant in neuropathological conditions such as epilepsy, where homeostasis is likely disrupted. Epilepsy is the second most prevalent neurological disorder and is a major burden on the Indian healthcare system. One of the most common symptoms of epilepsy is the occurrence of seizures. Mechanistically, seizures occur when neurons fire excessively and synchronously, and this has been attributed, in part, to an imbalance in excitatory and inhibitory neurotransmission. While it is intuitive that a disruption of homeostasis plays a role in seizure induction, the specific homeostatic signaling that gets altered have not yet been identified. Thus, my second research goal is to determine the contribution of local versus global homeostatic plasticity during seizure induction



Use of biosensors to distinguish local versus global homeostatic signaling

PDF 08

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LIGHTNING TALK

Keywords: microbial fuel cell, bioremediation, wastewater treatment, renewable bioenergy, power generation

Bioremediation of Low Level Uranium (VI) Waste Including Denitrification Using Microbial Fuel Cell

Nuclear wastes emerging from nuclear fuel cycle plants are generally rich in nitrates and heavy metals particularly radionuclides like Uranium (U). Nitrate has been identified as a major groundwater contaminant in many countries. Uranium is also an element of great concern due to the toxic effects it exerts on the environment. In this work, a novel process for simultaneous removal of U (VI) and nitrate is developed in microbial fuel cell (MFC). MFCs are emerging wastewater treatment systems with a proven potential for denitrification and simultaneous power production. MFCs can convert chemical energy present in the organic substrates to electrical energy using exo-electrogenic bacteria. The U (VI) removal was done by precipitating it as phosphate salt. This was achieved using microbial consortia which produced phosphatase enzyme which catalyzed the controlled release of phosphate from organic compounds. In this case, nitrate acted as an electron acceptor at cathode thereby allowing simultaneous nitrate and U (VI) removal. Since the process was performed in the MFC; the remediation was accompanied by power output. Ninety percent of initial U (VI) added in the biocathode could be recovered as Uranyl phosphate. The power density of 2.91 Wm-3 and nitrate removal rate of 0.130 kg NO3--N m-3 d-1 were achieved. The 16S rDNA-based community analysis revealed a high abundance of Pseudomonas species in biocathode. The work is extended to real effluents at BARC (Bhabha Atomic Research Centre), Mumbai. The low-level wastes were taken from nuclear fuel recycle division. The MFC system removed nitrate from these wastes while supporting 1.09 W m-3 of power density. This study demonstrates the applicability of MFC for simultaneous nitrate and U (VI) removal while producing electrical energy.

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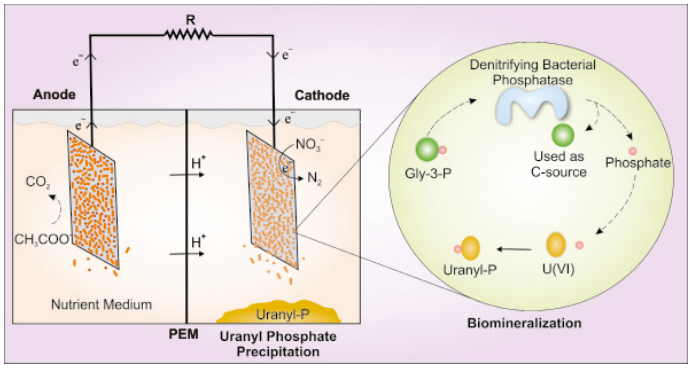

The mechanism of anodic and cathodic reactions in MFC for simultaneous removal of nitrate and U (VI)

PDF 09

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LIGHTNING TALK

Keywords: DNA replication, transcription, protein folding, protein aggregation, biophysics

Mechanism and energetic cost of accurate DNA replication

Replicative DNA polymerases have evolved ways to replicate genomic DNA accurately. Build into the mechanism is a proofreading exonuclease activity that excises nucleotides incorrectly incorporated by the polymerase. Considering that wrong incorporations are rare events, occurring one in a million times, it was surprising when we observed that replicative polymerases excise close to 7% of the correctly incorporated nucleotides. Shuttling of the primer-end into the exonuclease site spontaneously or processive degradation of nascent DNA were not causing excessive excision. Instead, we found that replication hurdles were responsible for excessive excision, promoting the polymerase to idle at the site with repeated synthesis and excision events. Such idlings can protect the primer-end from mutagenic extensions, but it comes with a high energetic cost. We asked what happens when hurdles are insurmountable? Our single-molecule and ensemble kinetics show that in such cases, the helicase keeps moving forward, taking the associated non-replicating polymerase with it. Eventually, the helicase-polymerase complex disrupts a codirectional transcription complex and uses the nascent RNA as a primer to resume DNA synthesis. Our studies reveal previously unrecognized roles of proofreading activity and plasticity in the polymerase and helicase enzymes ensuring accurate and timely DNA replication.

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PDF 10

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LIGHTNING TALK

Keywords: protein aggregation, amyloids, alzheimer's disease, aging, proteomics

Amyloids in Alzheimer's: Structure and composition

Amyloid deposition is the underlying cause of several neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease, etc. Deposition of amyloid plaques in the extracellular spaces is the hallmark feature of AD pathology. In the past century, scientists have recognized different biochemical features and provided structural details of the amyloid fibrils formed inside brain tissues. The major limitation of many such structural studies on amyloid fibers is our inability to isolate highly pure amyloid fibrils and plaques from diseased brains, which is a prerequisite for X-ray and NMR-based structural studies. Therefore, not too many solid-state NMR structures of brain-derived amyloid fibrils could have been produced despite all the technological advances. Recently, we got success in developing a robust purification protocol for amyloid purification. The method is primarily based on the existing sucrose-gradient ultracentrifugation strategy, which additionally includes ultrasonication (provides high shearing energy) to remove non-specific proteins present in the SDS insoluble fraction of brain tissues. Electron microscopy imaging, followed by immunogold labeling and fibril-specific LOC antibody confirms the purity and compositions of the amyloid fibrils. ELISA provides absolute concentrations of different APP cleavage products (Aβ38, Aβ340, Aβ42, etc.). The amyloid-beta concentrations obtained from this purification method are several hundred folds higher than various previous reports. Detailed mass spectrometry proteomics also confirms the purity of the isolated fibrils. Considering the lack of detailed NMR structural studies on naturally-derived amyloid fibrils so far, this new method of purification may provide tools for obtaining ultra-structural details of many types of disease-causing proteinaceous formations in various pathological conditions.

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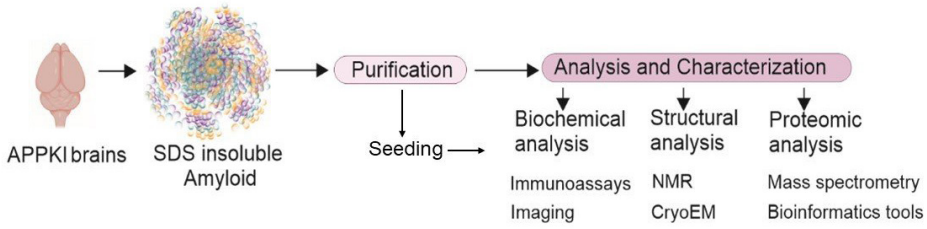

A detailed workflow for understanding the structure and composition of amyloid fibrils using biochemical methods and advanced proteomic approaches

PDF 11

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LIGHTNING TALK

Keywords: epigenetics/(epi)genomics, computational biology/bioinformatics, machine learning, single-cell (epi)genomics, aging and cancer

Decoding Biases, Hypotheses & Regulation in Big Genomic Datasets

The deluge of sequencing studies has presented many computational challenges over the last decade. My doctoral work addressed two in particular: a) how to correctly distinguish biological from technical variations and b) how to integrate different -omics datasets.

Batch effects are a common source of technical variation in transcriptomic datasets that can easily confound the interpretation of authentic biological signals that are often unknown. In my first project, we developed a universal batch detection algorithm, DASC, that integrates data shrinkage and non-negative matrix factorization to identify latent/hidden batch factors across microarray, bulk and single-cell RNA-seq datasets (1).

Another source of spurious results is the failure to measure baseline variability. For example, I read a study that suggested genes longer than 100kb are preferentially misregulated in neurological diseases such as Rett syndrome (2). This result was intriguing, but reading the paper closely revealed some statistically suspect tactics, so we investigated the dataset further. I realized that the study did not establish or assess the baseline (intra-sample variation) against which the significance of length-dependent changes could be measured. Therefore, I developed a rigorous statistical approach based on the assessment of intra-sample variation in contrast with inter-sample variations. As a result, I found that the "long gene effect" could be an artifact of PCR amplification-based platforms in MeCP2-related syndromes(3,4).

The last thrust involved projects towards understanding epigenetic regulation of gene expression through multi-omics data integration. In one such project, we demonstrated that the H3K27ac-marked active enhancer state could distinguish between different stages of the progression of colorectal cancer. I further defined epigenetic subtypes (EpiC) based on enhancers that correlated with previously described transcriptomic subtypes, and this helped us devise therapeutic strategies of enhancer-blocking bromodomain inhibitors with pathway-specific inhibitors for EpiC groups (5).

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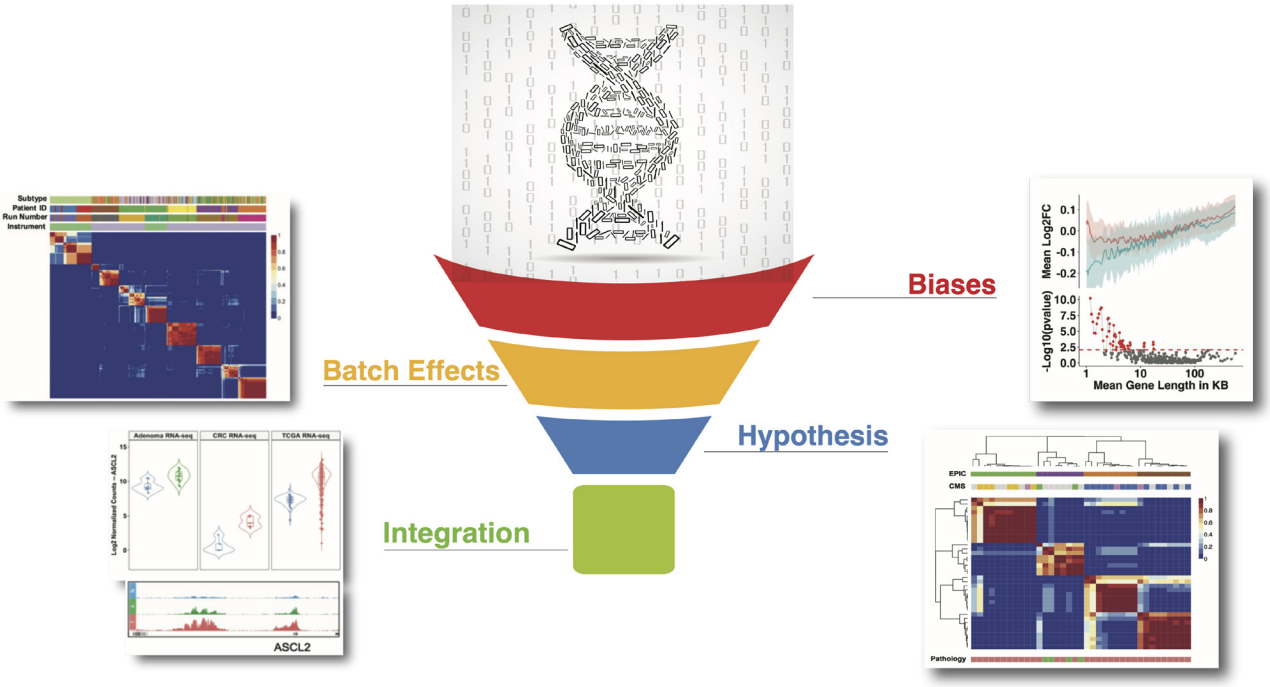

Credits: Raman AT. A research parasite's perspective on establishing a baseline to avoid errors in secondary analyses. Gigascience. 2021 Mar 12;10(3):giab015. doi: 10.1093/gigascience/giab015. PMID: 33710326; PMCID: PMC7953484.

PDF 12

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LIGHTNING TALK

Keywords: autoimmune diseases, rheumatoid arthritis, multiple sclerosis, ion channel proteins, electrophysiology

Pharmacophore modelling and atom based 3d qsar for crac channel inhibitiors

Upregulation of store-operated Ca2+ influx via ORAI1, an integral component of the CRAC channel, is responsible for abnormal cytokine release in active rheumatoid arthritis, and therefore ORAI1 has been proposed as an attractive molecular target. In this study, we attempted to predict the mechanical insights of ORAI1 inhibitors through pharmacophore modelling, 3D-QSAR, molecular docking and free energy analysis. Various hypotheses of pharmacophores were generated and from that, a pharmacophore hypothesis with two hydrogen bond acceptors, one hydrogen bond donor and two aromatic rings (AADRR) resulted in a statistically significant 3D-QSAR model (r2 = 0.84 and q = 0.74). We believe that the obtained statistical model is a reliable QSAR model for the diverse dataset of inhibitors against the IL-2 production assay. The visualization of contours in active and inactive compounds generated from the 3D-QSAR models and molecular docking studies revealed major interaction with GLN108, HIS113 and ASP114, and interestingly, these residues are located near the Ca2+ selectivity filter region. Free energy binding analysis revealed that Coulomb energy, van der Waals energy and non-polar solvation terms are more favourable for ligand binding. Thus, the present study provides the physical and chemical requirements for the development of novel ORAI1 inhibitors with improved biological activity.

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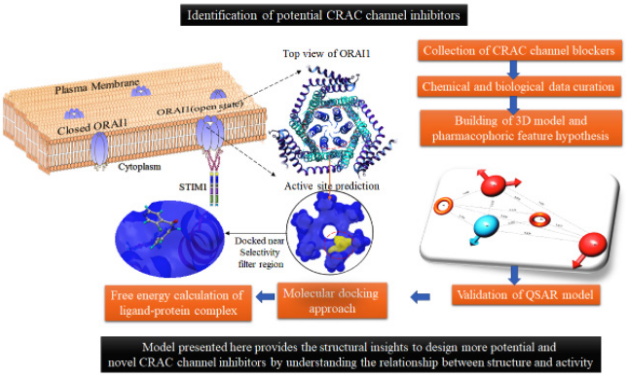

Model presented here provides the structural insights to design more potential and novel CRAC channel inhibitors by understanding the relationship between structure and activity.

PDF 13

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LIGHTNING TALK

Keywords: Withania somnifera, CRISPR/Cpf1 genome editing, COVID-19, herbal formulations, tissue specific genome editing

Development of rapid in vitro root regeneration of Withania somnifera (L) Dunal and identification of active antiviral compound

In recent years, herbal based medicinal products attracted national and international attention due to their comparatively safe and satisfactory efficacy. W. somnifera (Ashwagandha or Indian Ginseng), is an indigenous important medicinal plant for more than 3000 years with a wide range of applications. Among the various plant parts used, roots are specifically used in medicinal and clinical applications. The important application of Withania can be categorized into two broad areas such as (i) use of the extract for ayurvedic medicinal purpose to treat cancer, tumour, different types of stress, Alzheimer's disease, neurobehavioral disorder etc. and (ii) the secondary metabolite, withanolide for the treatment and management of COVID-19 disease due to their antiviral, immune booster, anti-inflammatory and immunomodulatory properties (Saggam et al., 2021; Khanal et al., 2021). Therefore, realization of commercial potential of the plant influences for development of chemotype containing more secondary metabolites. In the current study, a rapid in vitro regeneration system for roots in presence of hormone (in vitro root suspension culture) was developed. Further, enhancement of its major bioactive compounds in in vitro grown roots shall be studied by applying elicitors and abiotic stress. A pilot study shall be carried out to scale up the in vitro grown roots with increased production of metabolites. The probable role of Ashwagandha in various stages for management of COVID- 19 is proposed (Saggam et al., 2021). The novel active/ known metabolites in response to elicitors stress treatment shall be screened for their antiviral property.

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PDF 14

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LIGHTNING TALK

Keywords: tumour microenvironment, fibroblast, ganglioside, drug delivery system, cancer therapy

Delineating the fibroblast and ganglioside interplay in regulation of tumour microenvironment

In the past, cancer cells were the primary focus for understanding tumourigenesis. However, a recent renaissance in oncology research has highlighted the significance of Tumour Microenvironment (TME) in cancer progression, which was further validated by the "seed and soil hypothesis" corroborating the intricate regulation of cancer cells by TME. The TME is constituted by the reciprocal interaction of the tumour cells with tumour stroma comprising of the structural extracellular matrix (ECM) components and non-malignant stromal cells such as fibroblasts, immune cells, endothelial cells, etc. [1]. The fibroblasts are the most abundant tumour stromal population of TME, endowed with the potential to modulate the properties and functions of healthy tissue as well as neoplastic cells in either tumour inhibiting or promoting manner depending on their state as normal fibroblasts (NF) or cancer-associated fibroblast (CAF), respectively. Thus, the fibroblasts serve as the "architects" of cancer pathogenesis, wherein, the crosstalk between the cancer cells and TME play a critical role in modulating the fate of cancer [2-5].

Tumourigenesis is a complex process where multiple factors play crucial role in triggering the generation of an optimal niche for cancer onset and progression. The gangliosides (GSL) have been recognised as one of the most critical tumour-associated factors involved in tumourigenesis. GSL are the sialylated glycolipids, which exhibit characteristic over-expression in cancer cells compared to normal tissues, which are often shed in TME, and are reported as vital cell surface receptors, important biomarkers and modulators of invasion, metastasis, cellular signalling, host immune response and tumor-stromal cell communication [6-8]. However, role of GM2 (a key GSL) on fibroblast, is not yet elucidated, hence, instigating us to understand and delineate the significance of GM2 on fibroblast activation, its precise mechanism and impact on downstream modulation of the pro-tumourigenic microenvironment.

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PDF 14
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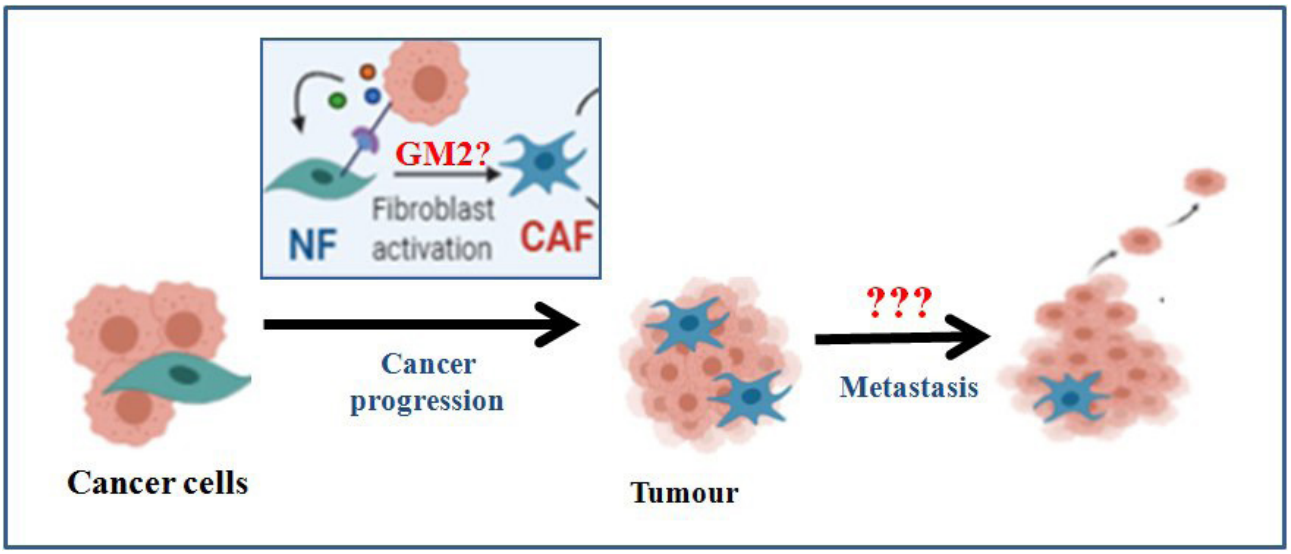

Pro-tumourigenic role of the ganglioside GM2 on modulation of TME: The pivotal involvement of the fibroblast

PDF 15

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LIGHTNING TALK

Keywords: lateral root development, comparative plant development, synthetic biology, cell fate transitions, cell proliferation

Development of lateral organ in plants : proliferating to diverse fates

Unlike animals, plants exhibit tremendous potential to form new organs throughout their lifespan. It is best exemplified by the formation of root branches on the primary root, called lateral root and is an important organ system for efficiently 'forage' nutrients and water. Depending on the species of plant, lateral roots originate from one or more cell types (e.g., only pericycle in Arabidopsis vs pericycle, endodermis & cortex in legume like Medicago) but needs to undergo three crucial steps to establish a new self-sustaining meristem of lateral organ: attain proliferative potential, recruit the same or surrounding cell types and collectively undergo cell fate transitions. Further, same cell types exhibit tremendous developmental plasticity and upon favorable signals can form diverse lateral organs (pericycle originated shoot meristem - upon ectopic hormone treatment in Arabidopsis or pericycle, endodermis and cortex originated nodules - upon bacterial infection in Medicago). Independent of the model system or treatment, cells undergoing fate transition attains cell proliferative property and recruits the same developmental pathway to initiate organ formation and thereby offers an excellent model system to understand the molecular basis of morphological and functionally diverse developmental outcomes in Plantae. I would hypothesize that developmental signals along with preexisting cell type and its proliferative potential would determine the fate plasticity/constraints of the lateral organ. Understanding how different cell types (across model systems) respond to fate determining/ proliferative cues, would shed light on species and cell-type specific mechanisms that form the basis of diversity of lateral organs in plantae. Unraveling these mechanistic nuances would be crucial for our ability to engineer favorable developmental and functional traits in organisms it otherwise doesn't.

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PDF 15

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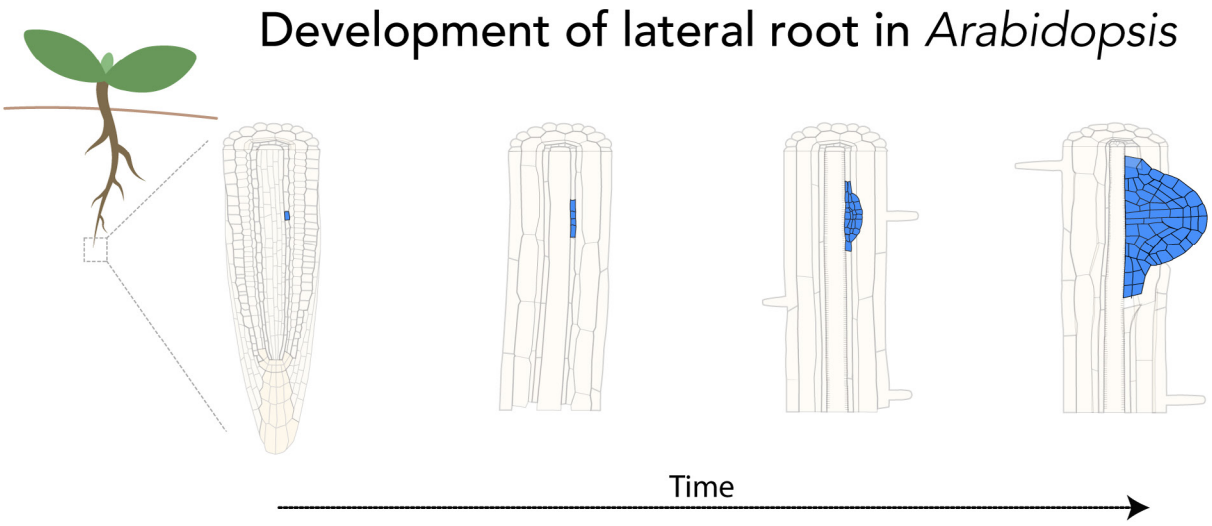

Lateral Root Development in Arabidopsis

PDF 16

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LIGHTNING TALK

Keywords: synthetic biology, adeno-associated viruses, gene therapy, biological engineering

A synthetic biology approach towards the engineering of molecular determinants of adeno-associated viruses for its efficient manufacturing

Adeno-associated viruses (AAV) are becoming increasingly popular for use in gene therapy applications because of their non-pathogenic nature, superior safety profile and ability to transduce both dividing and non-dividing cells. The popularity is evident by recent market approvals and hundreds of ongoing clinical trials for the treatment of genetic disorders using AAV based gene therapies (1). Increased therapeutic usage has caused a surge in demand of clinical/good manufacturing practice (GMP)-grade rAAVs. Triple-plasmid transient transfection in mammalian human embryonic kidney (HEK) 293 cells is the commonly used method for rAAV production (2). This method is quick and easy to establish and was important with regards to supply of rAAV material for initial clinical studies. However it is not suitable to address the growing commercial demand of rAAV because of lack of scalability & reproducibility, cell aggregation and high transfection cost exist, making it incapable to cater to the present/forthcoming demand (3). Our research is aimed to develop an innovative rAAV manufacturing process by adopting a synthetic biology-based approach of engineering its key determinants: genetic sequence/code containing the information for rAAV production and the mammalian cells and its machinery used for rAAV production. Our aim is to develop a process that is scalable, reproducible, cost-effective, and will efficiently address the ever-increasing rAAV demand.

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PDF 17

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LIGHTNING TALK

Keywords: neurodegeneration, stress granules, endoplasmic reticulum stress, excitotoxicity, organoids

Targeting aberrant protein aggregation in neurodegenerative diseases

Protein aggregation is a hallmark of various neurodegenerative diseases including amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) causing a chronic traffic jam like situtation. The cellular pathways by which protein aggregates contribute to neurodegeneration is not well understood. A class of RNA binding protein known as fused in sarcoma (FUS) is implicated in ALS/FTD. FUS protein is characterized by the presence of prion like low complexity domains increasing its propensity to aggregate. What drives FUS mediated neurodegeneration is not well understood. We study the molecular mechanisms by which mislocalization of FUS from nucleus into cytoplasmic aggregates triggers neurodegeneration in vitro (rodent neurons and human iPSC derived neurons) and in vivo (Drosophila). We show expression of disease linked mutant forms of FUS in neurons is sufficient to cause a cellular integrated stress response that increases levels of phosphorylated eukaryotic translation initiation factor (peIF2 alpha). Increased levels of peIF2 alpha triggers aberrant formation of membraneless organelles called stress granules. These stress granules have altered dynamics affecting neuronal function and ultimately cause neuronal death. We elucidate neuronal pathways impaired by these aberrant stress granules and identify novel genetic modifiers (see references) which prevent FUS mediated neurodegeneration in models of ALS and FTD.

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PDF 18

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LIGHTNING TALK

Keywords: directed evolution, protein engineering, de novo protein design, metalloproteins, redox sensors

Soluble TREM2 inhibits secondary nucleation of Aβ fibrillization and enhances cellular uptake of fibrillar Aβ

Triggering receptor expressed on myeloid cells 2 (TREM2) is a single-pass transmembrane receptor of the immunoglobulin superfamily that is secreted in a soluble (sTREM2) form. Mutations in TREM2 have been linked to increased risk of Alzheimer's disease (AD). A prominent neuropathological component of AD is deposition of the amyloid-β (Aβ) into plaques, particularly Aβ40 and Aβ42. While the membrane-bound form of TREM2 is known to facilitate uptake of Aβ fibrils and the polarization of microglial processes toward amyloid plaques, the role of its soluble ectodomain, particularly in interactions with monomeric or fibrillar Aβ, has been less clear. Our results demonstrate that sTREM2 does not bind to monomeric Aβ40 and Aβ42, even at a high micromolar concentration, while it does bind to fibrillar Aβ42 and Aβ40 with equal affinities (2.6 ± 0.3 μM and 2.3 ± 0.4 μM). Kinetic analysis shows that sTREM2 inhibits the secondary nucleation step in the fibrillization of Aβ, while having little effect on the primary nucleation pathway. Furthermore, binding of sTREM2 to fibrils markedly enhanced uptake of fibrils into human microglial and neuroglioma derived cell lines. The disease-associated sTREM2 mutant, R47H, displayed little to no effect on fibril nucleation and binding, but it decreased uptake and functional responses markedly. We also probed the structure of the WT sTREM2–Aβ fibril complex using integrative molecular modeling based primarily on the cross-linking mass spectrometry data. The model shows that sTREM2 binds fibrils along one face of the structure, leaving a second, mutation-sensitive site free to mediate cellular binding and uptake. These findings inform mechanisms by which TREM2 modulates key processes in AD progression

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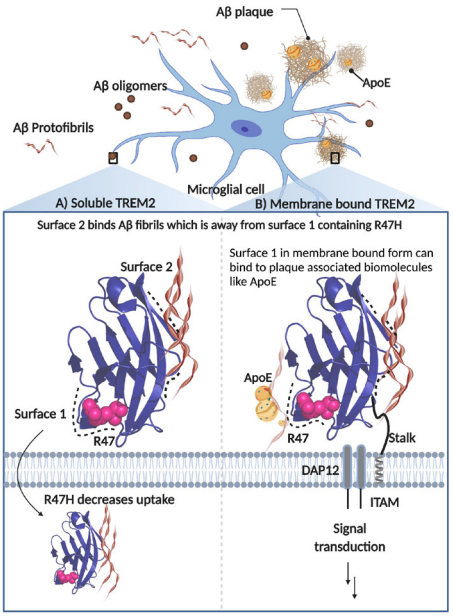

Schematic representation showing binding surfaces of TREM2 in soluble and membrane bound form

PDF 19

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LIGHTNING TALK

Keywords: metabolism, development, genetics, Drosophila melanogaster, cancer

Lactate and glycerol-3-phosphate metabolism cooperatively regulate larval growth in a tissue nonautonomous manner

The dramatic growth that occurs during Drosophila larval development requires the rapid conversion of nutrients into biomass. In response to these biosynthetic demands, larval metabolism exhibits the hallmark features of aerobic glycolysis, a metabolic program ideally suited to synthesize macromolecules from carbohydrates. Central to the biosynthetic potential of aerobic glycolysis is lactate dehydrogenase (LDH), which promotes glycolytic flux by regenerating NAD+. We have seen that although Ldh mutants accumulate elevated NADH levels, larvae compensate for this metabolic insult by increasing glycerol-3-phosphate (G3P) production, which serves as a backup mechanism to regenerate NAD+, and the cooperative regulation of lactate and G3P metabolism imparts metabolic robustness on the larval glycolytic program1,2. Further, lack of Ldh and Gpdh1 together, exhibit developmental delays, synthetic lethality, and aberrant carbohydrate metabolism1. We understand the effect of the loss of Ldh and Gpdh1 in the whole body, tissue-specific roles of both enzymes remain unexplored. To address this deficiency, we used RNAi to understand how tissue-specific depletion of Ldh and Gpdh1 affects larval growth and metabolism. Our results demonstrate that while individual loss of either Ldh or Gpdh1 in fat body, muscle and neurons does not affect larval development, loss of both Ldh and Gpdh1 within either the fat body, muscle or neurons leads to systemic growth defects in larvae. Hence, Ldh and Gpdh1 can influence larval growth and metabolism in a cell nonautonomous manner, indicating that the cooperative activity of these two enzymes within individual tissues is capable of inducing systemic signals that coordinate intercellular metabolic states with growth of the entire organism

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PDF 20

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LIGHTNING TALK

Keywords: Piriformospora indica, root development, expression profiles, sericulture, host-plant

WRKY6 restricts Piriformospora indica-stimulated root development in Arabidopsis under phosphate limitation

Arabidopsis root growth is stimulated by Piriformospora indica, phosphate limitation and inactivation of the WRKY6 transcription factor. Combinations of these factors induce unexpected alterations in root and shoot growth, root architecture and root gene expression profiles. The results demonstrate that P. indica promotes phosphate uptake and root development under Pi limitation in wrky6 mutant. This is associated with the stimulation of PHOSPHATE1 expression and ethylene production. Expression profiles from the roots of wrky6 seedlings identified genes involved in hormone metabolism, transport, meristem, cell and plastid proliferation, and growth regulation. 25 miRNAs were also up-regulated in these roots. We generated and discuss here a list of common genes which are regulated in growing roots and which are common to all three growth stimuli investigated in this study. Since root development of wrky6 plants exposed to P. indica under phosphate limitation is strongly promoted, we propose that common genes which respond to all three growth stimuli are central for the control of root growth and architecture. They can be tested for optimizing root growth in model and agricultural plants.

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PDF 21

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LIGHTNING TALK

Keywords: C. elegans, innate immunity, cell signaling, host-pathogen interactions, ageing

Neuronal C-type lectins mediate recognition of oomycete pathogens in C. elegans

We have previously shown that C. elegans can respond to an innocuous extract made from oomycete infected animals by triggering a recognition response characterized by the induction of chitinase-like (chil) genes in the hypodermis. Through a forward genetic screen aimed at identifying suppressors of chil gene induction upon treatment with this extract, we recovered loss-of-function mutations in ceh-37, clec-27 and clec-35 genes which led to complete loss of oomycete recognition response in C. elegans and made animals more susceptible to infection by the oomycete Myzocytiopsis humicola. Using smFISH and fluorescent reporters, we found clec-27 and clec-35 to be expressed in neurons while RNA-seq analysis revealed changes in the expression of these genes in a ceh-37 mutant background. Furthermore, neuronal rescue of clec-27 function specifically in ceh-37 expressing neurons, and particularly in AWA, was sufficient to restore chil gene induction in clec-27 mutants upon exposure to oomycete extract. Interestingly, clec-27 and clec-35 are neighboring genes sharing a bidirectional promoter, an organization which indicates coregulation of the two genes and a possible requirement to produce the two proteins in stoichiometrically equal amounts. These observations suggest that CLEC-27 and CLEC-35 could be forming a heterodimeric receptor involved in oomycete recognition in AWA neurons. Additionally, when these mutants were exposed to the phylogenetically distinct oomycete Haptoglossa zoospora, both clec-27 and clec-35 mutant animals showed chil gene induction, whereas ceh-37 mutants did not. This suggests that CLEC-27 and CLEC-35 are receptors specifically involved in the detection of M. humicola and a different receptor(s) in ceh-37 expressing neurons mediates detection of H. zoospora. Overall, our study provides evidence for neuronally expressed C-type lectins as pathogen recognition receptors in C. elegans which mediate detection of a newly identified class of natural pathogens of C. elegans in a pathogen-specific way.

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PDF 22

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LIGHTNING TALK

Keywords: Argonaute, epigenetics, soma-to-germline transfer, C. elegans, small RNAs

Argonaute navigating the balance between protein translation and small RNA synthesis.

In C. elegans germline two major small RNA pathways operate- piRNAs and CSR-1 pathway. piRNAs act by recruiting an RNA-dependent RNA polymerase (RdRP) which synthesizes antisense secondary small RNAs (22G-RNAs). These 22G-RNAs are loaded onto Worm Specific Argonautes (WAGOs) and mediate gene silencing. On the other hand, CSR-1 loads 22G-RNAs antisense to most of the germline-expressed mRNAs which are synthesized by RdRP EGO-1 using mRNA templates. CSR-1 is essential for fertility and embryonic viability and possesses a catalytic activity in vitro. Despite the essential function of CSR-1, how CSR-1 targets are determined, and 22G-RNA biogenesis is triggered remains unknown. This is specifically intriguing due to the absence of any known primary trigger for CSR-1 22G-RNAs.

We show that CSR-1 slicer activity is primarily involved in triggering the synthesis of 22G-RNAs on the coding sequences of germline mRNAs and post-transcriptionally regulates the expression of a small fraction of targets in the germline. CSR-1-cleaved mRNAs prime the RNA-dependent RNA polymerase, EGO-1, to synthesize 22G-RNAs in phase with translating ribosomes, in contrast to 22G- RNAs loaded by other Argonautes which are mostly synthesized in phase-separated germ granules. Moreover, codon optimality and efficient translation antagonize CSR-1 slicing and small RNAs biogenesis. We propose that codon usage differences encoded into mRNA sequences might be a conserved strategy in eukaryotes to regulate small RNA biogenesis and Argonaute targeting.

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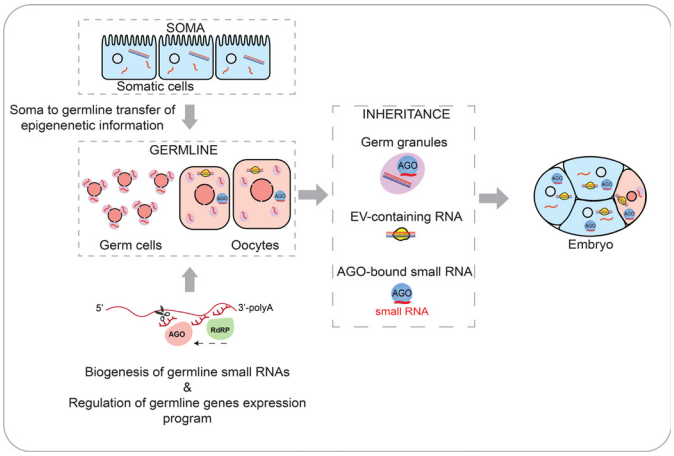

small RNA biogenesis, soma-to-germline transfer to mediate epigenetic inheritance

PDF 23

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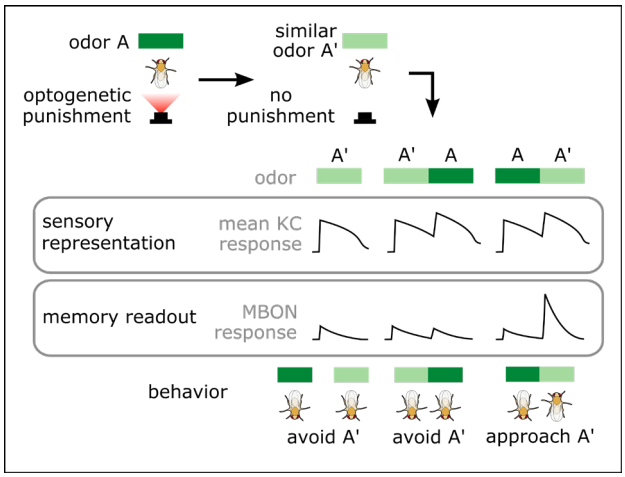
LIGHTNING TALK

Keywords: memory, behaviour, neurophysiology, calcium-imaging, comparative-physiology

One engram, two ways to read it

Animals learn when punishment or reward is predicted by neutral stimuli like tones or odors. Synaptic plasticity maps the predictor to the appropriate behavioral drive, forming a memory trace. But if the predictor is presented as one of two options, the optimal response is uncertain and depends on the alternative. Can a single memory trace evoke different behaviors, depending on stimulus context? We used optogenetics in Drosophila to form an odor-punishment association restricted to a single set of synapses, ie. a single memory trace. These flies showed flexible behavioral responses to a given odor stimulus. Depending on the choice, flies either generalized the association from the learned odor (A) to an unreinforced, similar odor (A'), or discriminated between them. We measured neuronal activity in the fly memory circuit, the mushroom body. The mushroom body output neuron (MBON) downstream of the memory trace had indistinguishable responses to single pulses of odors A and A' - generalizing across them. But if odors were presented as transitions from A to A', mimicking the fly crossing an odor boundary, MBON responses to A' were dramatically altered, allowing discrimination. Receiving odors in a specific sequence caused the MB circuit to alter the output of the memory trace. We tested this behaviorally. When odors were presented singly, flies responded to the punished odor, A and A' indistinguishably. Only when A transitioned into A', fly behavior switched and they were attracted to A'. An association assigns valence or meaning to a stimulus. But valence is subjective and ever-changing, depending on ongoing events in the environment. Our study reveals a novel way for animals to modulate how a test stimulus evokes behavior, based on ongoing stimulus dynamics. This is an important step to move beyond a plasticity-centric view of memory recall.



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LIGHTNING TALK

Keywords: protein function, protein regulation, signal transduction, cellular homeostasis, crop productivity

Arabidopsis heterotrimeric G protein α subunit GPA1 regulates CO2 signaling in guard cells

Arabidopsis heterotrimeric G protein α subunit GPA1 regulates CO2 signaling in guard cells

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Heterotrimeric G proteins, composed of Gα, Gβ and Gγ subunits, are essential evolutionarily conserved eukaryotic signaling hubs that play fundamental roles in developmental processes and abiotic and biotic stress responses. The Arabidopsis genome harbors one canonical Gα (GPA1), three extra-large Gα (XLG1, XLG2 and XLG3), one Gβ (AGB1), and three Gγ (AGG1, AGG2 and AGG3) subunit genes. We previously constructed guard cell signal transduction networks and modelled the regulation of stomatal apertures in response to two stimuli, the stress hormone ABA and elevated intercellular CO2 concentrations in leaves. [1,2]. Here, we pursued molecular genetic, biochemical and physiological approaches to reveal how G proteins regulate CO2 signaling in guard cells.

Using stomatal aperture and gas exchange assays, we identified that the gpa1-3 null mutant exhibits hyposensitivity in high CO2-induced stomatal closure. We show that the GPA1 subunit physically interacts with the components known to act earliest in the guard cell CO2 signaling pathway including the β carbonic anhydrases CA1 and CA4, the protein phosphatase ABI2, and protein kinases OST1 and HT1. In vitro kinase assays show that the OST1 kinase phosphorylates and forms a complex with GPA1. Yeast three-hybrid and co-immunoprecipitation assays reveal that GPA1 disrupts the OST1-ABI2 interaction. Because such disruption of OST1-phosphatase binding is known to promote stomatal closure, this is a possible mechanism by which the loss of GPA1 in the gpa1 knockout mutant confers CO2 hyposensitivity. Taken together, our results show that GPA1 regulates high CO2-induced stomatal closure in guard cells.

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PDF 25

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LIGHTNING TALK

Keywords: viruses, membrane receptors, virus like particles, therapeutics, bionanotechnology

Plant virus like particles – vehicle for intracellular antibody delivery

Intracellular delivery of antibodies has become potentially one of the most efficient and important approach for therapeutics. However, antibody delivery is subjected to a major challenge as they cannot cross the cell membrane barrier. Thus nanoparticles-driven intracellular delivery of antibodies has become one of the most advantageous strategies. The ability of viruses to self-assemble into particles of uniform size and shape and an ordered backbone structure make them ideal platforms for nanotechnology. Virus based nanocarriers are biodegradable and biocompatible as they are primarily composed of proteins, however the pathogenic effects due to the virus-host interactions cannot be neglected. In this regard, plant virus based nanocarriers exhibit an advantage being non-pathogenic to mammalian system. A flexuous rod shaped virus which infects pepper plants was studied to form virus like particles (VLPs) which could internalize into different mammalian cells via endolysosomal pathway. Therefore, a chimera was generated by genetic engineering of IgG binding B domain of protein A at the N-terminus of VLPs. These chimeric nanoparticles were able to deliver functional therapeutic antibodies intracellularly for the treatment of various malignancies. These chimeric VLPs have higher antibody binding affinity as compared to protein A, therefore could also be used in future immunodiagnostic applications.

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PDF 26

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LIGHTNING TALK

Keywords: Drosophila, Genetics, live-imaging, ventral nerve cord, tissue-mechanics

Mechanics of Drosophila Ventral Nerve Cord Condensation

During development organs achieve their final shape and size by growing. In Drosophila, ventral nerve cord (VNC) unlike other organs achieves final shape and size by shrinking. We characterized the VNC condensation by combining in toto live-imaging with biophysical and genetic manipulations. The analysis of the VNC condensation reveals that it is not a unidirectional continuous process but an oscillatory process as there are alternating contractions at anterior and posterior ends. The process of condensation is dependent on coordinated mechanical action of the neurons and glia. The VNC tissue has heterogeneous force distribution along its longitudinal axis. These outcomes are consistent with a viscoelastic model of condensation, which incorporates time delays due to the different time scales on which the mechanical processes act, and effective frictional interactions. In summary, we have defined the complex and progressive mechanics driving VNC condensation, providing insights into how a highly viscous tissue can autonomously change shape and size.

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PDF 27

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LIGHTNING TALK

Keywords: single-molecule imaging, multifunctional dyes, cell-type pharmacology, fluorescent dyes, cellular imaging

Chemical tools for imaging and manipulation of living systems

Advances in our understanding of cellular processes are often limited by our ability to visualize and manipulate biomolecules. Innovations in fluorescence microscopy have led to imaging and tracking individual fluorophore-tagged proteins with "superresolution". The demand for more photons is driving a renaissance in small-molecule fluorophores, which show superior properties to fluorescent proteins and can be deployed with genetic specificity. However, organic fluorophores that also allow manipulation of labeled proteins is still in its infancy. I have developed three sets of tools to fill this gap.

Multifunctional dyes leverage the brightness and tunable cell permeability of far-red Janelia Fluor (JF) dyes to push their utility from solely imaging labeled proteins to also manipulating them via the dye-linked cargo (e.g., affinity tags, pharmacologics). They have three components working in unison: genetic targeting ligand; JF dye for fluorescence readout; and small-molecule cargo. We have demonstrated their potential for affinity purification of intracellular proteins, recruiting proteins from heterochromatin to specific proteins in euchromatin, and recruiting proteins to specific DNA sequences for increased transcription. These dyes are enabling superior reagents for cell biology and pharmacology; thereby, representing a new avenue in the development of dyes.

Single-molecule imaging dyes: I have developed two strategies to obtain fluorogenic (nonfluorescent to fluorescent) dyes to overcome the current limitations of activatable labels for localization microscopy of proteins. The first type becomes fluorescent upon photoactivation whereas the second type becomes fluorescent upon bioorthogonal reaction with a genetically encoded non-canonical amino acid.

Cell-type and optical pharmacology: Most pharmacophores are studied in a population of mixed cell-types due to a lack of tools to unravel their activity on their protein targets in defined cell-types. I have combined dyes with pharmacologics for exerting optical control over their targeting to genetically defined cell-types, and for photopharmacological manipulation of endogenous receptors without any genetic manipulation.

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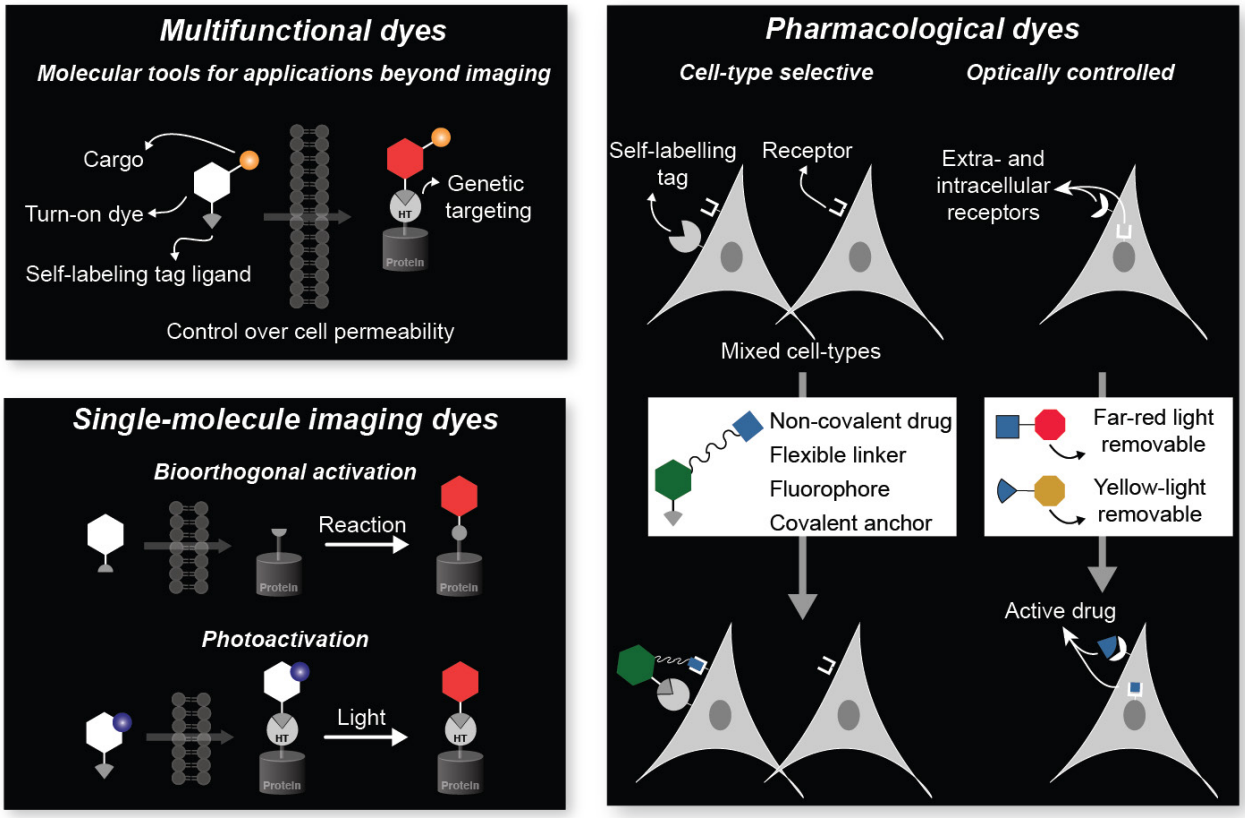

A toolbox of dyes for genetic targeting, imaging, and manipulation of proteins

PDF 28

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LIGHTNING TALK

Keywords: myeloid cells, brain tumor, immune microenvironment, microglia, neuroimmune

Immunophenotyping of human brain tumors identifies Triggering Receptor Expressed on Myeloid cells 2 (Trem2) anti-glioma axis

Gliomas are recalcitrant brain tumors. Anti-glioma immunity and immunopathogenic responses are critical contributors for better survival of isocitrate dehydrogenase-mutant (IDHmut) over wild-type (IDHwt) gliomas. Despite this correlative pattern of immunity and survival, an unbiased understanding of cell-type specific transcriptomic and epigenomic states of glioma-derived immune cells remains elusive. To this end, we performed single-cell RNA-sequencing (scRNA-seq) and single cell- Assay for Transposase-Accessible Chromatin using sequencing (sc-ATAC-seq) on ~100,000 tumor-associated immune cells from seventeen IDH mutation classified primary and recurrent human gliomas and non-glioma brains (NGBs). Our analyses revealed seven myeloid and seven lymphoid cell-types within and across glioma subgroups. We noted microglial (MG) attrition with increasing disease severity concomitant with invading monocyte-derived cells (MDCs) and lymphocytes. As tissue macrophages exhibit multifaceted polarization in response to microenvironmental cues, we clarify the existence of microglia/macrophage functional states beyond M1/M2 paradigms exemplified by the presence of palmitic-, oleic- acid, and glucocorticoid responsive polarized states. Specifically, certain MG and monocyte-derived subpopulations were associated with antigen presentation (AP) gene modules, akin to cross-presenting dendritic cells. Furthermore, immune-related gene ontology analysis identified enriched AP and phagocytosis gene modules in distinct MG clusters. Importantly, the phagocytic immunomodulator; TREM2 was upregulated in these antigen presentation cells (APC)-like MG. Contrary to tumor-promoting role of TREM2 myeloid cells in non-brain cancers, we delineated anti-glioma role of TREM2 as evidenced by the inability of GL261 glioma bearing TREM2-/- mice to restrict tumor growth relative to C57/BL6 mice. Additionally, our sc-ATAC-seq analyses revealed shared and differential cis-regulatory elements in NGBs, IDHmut, IDHwt glioma-associated immune cells. In particular, genes associated with IFN-/IL-12/IL-10 pathway were negatively regulated in IDHmut/IDHwt MG compared to homeostatic MG in NGBs. In summary, our study sculpts transcriptional and epigenomic details and re-defines glioma-specific immune contexture, and specifically identifies TREM2 as an anti-glioma immunotherapy target.

PDF 29

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LIGHTNING TALK

Keywords: adult stem cell, cancer biology, transcriptomics and epigenomics, organoids, systems biology

Human distal lung maps and lineage hierarchies reveal a bipotent progenitor

Mapping the spatial distribution and molecular identity of constituent cells is essential for understanding tissue dynamics in health and disease. We lack a comprehensive map of human distal airways, including the terminal and respiratory bronchioles (TRBs) implicated in respiratory diseases1–4. Here, using spatial transcriptomics and single cell profiling of microdissected distal airways, we identify previously uncharacterized, molecularly distinct TRB cell types. These include airway associated LGR5+ fibroblasts and TRB-specific alveolar type-0 (AT0) and TRB-secretory cells (TRB-SCs). Connectome maps and organoid-based co-cultures reveal that LGR5+ fibroblasts form a signalling hub in airway niche. AT0 and TRB-SCs are conserved in primates and emerge dynamically during human lung development. Using non-human primate lung injury model, and human organoids and tissue specimens, we show that alveolar type-2 cells (AT2) in regenerating lungs transiently acquire an AT0 state from which they can differentiate into either alveolar type-1 cells or TRB-SCs. This differentiation program is distinct from that identified in the mouse lung5–7. Our study revealed mechanisms driving bi-potential AT0 cell-state differentiation into normal or pathological states. In sum, our study revises human lung cell maps and lineage trajectories, and implicates a novel epithelial transitional state in primate lung regeneration and disease.

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PDF 29

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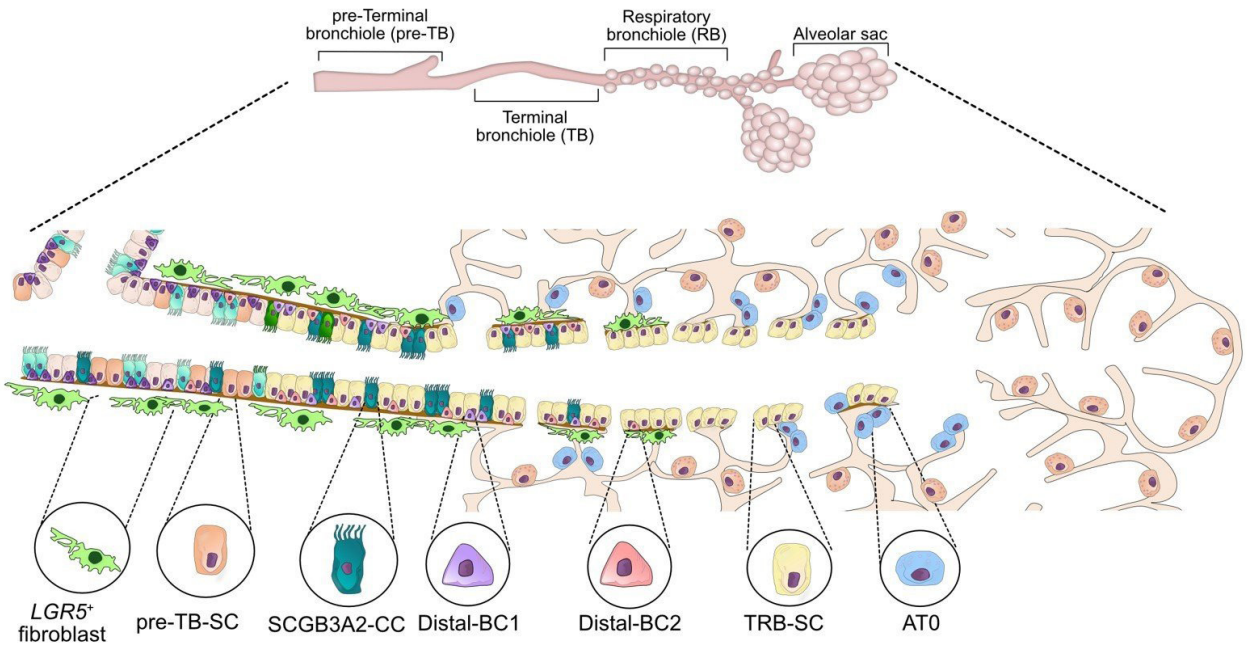

Schematic showing the human distal airways and alveoli with newly characterised cells highlighted in circles.

PDF 30

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LIGHTNING TALK

Keywords: fatty-acyl amp ligases, diacylglycerol, triacylglycerol, neo-functionalization, stress adaptation

Recruiting coenzyme-A independent fatty acid activation mechanism in eukaryotes for regulating diacylglycerol pools

Diacylglycerol is a well-established second messenger in signal transduction and a known modulator of different membrane properties. Regulating different subsets of diacylglycerols modulates physiological processes is a long-standing notion in the field. However, mechanisms or molecular players capable of such a selective regulation is rare, as most enzymes of lipid metabolism are highly promiscuous. This study reports the recruitment, diversification, and repurposing of the ancient fatty acyl-AMP ligase (FAAL)-like domains found in a conserved Disco-interacting protein 2 (DIP2) for selectively regulating subsets of diacylglycerols using yeast, fly and mouse models. These specific DAGs are toxic to the system, which accumulates during the logarithmic growth phase in yeast and cannot be redirected to any other lipid except triacylglycerols (TAG). It is also important to note that the selective conversion to TAGs requires the upregulation of DIP2 and this reaction cannot be complemented by any of the known acyltransferases in the logarithmic phase. Genetic and chemical screens show that the adenylation activity of FAAL-like domains in DIP2 is neo-functionalized to direct the subset DAGs to specific TAGs. Such a temporal regulation of the DAG subsets by DIP2 is crucial for optimal vacuole-membrane fusion, osmoadaptation and regulation of endoplasmic reticulum stress in yeast. Thus, the study uncovers a metabolic dichotomy in the fate of DAG subsets guiding cellular homeostasis and environmental adaptation. DIP2 has been implicated in several cancers and autism spectrum disorders in humans and also important for virulence in pathogenic fungi, therefore the study provides new avenues to explore these pathophysiological conditions from a diacylglycerol metabolism perspective.

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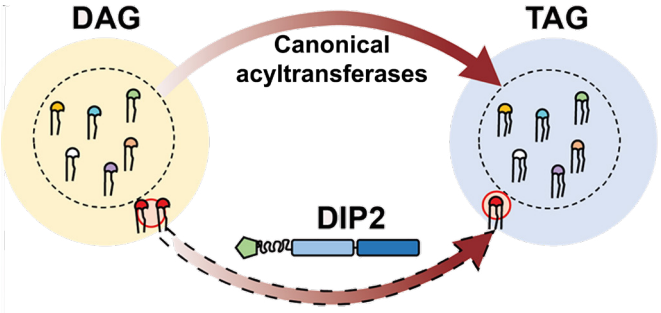

DIP2 regulates a specific subset of diacylglycerols for specific functions

Credits: Modified from Mondal et.al bioRxiv 2022

PDF 31

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LIGHTNING TALK

Keywords: neuroscience, biophysics, synaptic physiology, synaptic transmission, calcium channels

Role of presynaptic CaV2 channels in regulating synaptic vesicle release

The efficacy and kinetics of synaptic transmission relies on the levels and localization of voltage-gated Ca2+ channels (VGCCs) at the presynaptic active zone (AZ). CaV2 channels, a subset of VGCCs, includes CaV2.1, CaV2.2 and CaV2.3 that are primarily expressed in central nervous system synapses. Among them, CaV2.1 is most efficient in action potential (AP)-mediated synaptic vesicle (SV) release. During development, many fast firing presynaptic terminals modify from having mixed CaV2 subtypes to either CaV2.1 dominant or exclusive. Further, to achieve precision, CaV-SV coupling (relative positioning of CaV channels to SVs) switches from microdomain (loosely coupled) at immature stage to nanodomain (tightly coupled) SV release at mature stage. However, it is still unknown if these SV release states depend on the CaV2 subtype. Calyx of held (calyx), a fast firing presynapse like many central synapses transforms from having mixed CaV2 subtypes to CaV2.1 and switches its release state form micro- to nanodomain during development. Therefore, to understand the relation between CaV2 subtype and SV release states, we conditionally knocked out (CKO) CaV2.1 or both CaV2.1/2.2 at calyx. We observed a partial compensation of calcium current (ICa) in both CaV2.1 and CaV2.1/2.2 CKO calyces. However, we found distinct changes in readily releasable pool (RRP, i.e. AP mediated release) size and SV release kinetics in either CaV2.1 or both CaV2.1/2.2 ablated calyces without altering AZ ultrastructure during both release state. Hence, we propose that CaV2 channels play differential role in SV release states during development.

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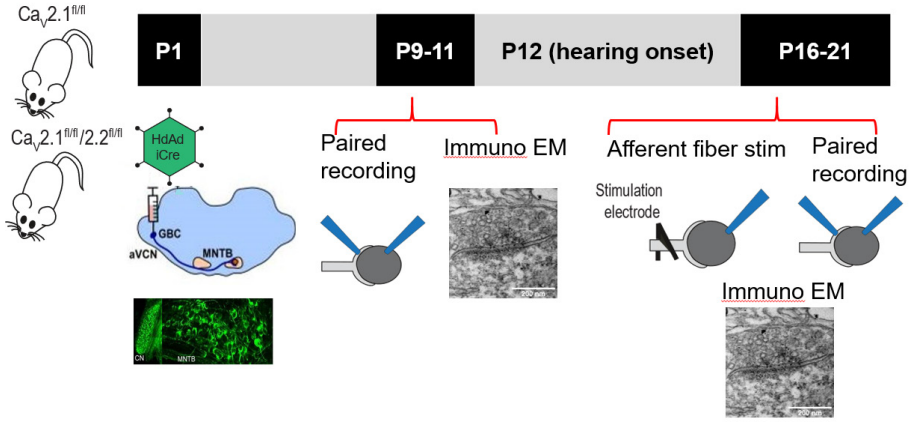
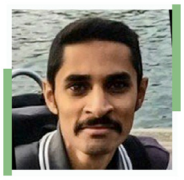


Experimental approach for identifying the role of presynaptic CaV2 channels in regulation synaptic vesicle release



PDF 32

RAJAS M RAO

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LIGHTNING TALK

Keywords: glycobiology, structural bioinformatics, post-translational modifications, molecular modelling, protein dynamics

How do glycosylations influence glycoprotein dynamics & functioning?

Glycosylations are among the most ubiquitous post-translational modifications, with about 20% of all the protein structures in the Protein Data Bank observed to be glycosylated. However, their roles in physiology & disease remains enigmatic. In this regard, molecular modelling techniques has proved to be effective to bridge this knowledge gap. In this work, we describe how changes in glycosylation composition can have significant impact on glycoprotein dynamics & functions, using in silico techniques. We use two examples of N-glycans in L1 domain of insulin receptor & glycosaminoglycans in Fibromodulin.

Insulin receptor (IR) have numerous N-glycans with sialic acid sugars. Experimental studies show that desialylation of IR glycans leads to onset of insulin resistance, & ultimately type-II diabetes. We demonstrate using multi-microsecond simulations that desialylation destabilized dynamics & protein-carbohydrate interactions of insulin-binding residues & perturbed allosteric dynamics of L1 domain. The observations provide a possible structural basis for destabilization of IR signaling & onset of insulin resistance.
Fibromodulin is an extracellular matrix proteoglycan, consisting of long-chain keratan sulphate glycosaminoglycans (GAG) with a smaller protein core. Experimental studies show that the carbohydrate composition of fibromodulin varies with age & diseases. In juvenile individuals, proteoglycan form was the predominant one, while in older-aged individuals, the fibromodulin without long-chain keratan sulphate GAGs were predominant. In diseases like macular corneal dystrophy (MCD), the sulphate groups of the keratan sulphate are absent. Our simulations show how such changes affect dynamics & surface accessibility of fibromodulin. We show that loss of keratan sulphate chains is characterized by loss of shielding, increasing vulnerability of fibromodulin to degradation by proteolytic enzymes, as observed in arthritis. In MCD, loss of sulphate groups disrupts shielding patterns & causes obstruction to protein residues involved in protein-protein interactions. Our observations from these two examples show how glycosylations influence glycoprotein dynamics and their functions.

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PDF 32

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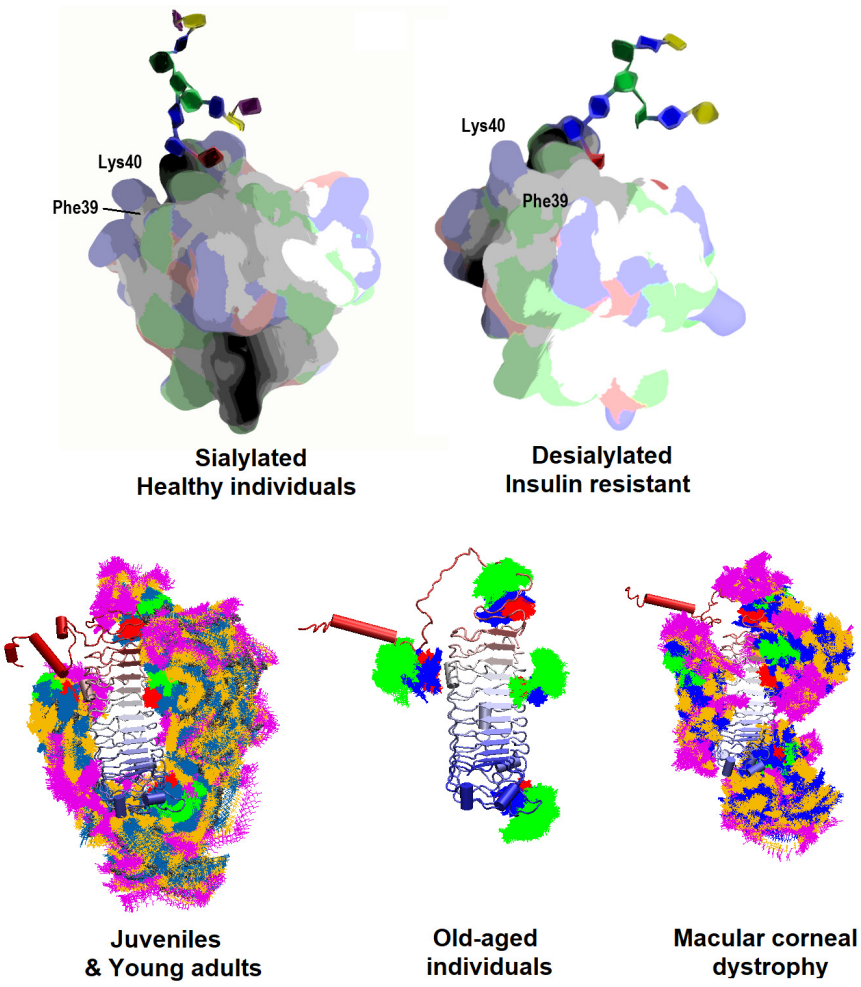

Top: Representation of glycan shadow projection patterns, a proxy for protein surface accessibility on the insulin receptor L1 domain in sialylated & desialylated conditions. Bottom: Snapshots of Fibromodulin showing net sampling of carbohydrate chains in glycosylation states corresponding to different conditions, i.e.., juvenile individuals, old-aged individuals & macular corneal dystrophy.

PDF 33

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LIGHTNING TALK

Keywords: cancer biology, proteomics, ageing, immunity, ageing pathologies

Cell transformation to epithelial-mesenchymal transition and metastases: Finding key pathways, novel signaling-axis and targets for antibody-mediated inhibition

How a cell transforms into a cancer cell and reaches circulation is crucial to understand towards developing preventive and therapeutic solutions. Using a cancer progression model of ovarian cancer, I earlier contributed to identifying transformation-associated pathways and key proteins [1-3]. At the inhibition side, monoclonal antibody-mediated targeting of membrane protein viz. Annexin A2 antigen enabled us to target cancer stem and progenitors cell populations in the tumor [4]. In the exploration of signaling axis involved in the cancer progression, I discovered a novel oncogenic function of CARF, i.e., a nuclear protein [5-7], in the Wnt/β-catenin signaling pathway in promoting epithelial-mesenchymal transition (EMT) and metastases [8-9]. I first analyzed the relevance of CARF levels in clinical tumors and observed its amplification (both at gene and mRNA levels) across several invasive and metastatic cancers. Cancer patient genomic and molecular analyses revealed that CARF activates the Wnt/β-catenin signaling axis, as evident by enhanced nuclear localization and function of β-catenin and subsequent increases in the levels of SNAIL1, SNAIL2, ZEB1, and TWIST1 that serve as its downstream gene targets. Markedly, inhibition of CARF led to a decrease in nuclear β-catenin and its key downstream effectors, involved in EMT progression. Of note, CARF targeting in vivo either by siRNA or shRNA yielded in suppression of tumor growth and lung metastasis. Conclusively, these recent data unravel the clinical and therapeutic relevance of CARF in EMT and cancer metastasis and its potency as a therapeutic target of aggressive cancers.

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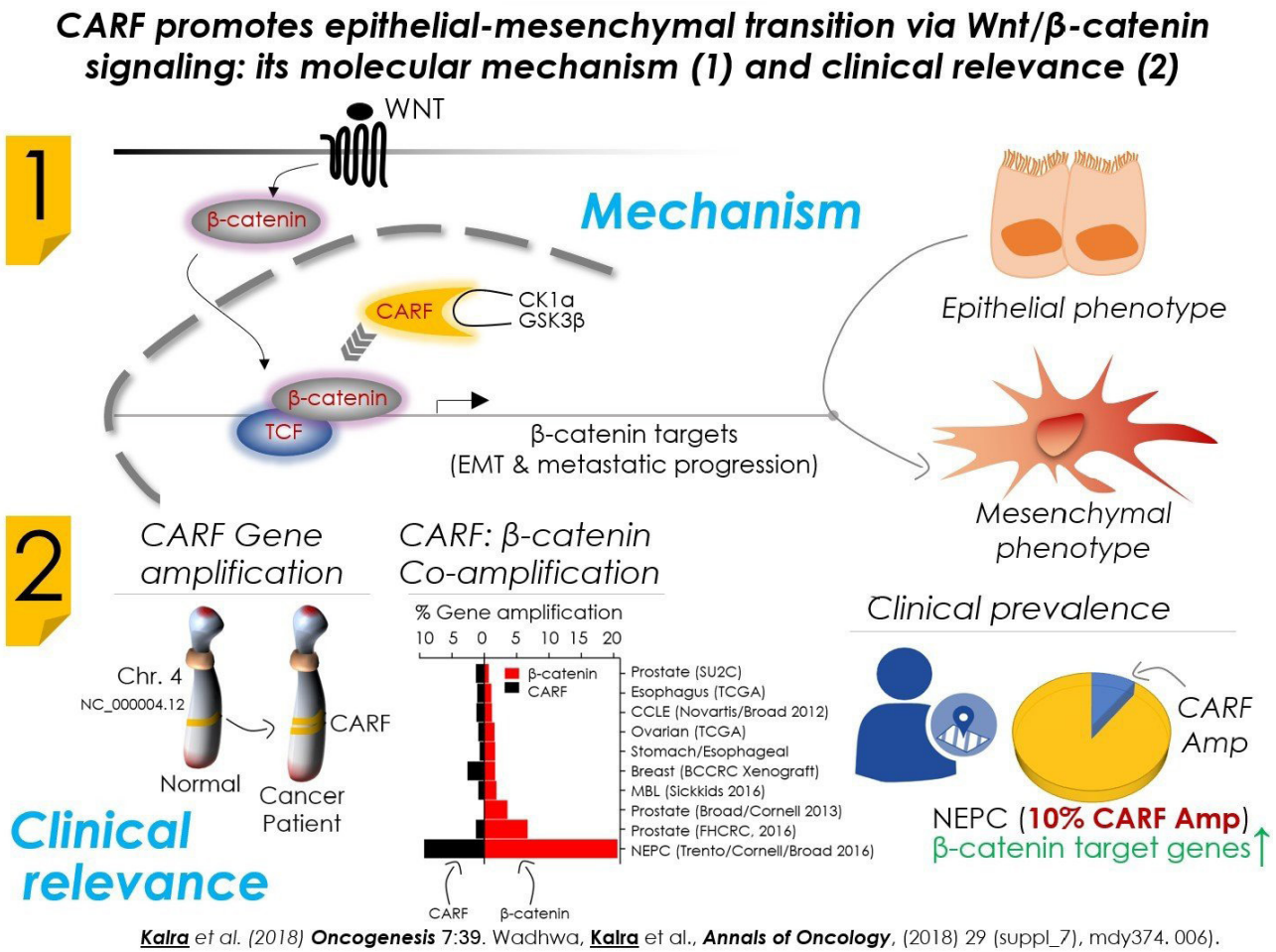

GRAPHICAL ABSTRACT: CARF promotes epithelial-mesenchymal transition via Wnt/β-catenin signaling: its molecular mechanism (1) and clinical relevance (2)
Credits: Self

PDF 34

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LIGHTNING TALK

Keywords: ion channels, calcium dynamics, immune cells, wound healing, cancer immunotherapy

Harnessing the therapeutic potential of ion channels

Ion channels regulate cellular functions by modulating calcium, membrane, cytoskeletal, and organelle dynamics. Cells sense and respond to the environment via their pool of ion channels. The thermosensitive TRP channels regulate the activation of immune cells like T cells, both under physiological T-cell receptor stimulation and during fever.1 During my PhD at NISER Bhubaneswar, I have demonstrated the functional expression of heat sensitive channels TRPV1, TRPV41, and cold sensitive channels TRPA12, TRPM83 in T cells; defined their relevance in T cell activation, proliferation and cytokine production.

My 1st Postdoctoral training was at Karolinska Institutet & Hospital, where I demonstrated that the antidiabetic drug Metformin can be repurposed to induce antimicrobial peptide production by uroepithelial cells in AMPK/TRPA1 dependent manner for improving antibacterial activity against Escherichia coli causing urinary tract infections.4 I am currently Marie Curie Scientia Fellow at University of Oslo. I use multi-color live cell imaging and high-throughput flow-cytometry, genetic engineering to fine-tune strategies for utilizing lysosomal, mitochondrial TRP channels in improving anti-cancer efficacy of Natural Killer cells.

My research proposal for Indian institutes involves understanding the physiological and pathological function of ion channels in immune cells, and devise strategies for superior tissue restoration, including cancer immunotherapy.

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PDF 34

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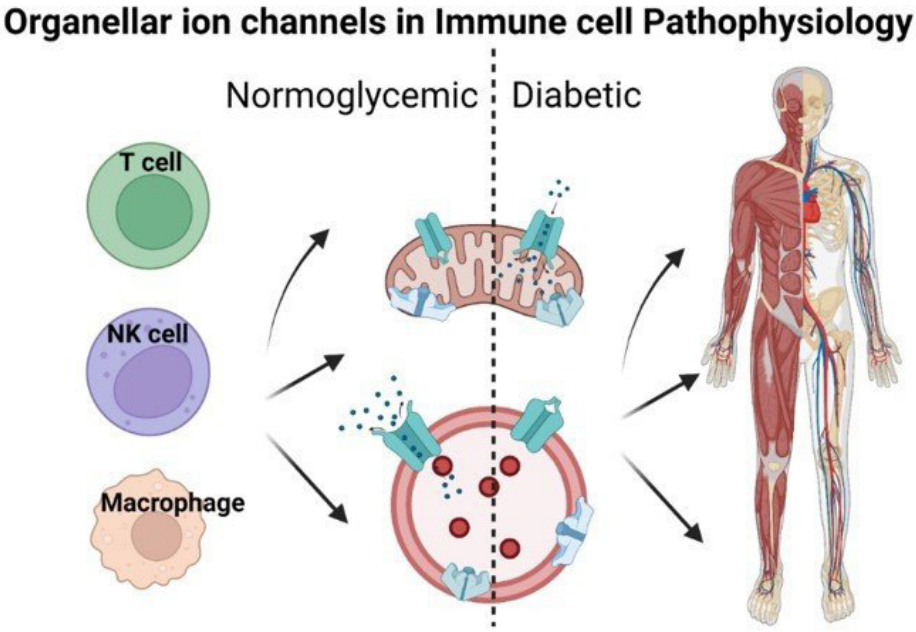

Modulation of Organellar Ion channels in Immune cell pathophysiology
Credits: self

PDF 35

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LIGHTNING TALK

Keywords: immune cells, infectious diseases, vaccines, follicular helper t cells, autoimmune diseases and cancer

Immune responses in the settings of infections and vaccines

The human immune system is a potent and orchestrated defense system capable of continuously fighting disease causing agentsthrough production of specific antibody molecules and lymphocytes capable of reacting and inactivating foreign or infectious agents. While the immune system is well equipped to fight most of the infectious agents, it fails to do so in case of highly variable viral diseases such as hepatitis B, influenza, HIV and more recently COVID-19 requiring therapeutic interventions for disease control or vaccines for prevention. Broadly neutralizing antibodies (BnAbs) directed at conserved regions of surface proteins hold great potential for vaccine and drug design because of their ability to neutralize most strains of antigenically variable pathogens. The rare and sporadic development of these potent BnAbs in a subset of patients and identification of multiple bnAbs targets in HIV-1, influenza, zika and numerous viral envelope proteins has guided immunogen design and given strong impetus to vaccine field. However, a successful vaccine strategy for inducing bnAbs require selective and efficient elicitation of specific germline precursors and is further dependent on T follicular helper cells and germinal center responses and memory formation. Using knock in (KI) mice expressing Ig V(D)J/VJ sequences encoding predicted germline sequences of BnAbs for specific viral envelope proteins and surrounding glycans, we have defined and progressed further in designing iterative immunizations aimed at eliciting BnAbs against HIV and other infectious diseases. These studies provide breakthrough strategies and understanding of immunization regimens for vaccines limited not only to HIV-1 but have broad implications in other infectious diseases such as SARS-CoV-2.

References:

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PDF 36

RATAN MURTY

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LIGHTNING TALK

Keywords: visual recognition, intelligence, algorithms, artificial intelligence, generative algorithms

Reverse-Engineering Human Vision

The last quarter century has provided extensive evidence that some regions of the human cortex are selectively engaged in processing a single specific domain of information, from faces, places, and bodies to music, language, and other people's thoughts. This work dovetails with earlier theories in cognitive science highlighting domain specificity inhumancognition, development, and evolution.But many questions remain unanswered about even the clearest cases of domain specificity in the brain. In my talk I will describe a series of experiments that investigate two such outstanding questions about the cortical organization of the human ventral visual cortex (VVC).

References:

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PDF 37

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LIGHTNING TALK

Keywords: lipid metabolism, obesity, extracellular matrix, diabetes, cell signaling

Integrin-mediated regulation of intestinal lipid metabolism.

The small intestine has an underappreciated role as a lipid storage organ. Small intestinal epithelial cells or enterocytes temporarily store dietary lipids in cytosolic lipid droplets, limiting postprandial lipemia after a fatty meal. The action of triglyceride hydrolases subsequently breaks down these cytosolic lipid droplets for further processing to generate chylomicrons. In obesity, intestinal insulin resistance removes the suppressive effect of insulin on chylomicron production leading to more severe postprandial lipemia. Despite clinical significance, the precise mechanism that governs cytosolic lipid droplet homeostasis in enterocytes is understudied.

We have previously shown that integrin ligand Milk fat globule-EGF-like 8 (MFGE8) in addition to promoting dietary lipid uptake, augments lipid droplet hydrolysis in enterocytes [1,2]. Here we investigated the molecular signaling pathway that regulates hydrolysis of diet-derived lipid droplets downstream of the MFGE8. We report that MFGE8 regulates the transcription of carboxylesterase1 family of hydrolases via controlling lipid-sensing transcription factor Hepatocyte nuclear factor-4 gamma (HNF4γ), as revealed by RNA sequencing and chIP sequencing analysis. Mice deficient in Hnf4γ or Ces1d (mouse ortholog of human Ces1) accumulate cytosolic lipid droplets in enterocytes after a meal owing to impaired TG hydrolase activity as confirmed by activity-based proteome profiling. Mechanistically, MFGE8 promotes fatty acid absorption, which subsequently stabilizes the HNF4γ protein level leading to augmented Ces1 gene transcription potentiating postprandial lipemia. Our data, therefore, identify a crucial link between dietary fat absorption and postprandial lipemia, which have significant implications in obesity and diabetes. We have also demonstrated that MFGE8-integrin axis confers peripheral insulin resistance [3], providing further scientific basis for developing integrin-based therapeutic regime to combat obesity and diabetes. My future research will focus on understanding how extracellular matrix and tissue fibrosis regulate lipid droplet homeostasis at the cellular level, which has implications in multiple metabolic disease forms [4] including hepatic steatosis and obesity.

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PDF 37

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PDF 38

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LIGHTNING TALK

Keywords: host-pathogen interaction, autophagy, ubiquitin, innate immune signaling, mitochondria

Phosphoribose linked serine ubiquitination of syntaxin17 regulates formation of bacterial vesicles which escape lysosomal degradation.

Legionella pneumophila is a pathogenic gram negative bacteria that causes a severe form of pneumonia called Legionnaires' disease. Upon infection it injects more than 300 effector proteins into the host cell which rewires the host cell metabolism to facilitate bacterial growth and replication. SidE proteins are one such class of effectors which hijack the host cell ubiquitination machinery by phosphoribosylating Ubiquitin (PR-Ub) and then attaching it to serine residues of host proteins. Around 180 host proteins are PR-ubiquitinated during infection suggesting a global effect of host cell metabolism. The autophagosomal SNARE proteins Syntaxin17(STX17) and SNAP29 were found to be PR-ubiquitinated during infection. Modification of STX17 by PR-ub helps in generating bacterial vesicles which escape lysosomal fusion. This process of vesicle synthesis hijacks the autophagic machinery of the host cell. Using microscopy based studies and proximity labelling approaches we deciphered the molecular interactions that occur between STX17 positive bacterial vesicles and host proteins which prevents lysosomal degradation of intracellular bacteria.

References:

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PDF 39

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LIGHTNING TALK

Keywords: single-cell, genomics, rna-seq, evolution, chromatin

Unraveling the role of sequence and chromatin state on the evolution of transcriptional regulation using single-cell data

The seminal works of Britten & Davidson and King & Wilson proposed that phenotypic differences observed in species with high genetic similarity could arise from differences in regulatory mechanism of the genes. Regulation of a gene depends not only on the sequence context of its cis-regulatory elements (CREs) and the associated chromatin and epigenetic state. Despite the rapid turnover (birth and death) of active CREs at orthologous regions, the expression of orthologous genes and gene-regulatory circuits in homologous tissues is largely conserved across mammals. This functional homology of gene expression is dependent on the molecular homology of the combinatorial regulatory system and its underlying sequence. However, a comprehensive understanding of the role of molecular homology in driving functional homology remains largely uncharacterized. In particular, there is a lack of quantitative models that can characterize the evolution of gene expression using sequence, epigenetic, and chromatin state.

The rapid development of single-cell based transcriptomics, epigenomics, and multimodal technologies that allow simultaneously profiling the gene expression and chromatin landscapes in diverse cell populations provides unprecedented opportunities to characterize the evolution of gene expression in homologous cell types across species. My central hypothesis is that conserved gene expression is a function of both conserved sequence and conserved epigenetic and chromatin state. We profiled chromatin state and gene expression in the motor cortex of four species: pig, ferret, sheep, and chicken. We characterized conserved and lineage-specific chromatin states and associated transcriptional regulation. I am developing computational methods to analyze this data to answer two long-standing questions: 1) contribution of cis-regulatory activity in transcriptome evolution; and 2) to what extent can evolution in gene expression be explained by sequence evolution alone.

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PDF 40

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LIGHTNING TALK

Keywords: zebrafish, chemical genetics, cardiovascular biology, thoracic aortic aneurysm, heart failure

Molecular dissection and chemical intervention of cardiovascular diseases in zebrafish

Cardiovascular disease (CVD) is the leading cause of death in India. Aortopathies are a group of CVDs affecting the aorta and include degenerative aortic disease, bicuspid aortic valve disease, and hereditary aortopathy. Thoracic aortic aneurysm and dissections (TAAD) are major complications of degenerative and hereditary aortopathy. Thoracic aortic aneurysm (TAA) is a progressive pathological expansion of the aorta and may cause aortic dissection and rupture, which is a life-threatening complication in humans. Mutations in genes related to transforming growth factor-β (TGF-β) signaling are associated with TAA and therefore suspected to play a role in TAA development and progression. To better understand the role of TGF-β signaling in TAA, I developed a zebrafish model of thoracic aortic aneurysm by creating and characterizing double homozygous mutations in the latent TGFβ binding protein (ltbp) 1 and 3 genes. Beyond establishing a relevant model system for TAA research, our results provided significant insight in understanding the contribution of TGFβ signaling in disease pathogenesis, which has been controversial in the field for many years. To date, there is no drug in the clinic that can prevent and or restore aortic wall deterioration. I designed a small molecule screening platform in zebrafish. A pilot screening data demonstrated that this platform can be used as a potential tool to find novel therapeutic compounds to treat TAAs.

In my independent research program, I have three main goals. First, I will interrogate fundamental cellular signaling pathways underlying the development of zebrafish outflow tract (equivalent to the human aorta). Second, I will investigate the role of vascular smooth muscle cells [(VSMC), which are the major component of the middle layer of the aorta] in the disease pathogenesis of TAAs and myocardial infarction. Finally, I will perform small molecule screening to ameliorate disease phenotypes, primarily using zebrafish as a model system.

References:

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PDF 40

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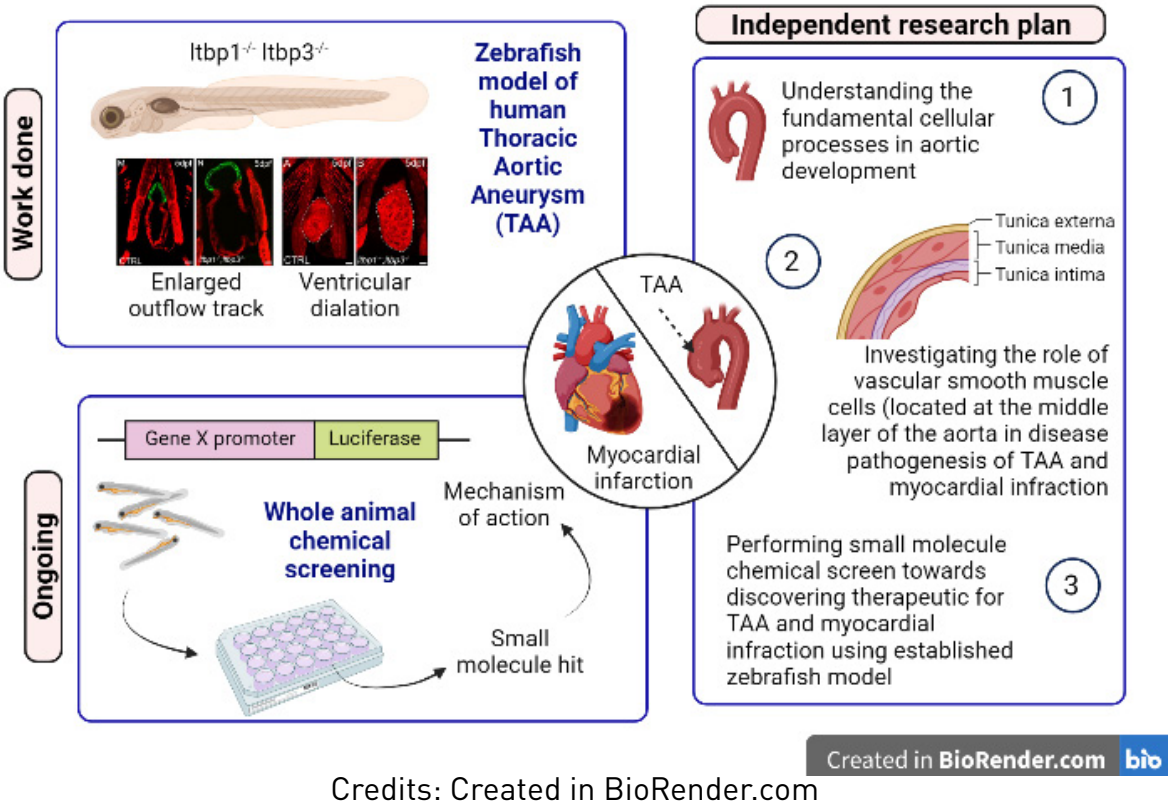

Credits: Created in BioRender.com

PDF 41

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LIGHTNING TALK

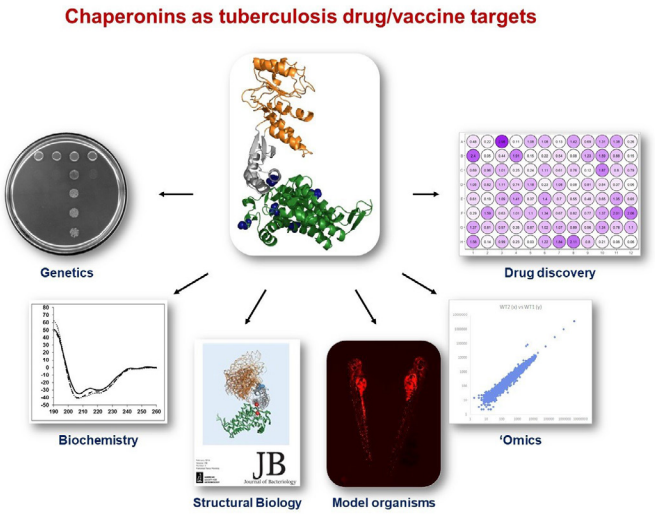
Keywords: tuberculosis, latency, chaperonins, groel, zebrafish

Chaperonins and Tuberculosis; exploring the connection.

Tuberculosis, caused by Mycobacterium tuberculosis (Mtb), is the second largest killer after AIDS. Mtb evades immune attack by residing in granulomas formed principally by human macrophages. Molecular events towards granuloma formation, although are not completely understood, depend, in part, on a non-essential chaperonin homologue, Cpn60.1. Since pathogenicity and slow growth make Mtb difficult to study, in my project I developed an infection system using a related bacterium, M. marinum, that infects Zebrafish and forms caseating granulomas similar to M. tuberculosis infection in humans. I have generated M. marinum cpn60.1 knock-out, confirmed by WGS and compared its infectivity in zebrafish. While the mutant is indistinguishable with its wild type in planktonic growth, it showed lower infectivity and persistence in the zebrafish embryos, resulted in lower expression of immune markers and showed differences in non-polar membrane lipid composition, suggesting an important role for Cpn60.1 in mycobacterial infections. Although quantitative proteomic and RNAseq studies suggested a chaperonin function to Cpn60.1, zebrafish infection studies with ATPase mutants that lack chaperonin activity, established that Cpn60.1 moonlights as a cytokine stimulator. Moreover, Cpn60.1 knockout failed to form biofilms, suggesting a morphological differences in the bacterial cultures. Since Cpn60.1 plays an important role in TB establishment, these studies, therefore, bear the potential for novel non-antibiotic related treatments for TB.

References:

This part of the work is unpublished.



Multipronged approach to develop chaperonins as tuberculosis drug/vaccine candidates

PDF 42

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LIGHTNING TALK

Keywords: altruism, cooperation, multicellularity, endosymbiosis, programmed cell death, Dictyostelium, Pseudomonas, cheating

How do microorganisms avoid exploitation?

The evolution of cooperation by natural selection is puzzling. This is because cooperation is a phenomenon where organisms perform certain behaviors which are beneficial to other individuals (e.g., alarm calls by meerkats to alert conspecifics to potential danger) and, in certain instances, can even reduce the fitness of cooperators (altruism). Furthermore, the non-cooperating mutants (cheaters) can evolve and destroy the established cooperation. Despite these challenges, cooperation is rampant and observed in organisms spread across the tree of life. Microorganisms show a range of cooperative behaviors such as starvation-resistant fruiting body formation in Dictyostelium amebae and Myxobacteria and production and sharing of metabolically expensive molecules (public goods) in bacteria. These behaviors can be exploited by mutants which either do not form dead stalk cells in fruiting bodies of amoebae or do not produce public goods in bacteria. I will use examples of cooperative behaviors in Dictyostelium amoebae and Burkholderia, and Pseudomonas bacteria to show the molecular mechanisms of how these organisms avoid exploitation and maintain stable cooperation.

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PDF 43

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LIGHTNING TALK

Keywords: transcription factors, cell-free DNA, structural epigenome, DNA methylation, cancer monitoring

Using cell-free DNA to improve cancer survival

In India, ~95% of non-small cell lung cancers (NSCLC) are diagnosed at stages III/IV compared to 70% in the USA (Vashistha et al., 2019). Early detection of lung cancers significantly improves survival (Blandin Knight et al., 2017). Although low-dose computed tomography works well for early detection, its footprint is far from ubiquitous in India. Blood collection on the other hand is far more feasible at most testing centers. Thus, a highly sensitive and specific blood test to detect lung cancer can enable detection earlier than what is currently happening for a wider swathe of the population.

DNA from the tumor and its microenvironment can be detected as part of circulating cell-free DNA (cfDNA) in human plasma (Zukowski et al., 2020). cfDNA is a product of endogenous nuclease activity in dying cells, comprising nucleosomal and transcription factor (TF)-bound DNA. These enable the mapping of chromatin structure in the tissue-of-origin. Thus, cfDNA carries both the genotype and phenotype of the tumor. I developed methods to track TF-binding and tissue-of-origin of cfDNA in breast cancers (Rao et al., 2021). Importantly, my method can detect Estrogen Receptor protections at a low level of tumor DNA in plasma to identify ER+ solid tumors.

I aim to establish a research program in India to develop cost-effective blood tests for NSCLC. Tobacco smoking is strongly associated with mutation load and induces apoptosis, thus contributing to both genotype and phenotype of the lung to cfDNA. Thus, cfDNA sequencing and analysis will enable us to track lung health in routine intervals. Significantly, the proposed approach is easily extendable to other cancers, including breast cancer. With rapidly reducing sequencing costs combined with enrichment of actionable regions in the genome and high-level multiplexing of samples, my goal is to develop tests that cost less than ₹2,000.

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PDF 44

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LIGHTNING TALK

Keywords: single-molecule biophysics, protein misfolding and aggregation, nanopores, protein aggregation in neurodegeneration, protein structure-function

Single-particle characterization of protein aggregation

Protein aggregation is a hallmark of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, etc. (1, 2) Aggregation reaction initiates with nucleation leading to the formation of oligomers, protofibrils, and fibrillar aggregates. Small soluble oligomers are recognized as key toxic species implicated in disease pathology and are challenging to characterize using conventional methods. (3, 4) The size and shape of oligomers correlate well with their toxicity, and only certain sized oligomers, with specific shapes, are most toxic. (5) There is an urgent need for a novel label-free approach for the biophysical characterization and quantitative analysis of these species in a solution. We demonstrate the ability of resistive-pulse analysis using the solid-state nanopores to characterize protein aggregation on a single-particle level. We can follow the aggregation kinetics of native and disease-associated mutant proteins and quantitatively determine the size and shape of different aggregation species, including oligomers of various sizes, protofibrils, and fibrils, in solution. The cylindrical diameter estimates of protofibrils and fibrils enable us to determine the amyloid fibril polymorphism. The single-particle level biophysical characterization of oligomeric species will improve the understanding of their neuronal toxicity. Ultimately, the size and shape information of oligomers may facilitate their quantitative analysis as a biomarker and the development of drugs to prevent neurodegeneration in protein misfolding diseases.

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PDF 45

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LIGHTNING TALK

Keywords: Keywords: internal state, sensory cues, hunger, aggression, sleep

Hangry flies: Neuromodulation of protein hunger-induced aggressive behavior in Drosophila melanogaster

The relationship between hunger and aggression, especially in the presence of food-specific chemosensory stimuli is not well understood. One possibility is that hunger, which promotes feeding and food-seeking behaviors also increases aggression, to help animals acquire food. Another possibility is that since feeding is the most important behavior in extreme hunger conditions, it shuts down irrelevant and energy-costly social behaviors such as courtship, mating and aggression. Evidence for both hypotheses suggests that hunger circuits can modulate aggressive behavior depending upon context. Resolving this issue in a systematic manner is key to uncovering neuronal circuits which enable animals to perform a cost-benefit analysis while considering need and availability.

I address this question in Drosophila melanogaster, which display stereotyped and complex aggressive behaviors and serves as an excellent model system providing cell-type specific genetic access. Flies were raised on diets lacking essential nutrients (such as yeast/ amino acids/ sugar), then tested for aggressive behaviors in various contexts. Dietary restriction of yeast or only amino acids in adult flies results in decreased whole-body protein level and increased aggression only when flies encounter yeast subsequently in the assay chamber. To discover the neuronal circuits important for modulating protein-hunger induced aggression, we functionally screened for neurons whose activity is important for aggression induced only in the context of protein deprivation. The screen identified several promising candidates including neurons expressing Hugin, which is also important for feeding behavior. Silencing hugin neurons in protein-hungry state suppresses aggression context-specifically, whereas artificial activation of hugin neurons in fed flies increases aggression only in the presence of yeast. Detailed anatomical characterization and functional analysis of neuronal subsets will help to reveal mechanistic link between hunger and aggression circuits.

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PDF 45

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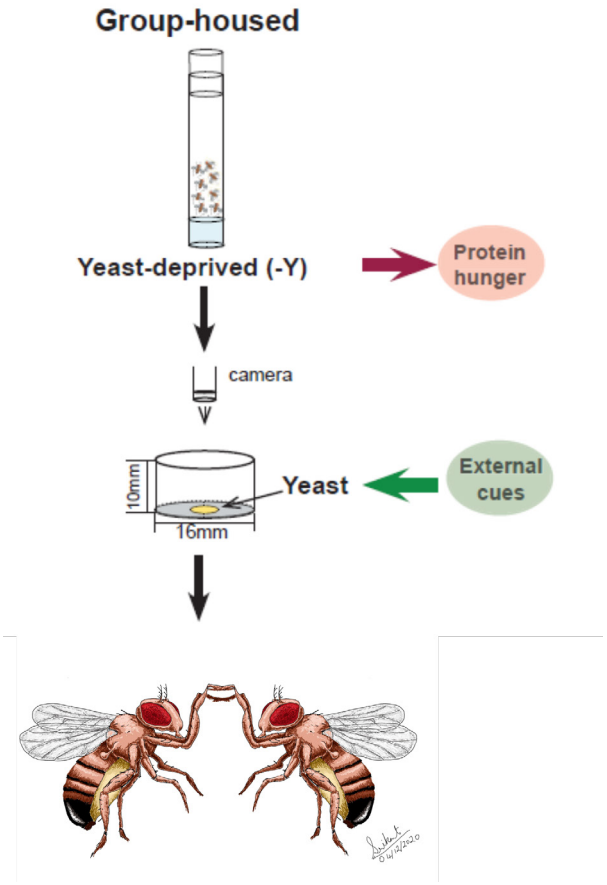

Dietary deprivation of yeast results in protein hunger state, which increases aggression in flies when they encounter a protein-rich source.

PDF 46

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LIGHTNING TALK

Keywords: inter-organelle contacts, lipid dynamics, genetics/proteomics screening, photoreceptors, retinal degeneration

CG3860, a lipid transfer protein, potential regulator of phototransduction.

Non vesicular lipid transfer has emerged as an important route to efficiently move various lipids across organelle membranes in a cell. Protein which are required for this transfer are named as lipid transfer proteins (LTPs). Oxysterol binding proteins (OSBP) and OSBP-related proteins (ORPs) is one such sub-group of LTP required to transfer oxysterols/phosphoinosites. In a recent RNAi genetic screen performed in our lab, knockdown of CG3860, in photoreceptors of Drosophila melanogaster, was found to suppress retinal degeneration found in retinal degeneration B protein hypomorph (rdgB9). CG3860 is a human homologue of ORP1 short form (ORP1S) and existing studies in mammalian cell lines have proposed the transfer of cholesterol from late endosome/lysosome to plasma membrane as its function. We have found that CG3860 is enriched in retinal tissue. Thus, to further understand its role in animal physiology we have generated two independent CRISPR/Cas9 mutant lines which were confirmed via qPCR. Both mutant lines (CG3860_4111 and CG3860_181) show reduced electrical response to light in comparison to wild type. CG3860_4111 mutant line was chosen for further characterization and shows light dependent retinal degeneration. Surprisingly, double mutant rdgB9;CG3860_4111 shows extreme enhancement of retinal degeneration which is an opposite result to the RNAi study and require further investigation. Electroretinogram (ERG) defect and light dependent retinal degeneration could possibly mean a regulatory role of CG3860 via its cholesterol transfer in the phototransduction pathway and how that exactly happens is currently actively investigated.

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PDF 47

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LIGHTNING TALK

Keywords: transcription, RNA polymerase, microbial genetics, phage therapy

Mycobacteriophage induced modifications in mycobacterial RNA polymerase

Mycobacteriophage D29 infects species belonging to the genus Mycobacterium including the deadly pathogen Mycobacterium tuberculosis. D29 is a lytic phage, although, related to the lysogenic mycobacteriophage L5. This phage is unable to lysogenize in mycobacteria as it lacks the gene encoding the phage repressor. Infection by many mycobacteriophages cause various changes in the host that ultimately leads to inactivation of the latter. One of the host targets often modified in the process is RNA polymerase. During our investigations with phage D29 infected Mycobacterium smegmatis (Msm) we observed that the promoters from both phage, and to a lesser extent those of the host were found to be more active in cells that were exposed to D29, as compared to the unexposed. Further experiments indicate that the RNA polymerase purified from phage infected cells possessed higher affinity for promoters particularly those that were phage derived. Comparison of the purified RNA polymerase preparations from infected and uninfected cells showed that several ancillary transcription factors, Sigma factor F, Sigma factor H, CarD and RbpA are prominently associated with the RNA polymerase from infected cells. Based on our observations we conclude that the higher activity of RNA polymerase observed in D29 infected cells is due to its increased association with ancillary transcription factors.

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PDF 48

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LIGHTNING TALK

Keywords: virus, RNA, mosquito, host, antivirals

Dengue RNA-protein interactions that modulate infection in the mosquito host

Arthropod-borne viruses infect both mosquito and mammalian hosts. While much is known about virus-host interactions that modulate viral gene expression in their mammalian host, much less is known about the interactions that involve inhibition, subversion or avoidance strategies in the mosquito host. A novel RNA-Protein interaction detection assay was used to detect proteins that directly or indirectly bind to dengue viral genomes in infected mosquito cells. Membrane-associated mosquito proteins Sec61A1 and Loquacious (Loqs) were found to be in complex with the viral RNA. Depletion analysis demonstrated that both Sec61A1 and Loqs have pro-viral functions in the dengue viral infectious cycle. Co-localization and pull-down assays showed that Loqs interacts with viral protein NS3 and both full-length and subgenomic viral RNAs. While Loqs coats the entire positive-stranded viral RNA, it binds selectively to the 3' end of the negative-strand of the viral genome. In-depth analyses showed that the absence of Loqs did not affect translation or turnover of the viral RNA but modulated viral replication. Loqs also displayed pro-viral functions for several flaviviruses in infected mosquito cells, suggesting a conserved role for Loqs in flavivirus-infected mosquito cells.

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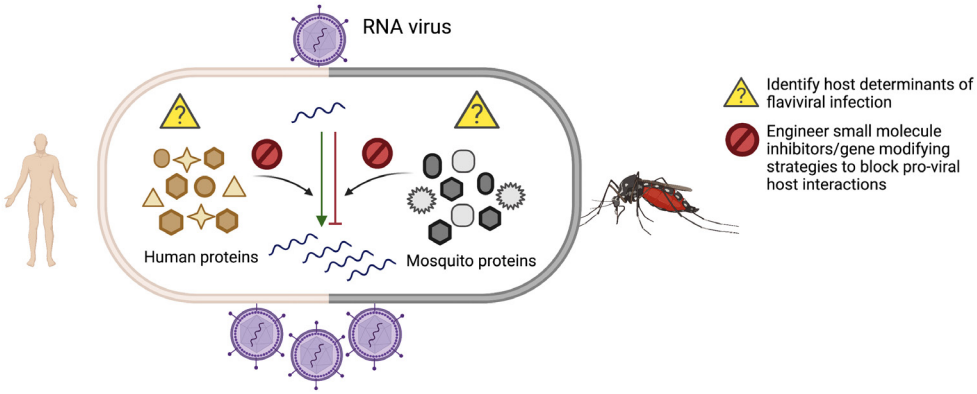

Identification of viral RNA replication regulators in human and mosquito hosts
Credits: Biorender.com

PDF 49

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LIGHTNING TALK

Keywords: development, stem cells, organoids, genome editing, disease modeling

Self-organization of embryonic stem cells into mammary organoids: novel approaches to modeling disease and development

The self-organization of embryonic stem cells (ESCs) to form organoids has opened new avenues to our understanding of stem cell and regenerative biology, organogenesis, and disease mechanisms. Although organoid culture conditions have been developed to generate "mini-organs" from tissue adult stem cells and pluripotent stem cells, the generation of mammary organoids from ESCs is a challenge. Taking cues on how the mammary gland develops in vivo, and how evolutionarily hair follicles have diverged to form the mammary glands, we report an optimized in vitro condition for the generation of mammary organoids, that mimic the tissue organization of a functional mammary gland. We have customized an organoid culture system by self-organizing ESCs that differentiate to form complex skin and associated skin appendages. We use stepwise modulation of BMP, TGFβ, and FGF signaling pathways to co-induce surface ectoderm and mammary mesenchymal cells within an embryoid body. We show that an antagonistic interaction between BMP and Hedgehog signaling in the spherical cell aggregate can block the formation of hair follicles in the dermal mesenchyme and promotes mammary lineages, concomitant with embryonic mammary commitment. We recapitulate the dermal-epidermal interaction in these organoids and the development of mammary lineages characterized by hormone sensing luminal and myoepithelial cells. The lactogenic hormonal stimulation led to the secretion of milk proteins into the organoid lumen further confirming the functional capacity of mammary organoids. We anticipate that the mammary organoids derived from ESCs will be a powerful model to study the evolution of skin appendages, understanding mammary organogenesis, and can be used as a complementary system to remodel breast cancer tumorigenesis.

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PDF 50

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LIGHTNING TALK

Keywords: R-loops, genome stability, DNA damage response, chromatin, eukaryotic transcription

Transcription dynamics prevent RNA-mediated genomic instability

I worked on different projects to understand the cross-talk between transcription and DNA damage. Our data provide a novel framework for interpreting the reciprocal interactions between transcription and DNA damage at distinct chromatin regions. We initially reported that Histone methyltransferase SETD2 coordinates nucleosome dynamics during transcription and further regulates DNA double-strand break repair in transcriptional units. However, I was particularly interested in understanding the molecular sensor of co-transcriptional R-loops (or RNA-DNA hybrids). In this regard, we reported that aberrant pausing of RNA polymerase II (RNAPII) initiates a signaling cascade whereby the serine/arginine protein kinase 2 (SRPK2) phosphorylates the DEAD-box helicase 23 (DDX23), culminating in the suppression of R-loops. We were the first to describe the role of SRPK2 and DDX23 in R-loop-mediated DNA damage. Also, RNAPII can signal DNA repair factors or initiate non-canonical transcription in the gene body. We also found intron evolution as a strategy to alleviate opportunistic R-loops in eukaryotes.

Building on these findings, I recently discovered a previously uncharacterized functions of Mixed-lineage leukemia (MLL) protein (a histone methyltransferase) and histone 3 lysine 4 di-methylation (H3K4me2) modifications at repetitive genomic DNA (e.g., centromeres and ribosomal DNA). To this end, I have found that sub-optimal levels of MLL augments cellular R-loops to pathological levels, which can lead to DNA damage. MLL and H3K4me2 maintain R-loops homeostasis both at canonical RNAPII transcribing genes as well as at centromeres; failure of which leads to aberrant pausing or hinderance of elongating RNAPII and hence downregulates centromere transcripts. Furthermore, downregulation MLL (and other proteins from the same family) challenges centromere DNA integrity. Altogether, our data reveal a novel molecular framework where both the H3K4 methylation and the methyltransferases regulate centromere stability and may prevent tumorigenic events.

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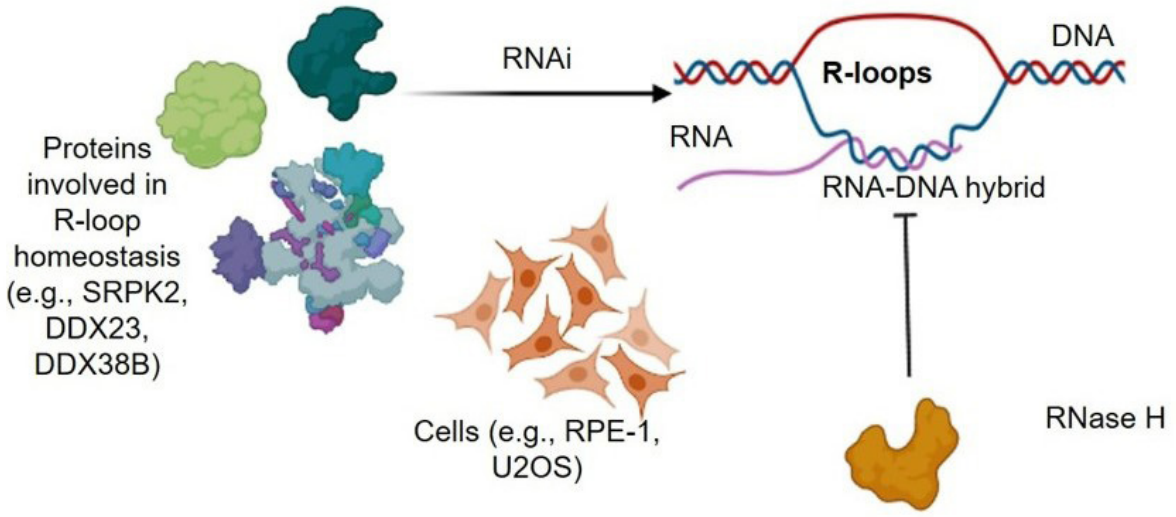

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LIGHTNING TALK

Keywords: cellular & organismal stress response, epigenetics, aging, chromatin biology, proteostasis

Understanding the mechanisms of neuronal regulation of stress response and inheritance of epigenetic memory of stress in C. elegans

When exposed to unfavorable conditions, cells maintain protein homeostasis by robust synthesis of heat shock proteins due to stress-induced activation of the transcription factor heat shock factor 1 (HSF1) – a process known as heat shock response (HSR). HSR is regulated cell autonomously in eukaryotic cells, however; in metazoans, HSR is also regulated cell non-autonomously by the nervous system. In Caenorhabditis elegans, neuronal regulation of HSR occurs through activation of thermosensory neurons and release of the neurotransmitter serotonin (5-HT). My work shows that 5-HT released by maternal neurons upon stress activates HSF1 and initiates a conserved transcriptional program in the germline, which ensures the viability of future offspring. The intracellular signal transduction pathway by which 5-HT release activates HSF1 is conserved in C. elegans and mammalian neurons and occurs through activation of Protein Kinase A which enables HSF1 to alter chromatin in soon-to-be fertilized germ cells by recruiting histone chaperone FACT (FAcilitates Chromatin Transcription), displacing histones and initiating protective gene expression1. This study uncovers a novel mechanism by which stress sensing by neurons is coupled to transcription response times of germ cells to ensure survival of future offspring.

In many organisms including C. elegans, the memory of early-life exposure to environmental stress is 'preserved' through unknown mechanisms and alters later-life cellular programs. My study uncovers a novel mechanism whereby in response to stress, the germline activity of the conserved transcription factor HSF1 recruits the repressive histone H3K9 methyltransferase MET-2 (SETDB1 in human) to insulin receptor daf-2 and other HSF1 target genes. The increased H3K9me2 levels persist in adults decreasing their stress responsivity but at the same time, enhancing their stress resilience by activating the C. elegans FOXO ortholog DAF-16. This mechanism represents a novel and consequential function of HSF1 in the establishment of a heritable epigenetic memory of stress2.

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PDF 52

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LIGHTNING TALK

Keywords: immunology, cancer biology, cell signaling, immunotherapy, post-translational modifications

Targeting pancreatic cancer by TAK-981: a SUMOylation inhibitor that activates the immune system and blocks cancer cell cycle progression in a preclinical model

Pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancer types, responsible for the death of more than 430000 patients worldwide yearly. PDAC has a 5-year overall survival of 9%. Poor survival from PDAC is attributed to its high aggressiveness, intrinsic chemotherapeutic resistance and lack of targetable oncogenic pathways, therefore necessitating new treatment avenues. The small ubiquitin-like modifier (SUMO) signaling cascade is critical for cell cycle progression and it's upregulation is associated with cancer growth. We have studied whether TAK-981, a novel highly selective and potent small molecule inhibitor of the small ubiquitin like modifier (SUMO) activating enzyme E1 could be used to treat a preclinical syngeneic PDAC mouse model and what is the potential mode of action of this inhibitor.

We found that SUMOylation is increased in PDAC patient samples compared with normal pancreatic tissue. In vitro TAK-981 decreased SUMOylation in PDAC cells without affecting the other related pathways, thereby causing a G2/M cell cycle arrest, mitotic failure and chromosomal segregation defects. TAK-981 efficiently limited tumor burden in the KPC3 syngeneic PDAC mouse model without evidence of systemic toxicity. In vivo treatment with TAK-981 enhanced the proportions of cytotoxic CD8 T cells and natural killer (NK) cells but transiently decreased B cell numbers in tumor, peripheral blood, spleen and lymph nodes. Single cell RNA sequencing of wild type mice lymph nodes and spleen revealed activation of the interferon response on TAK-981 treatment in lymphocytes including T, B and NK cells. TAK-981 treatment of CD8 T cells and splenocytes ex vivo induced activation of STAT1 and interferon target genes in IFNAR1 dependent manner.

Our findings indicate that pharmacological inhibition of the SUMO pathway represents a potential strategy to target PDAC via a dual mechanism: inhibiting cancer cell cycle progression and activating anti-tumor immunity by inducing interferon signaling.

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PDF 53

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LIGHTNING TALK

Keywords: mRNA, lipid nanoparticle, cancer therapeutics, molecular cell biology, confocal microscopy

CKAP5 as a potential therapeutic target in Ovarian Cancer

Targeting cancer cell mitosis is of great interest but present anti-mitotic agents are limited to tubulin binding agents and kinase inhibitors. There is a huge list of microtubule associated proteins that play important role in tubulin function but their therapeutic potential remains largely unexplored due to lack of specific targeting agents. In the present study, with the help of SNALPs we have explored the therapeutic effects of one such MAP, CKAP5, which performs various important functions in mitotic spindle assembly. Analysis of CKAP5 depletion in a solid cancer cell line panel suggested a chemoresistant ovarian cancer cell, NAR as most sensitive cell line. CKAP5 depletion led to various abnormalities in the cell mitosis, including loss of EB3 comet dynamics and stalled metaphase followed by apoptosis. Lethal effect of CKAP5 silencing was further confirmed by in vivo tumour reduction (6 folds) that is corroborated with increased survival post CKAP5 depletion (P<0.005).

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PDF 54

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LIGHTNING TALK

Keywords: computational chemistry, biophysical chemistry, complex liquids and proteins, drug delivery, statistical mechanics and MD simulations

When Two Worlds Meet: Interactions at the Interface of Chemical and Biological Systems

In this talk I will present an overview of my past and present work which has been done at the interface of complex chemical and biological systems. The focus areas of my research involves computational investigations understanding structural and dynamical behavior of complex fluids that form self-assemblies in bulk and under confinement to help the development of application based study relevant to electrochemical devices, and in biochemistry for drug delivery. Room temperature ionic liquid (RTILs) have been recognized for their high complexity originating from their self-assembly or nano-scale aggregate formation.[1, 2] Here long-ranged electrostatic interactions govern the relaxation process which motivates us to understand more on their dynamics. I will first discuss about the heterogeneous aspect of IL from atomistic and coarse-grained molecular dynamics simulation to connect the length- and time- scale.[3-5] Then, I'll emphasize on the structural and transport properties of ionic liquid crystalline (ILC) mesogens, and further developing these as model membrane systems, with hydrophilic and hydrophobic lamellar structure. Some of the future plans regarding development of pharmaceutically active ionic liquid-membrane (AP-IL) as a carrier agent of the drug molecule in targeted drug delivery techniques will be discussed. As interactions play a crucial role in the formation of protein corona on silica-nanoparticles (SiNP) surface to target specific disease cells. Investigations regarding the conformational and functional changes of the adsorbed proteins on the NP surface will also be highlighted. Relaxation and diffusion processes are the fascinating observables witnessed in many complex systems having extremely slow timescales. We will present both an overview of the scope of these processes and the mechanistic paths we have so far uncovered.

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PDF 55

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LIGHTNING TALK

Keywords: insect pollination, tactile sensing, multisensory integration, biomechanics

Insect feeding and plant pollination: mechanics and neural control in natural contexts

How insects find and feed from flowers has profound influence on plant pollination. Several studies have shown how insects use species-specific olfactory and visual cues to navigate to their host plants (1). On approaching flowers, moths and butterflies uncoil their extremely long mouthpart; the proboscis, to probe the flower and target a tiny nectary hole. They find and feed from the nectary within seconds, while hovering over flowers even as the flowers sway in the wind. Moreover, moths feed when light levels are limiting, and vision alone is insufficient to resolve the nectary. Additionally, moth proboscis is a unique structure: it is hydraulically uncoiled and hence has tunable mechanics, is heavily actuated with muscles at its base and along its entire length and finally, richly sensed at its base and along its entire length. Using these pollination interactions, my research aims to understand how insect's sensorimotor dynamics interact with body mechanics to achieve movement control. During my postdoc, I developed a behavioral paradigm to study the close-range interactions of moths with artificial 3D printed flowers and showed that moths actively probe floral surfaces (2). The ability of moths to sense floral features will have profound influence on pollination. Moreover, I studied how these interactions are affected by human activities such as artificial light at night (ALAN) and found that moths perform worse at higher light levels (3). These results provide insights into the dynamic process of multisensory integration of vision and touch in the context of insect pollination. My ongoing work records from mechanosensors at the proboscis base; pilfers to understand how they capture information about proboscis movements. My future research program will integrate behavioral studies, electrophysiology & computational neuroscience and mechanics with comparative studies and field observations to understand how neural systems and mechanics enable behavior in natural world.

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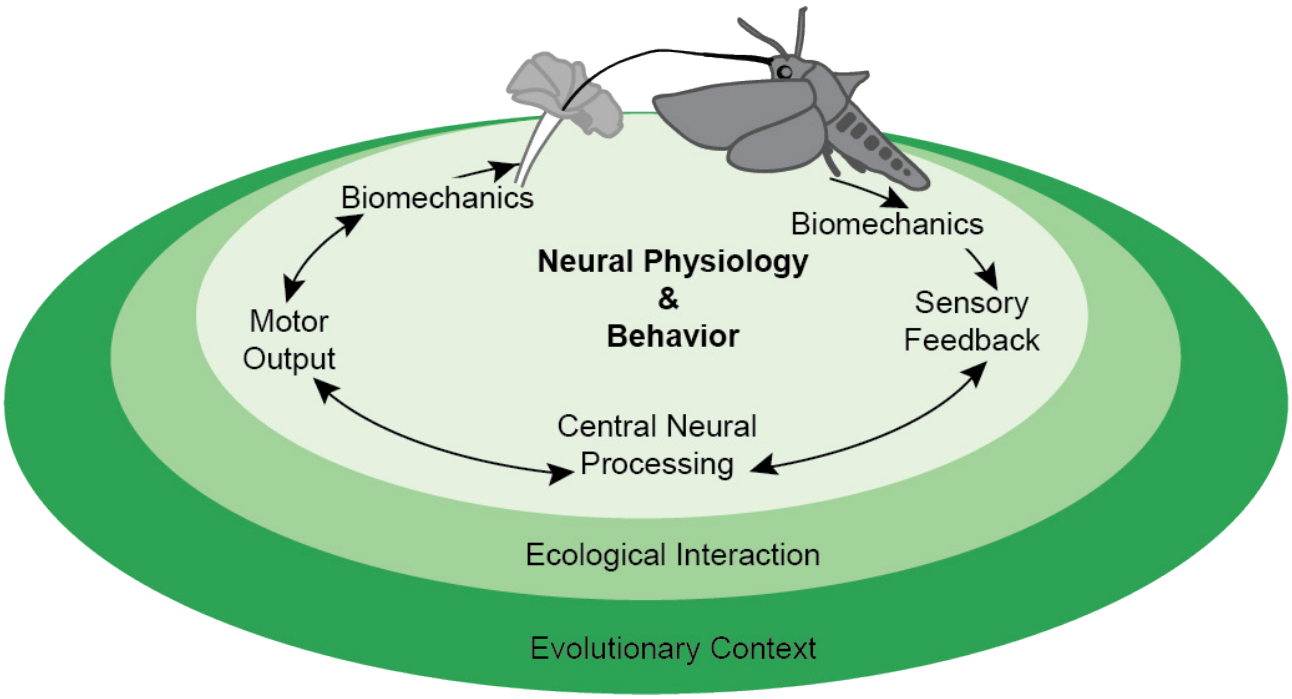

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LIGHTNING TALK

Keywords: Bacillus biofilms, antagonistic enzymes, directed evolution, iron-sulfur cluster enzymes, oxidases

A counter enzyme complex in B. subtilis glutamate metabolism

Glutamate is key metabolite for bacterial cells and maintaining adequate intracellular concentrations is crucial. However, at odds with this notion is the catabolic glutamate dehydrogenase of Bacillus subtilis, GudB, which is constitutively expressed including in glutamate-poor growth conditions. We posited that GudB has to be regulated at the protein level, yet unexpectedly found that it is regulated by binding to its "counter-enzyme" – glutamate synthase, GltAB. When in complex with GltAB, GudB's affinity for glutamate decreases ~20-fold, and addition of Glt's substrates, α-ketoglutarate and NADPH, renders it effectively inactive. This regulation is manifested in unique oscillatory progress curves when α-ketoglutarate is limiting. We used Native mass spectrometry to examine stoichiometry of the proteins in the complex and found that the entire complex is composed of 6 copies of GudB, GltA and GltB. Using cryo-electron microscopy we elucidated the complex's structure and the basis of GudB's inhibition. Counter-enzyme complexes have been seen in signaling, yet not in metabolism. What could be physiological relevance of the complex? While GudB inhibition seems to be a direct answer, this could have been based on a simple allosteric mechanism rather than such complex regulatory mechanism. Such unique mode of regulation may be needed for some unique biochemical demands. We indeed found that the complex formation happens only in the center of the Bacillus biofilm and not in the periphery where GudB is needed. Thus, GudB-GltAB complex formation is central to the metabolic division of labour between the central and peripheral cells and hence optimal biofilm formation.

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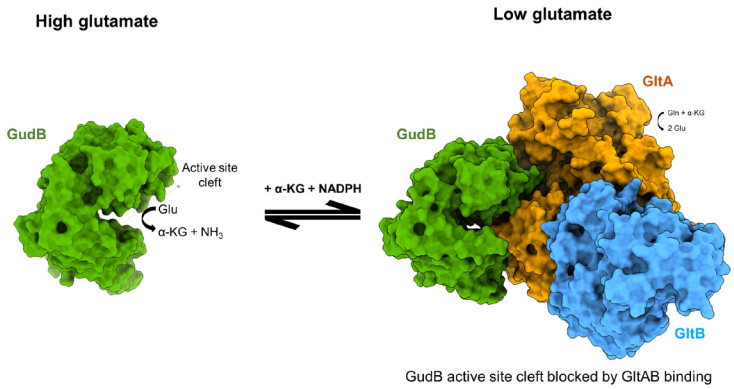

GudB (green) involved in glutamate degradation is regulated by GltAB (orange and blue) that is involved in gltuamate synthesis

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LIGHTNING TALK

Keywords: cytokinesis, endocytosis, polarity, super-resolution microscopy, spectroscopy

Mechanism of formation of nodes, membrane-less organelles in fission yeast

Membraneless organelles (MLOs) emerged as hotspots for efficiently regulating cellular activities. The mechanism of how these molecular condensates form and affect different cellular activities is not fully known (Owen and Shewmaker 2019). MLOs have roles in the pathogenesis of aging-related diseases, such as neurodegenerative or cancers (Alberti and Dormann 2019). In this study, we will explore the MLOs in fission yeasts, in particular nodes, assemblies of stoichiometric ratios of proteins associated with the plasma membrane (PM). Nodes are important precursors of a cytokinetic contractile ring which is a common cell division apparatus in amoebas, fungi, and animal cells. Recently it is also shown that nodes act as cell size sensors and aid in cell size homeostasis. We have shown that number of nodes scales with cell size (Sayyad and Pollard 2021). Despite their importance, it is not clear how they form, remain separated in broadband and interplays, and coordinate between different cellular processes.

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LIGHTNING TALK

Keywords: mitosis, cell cycle, cancer, metabolism, signaling

Polyoma Small T antigen promotes DBC1 protein degradation to antagonize AKT signaling via activation of LKB1.

Deleted in Breast Cancer 1 (DBC1) has been subject of much research interest, largely because of its conflicting role in cancers. Studies on the role of DBC1 in tumorigenesis are paradoxical and designate DBC1 both as a tumor suppressor and a tumor promoter. Using polyoma small T antigen (PyST), we have identified DBC1 as an important regulator of cell cycle and cellular transformation. We report that PyST associates with DBC1 and this interaction leads to down-regulation of DBC1. Further, when over-expressed with PyST, DBC1 markedly decreases the ability of PyST to cause G2/M arrest in the host cells. Our studies support a molecular mechanism by which DBC1 acts as a cellular oncogene. Using immunofluorescence we found that DBC1 localizes to spindle during mitosis which suggests that DBC1 might have an important role in mitotic progression, particularly under conditions of cellular stress. We further propose that DBC1 is a novel target of Liver Kinase B1 (LKB1). As LKB1 is a major energy sensor in cells, a link between DBC1 and LKB1 couples cell division with energy metabolism. Our results show that LKB1 negatively regulates phosphorylation (S473 and T308) as well as activity of AKT1 through DBC1 and Tribbles 3 (TRB3). These studies therefore provide an insight into a signaling mechanism that connects LKB1, DBC1, TRB3 and AKT. This signaling chain could be of major significance as a stress response pathway and can thus potentially be targeted to enforce a stronger mitotic arrest in cancer cells and other disease processes.

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