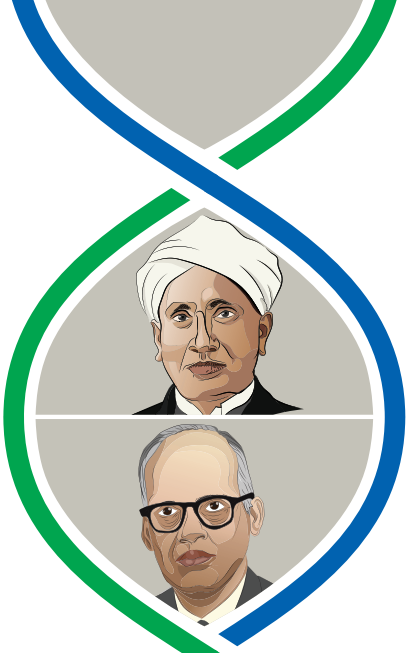
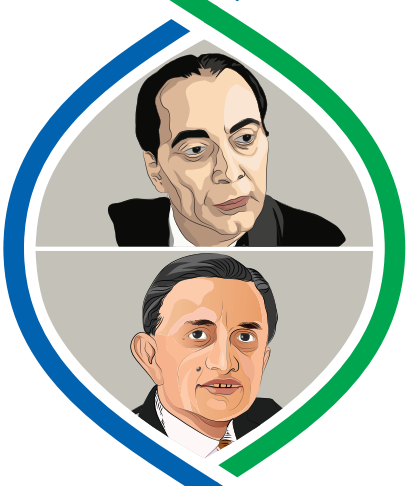
ENDLESS DISTINCTIONS, EVERLASTING IMPRESSIONS, ENDURING PAIRS.

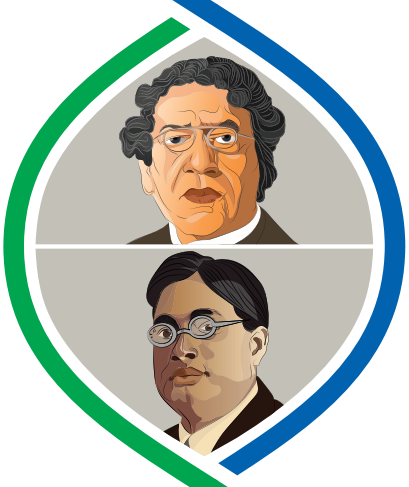
C V RAMAN
PHYSICS
G N RAMACHANDRAN



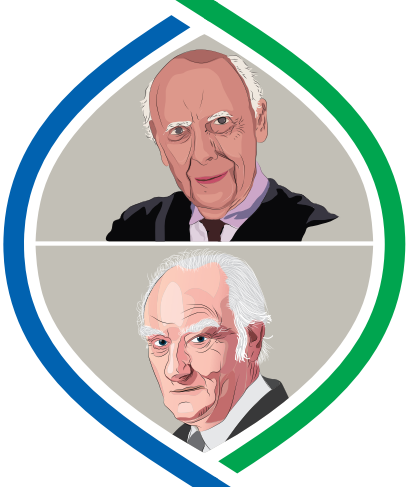
HOMI J BHABHA
TECHNOLOGY
VIKRAM SARABHAI



JAGADISH CHANDRA BOSE
SCIENCE
SATYENDRA NATH BOSE



JAMES WATSON
BIOLOGY
FRANCIS CRICK



Annual Report 2017-18

RGCB
DISCOVERIES FOR A BETTER TOMORROW

Water lily *(Nymphaea)* in the RGCB pond. The striking light in the center reflecting RGCB growing, blooming and glowing in the world of science.

Photographed by Dr Saraswati Nayar (RGCB)

ANNUAL REPORT
2017 - 2018

CELEBRATING
10
YEARS

AS A NATIONAL INSTITUTE OF
THE GOVERNMENT OF INDIA
DEPARTMENT OF BIOTECHNOLOGY

RGCB

DISCOVERIES FOR A
BETTER TOMORROW

I can think of no other edifice constructed by man as altruistic as a lighthouse. They were built only to serve.

George Bernard Shaw

Service to the nation through discovery, innovation and education.

RGCB

Photographed by Dr Ananda Mukherjee and Dr R Ajay Kumar (RGCB)

DIRECTOR'S REPORT

"If they were only two persons in the world, how would they get on? They would help one another, flatter one another, slander one another, fight one another and then make it up. They could neither live together nor do without one another."

Voltaire

We are thrilled and delighted to have completed our tenth year as a national research institute of the Department of Biotechnology, Ministry of Science & Technology, Government of India. We attained this recognition on April 1, 2007, and I strongly believe that RGCB has justified this trust and confidence that the Government of India put in us. We are indebted to the RGCB Governing Council and the RGCB Scientific Advisory Council. Indeed, RGCB and the Department of Biotechnology synergized very well and became a perfect pair.

The apparent attraction chemistry or synergy or complementary qualities that two people can develop is fascinating. Many a time, one feels smarter and performs better in the presence of a second person. There is much evidence for this positive dependence between performances of two individuals. It is mesmerizing to note that creative output, whether in arts, science or technology, or sports, involved a pair that always led to developments in the field. We all know that innovation and creativity is a result of a team of which the smallest unit is a pair. Trying to race ahead of a team member, and striving to perform at a higher level, often raises the standard of efforts in innovation. Over time, relationships that emerge between such competitors has an even stronger effect. It is therefore obvious that the individuals in great dyads will be very different from each other and yet have several common features. On the front and back covers of this annual report, we have featured unique examples of highly productive pairs, national and international, in various realms of life.

In philosophy, we have featured Sri Ramakrishna Paramahamsa and Swami Vivekananda. Exactly who Sri Ramakrishna was and his influence on modern India is a subject of several monographs and books. The entire essence of these volumes of work can be best understood with a ten-word sentence by Mahatma Gandhi - "His life enables us to see God face to face." Many of the Paramahamsa's disciples went on to become spiritual leaders but the brightest star was Sri Ramakrishna's chosen devotee, Narendranath Datta later known as Swami Vivekananda. Naren's intelligence and academic excellence was always the attention of his professors. While discussing Wordsworth, the Professor was trying to explain the ecstasy felt by a poet. He mentioned that an excellent example would be the spiritual ecstasy of Sri Ramakrishna, the priest of a temple in Dakshineswar. On their first meeting Sri Ramakrishna told Naren how he long awaited for him. A bewildered Naren felt Sri Ramakrishna was insane. Naren and Sri Ramakrishna were polar opposites. Naren was educated while Sri Ramakrishna was illiterate. Naren came from a wealthy family while Sri Ramakrishna was a destitute. Naren believed in intellect and rationality while Sri Ramakrishna was a God intoxicated mystic who spoke only from his heart. Any rational thinker would never have imagined or predicted that these two, one day, would have one of the greatest guru-disciple relationship. A brilliant example of a dialog between the teacher and student, sums up the spectrum and magnitude of life.

Swami Vivekananda:

"*Why do good people always suffer?*"

The Paramahamsa:

"A diamond cannot be polished without friction. Gold cannot be purified without fire. Good people go through trials, but don't suffer. With that experience, their life becomes better, not bitter".

Swami Vivekananda:

"You mean to say such experience is useful?"

The Paramahamsa:

"Yes. In every term; Experience is a hard teacher. She gives the test first and the lessons afterwards".

Another "guru – sishya" combination we have featured is C.V. Raman and G.N. Ramachandran. Sir Chandrasekhara Venkata Raman made India proud by becoming the first Indian to win the Nobel Prize for Physics. History chronicles Raman's feelings on the blue color of glaciers and the Mediterranean Sea. This led to his famous experiments on light, eventually leading to the 'Raman Effect' and the 1930 Nobel Prize in Physics. G.N. Ramachandran joined for his MSc degree at the Department of Electrical Engineering in the Indian Institute of Science, Bangalore. He soon realized that his passion and interests were in Physics. Professor C.V. Raman was the Director of the Indian Institute of Science, as well the Head of the Department of Physics. It takes a genius to recognize another genius and Ramachandran was allowed to join the Physics Department. Eventually G.N. Ramachandran better known as GNR became the most distinguished of Raman's students, missing the Nobel Prize for reasons unrelated to science. Ramachandran's success story was the triple helix model for collagen. He then described the principles of distribution of torsion angles in protein structure. This became the basis for a precise set of rules called Ramachandran Plot, which to this day is used to validate protein structures. This was a remarkable dyad in Indian Science – the teacher defined the immortal Raman effect and the student created the immortal Ramachandran Plot.

The two royal Bengal "Science Tigers", Jagadish Chandra Bose and Satyendra Nath Bose are another powerhouse pair that we also feature on our cover page. Satyendra Nath Bose was an Indian theoretical physicist who wrote "Planck's law and the light - quantum hypothesis" which Einstein translated into German and had published. Einstein later applied Bose's data to create the "Bose - Einstein Statistics".

The term Boson describing a particle that gives mass to everything is attributed to Satyendra Nath Bose. In 1958, he became Fellow of the Royal Society of London for his contributions to modern physics. The other science tiger from Bengal was Jagadish Chandra Bose, one of the greatest scientists India has ever produced. He is credited with much of the technology so relevant in our everyday lives including Microwave physics, Plant physiology and Biophysics. He invented Microwave technology and the whole new branch of solid-state physics. Bose created the concept of wireless communication and demonstrated the use of radio waves in 1895, two years before Marconi. In his later years, J.C. Bose abandoned physics to study plant biology, attempting to demonstrate that plants are living beings as much as humans and respond to emotional stimuli. Jagadish Chandra Bose was honored by Fellowship of the Royal Society of London in 1920.

Indians look at scientists with high esteem and on top of this list are Vikram Sarabhai and Homi Bhabha. Vikram Sarabhai is credited as being the Father of Indian space program. However, this was only possible because of the pioneering efforts of Homi Bhabha who was instrumental in the establishment of scientific institutions for the development of science and technology in modern India.

Steve Jobs and Steve Wozniak co-founded Apple. But long before, they were friends sharing a common interest in the music of Bob Dylan and creating technology. Here again, we have a dyad with totally contrasting characters that created the world's best-known computing technology. Steve Jobs was street smart, always confident and occasionally conceited, who then traveled across the world and took to Buddhism to find strength. Wozniak, on the other hand, was totally calm and focused. He was shy, composed and a quiet worker. The similarities were also striking. Both were tech geniuses, unconventional youngsters and college dropouts with immigrant parents. One could call it a perfect balance, except maybe it wasn't. It did however deliver.

We have featured other greats in arts and science. Every student of biology understands the contribution of James Watson and Francis Crick. Music lovers know the ethos of Carnatic music rendered by M.S Subbulakshmi and the Hindustani compositions of Bhimsen Joshi. Sonal Mansingh has mesmerized many with her performance of the Odissi dance while Rukmini Arundale immortalized the renaissance of Bharatanatyam.

In this annual report, we have presented our scientists as pairs striving to deliver relevant research findings. As you read through the reports, it will become clear why RGCB is today rated as one of the most successful and pioneering institutes for disease biology research, education and most characteristically, a place where true translation of research results to public health, societal needs and clinical intervention happens. RGCB is an integral entity in the Indian science scenario. A perfect pair – RGCB and Indian Science.

I must place on record gratitude to my three scientist colleagues who spent several weeks collecting, compiling and editing data for this report. Thank you Asha Nair, Debasree Dutta and Surya Ramachandran. Our young photographer, Harish, spent long hours providing images for both this report as well as our website and did a marvelous job. And finally and in no way the least, my sincere appreciation for three friends who patiently designed the annual report putting up with all my constant tantrums. Thank you Manjit, Rahul and Roy.

Professor M Radhakrishna Pillai
FRCPath, PhD, FASc, FNASc, FAMS, FNA

CONTENTS

SIGNIFICANCE OF A **PAIR**

GOOD THINGS COME IN PAIRS: EMERGING RELATIONSHIPS AND BETTER PERFORMANCE

History has seen the strength of two minds and souls working together to bring forth groundbreaking revolution such as Steve Jobs and Steve Wozniak in computing, M S Subbulakshmi and Bhimsen Joshi in music, Sri Ramakrishna Paramahamsa and Swami Vivekananda in spirituality. There is a significant energy in such duos. RGCB's power duos have achieved so much in the past year. This annual report is a testament to their achievements.

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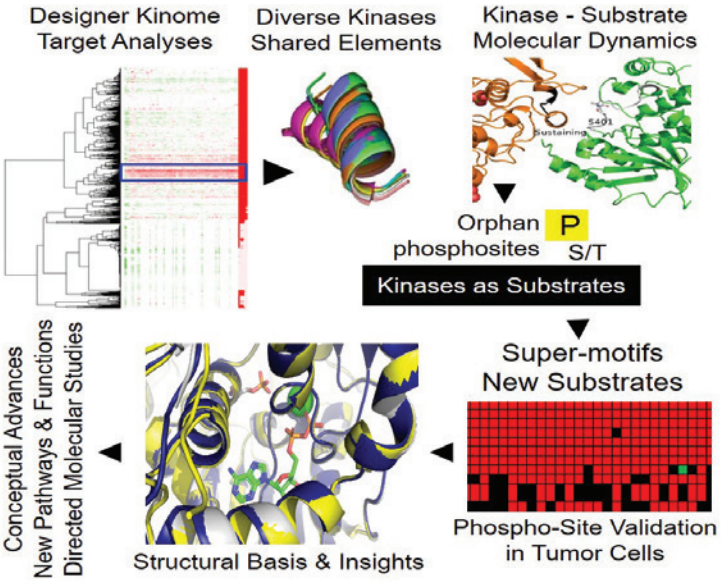
Relevant Publication

Signaling Coupled Epigenomic Regulation of Gene Expression. ***[Oncogene 36(43):5917-5926, 2017.]***
Kumar R, Deivendran S, Santhosh Kumar TR, Pillai MR

Protein kinase D1 regulates subcellular localisation and metastatic function of metastasis-associated protein 1. ***[Br J Cancer. 118(4): 587-599, 2018.]***
Ganju A, Chauhan SC, Hafeez BB, Doxtater K, Tripathi MK, Zafar N, Yallapu MM, **Kumar R**, Jaggi M.

FROM CANCER GENOMICS-

Our lack of a full understanding of the biology of cancer and an immense focus on a single gene/ protein approach might represent some of the barriers to achieve a major breakthrough towards our effort to combat cancer progression and prolong the life of cancer patients, for most but not all, cancer-types. Although current approaches so far had been very fruitful and were essential to reach to the current stage of knowledge gains in cancer biology and will continue to be important to learn more about the nature and functions of individual gene or protein, it is now clear that novel approaches might be required for further significant gains. We believe that the next level of major gains in cancer biology and therapeutics are likely to be driven by questions at the interface of cancer and system biology. The laboratory research theme involves integration of signal-dependent cellular pathways and question-oriented harvest of growing postgenomic cancer data-sets to distil the shared and specific elements of coordinated regulation of cellular pathways in human cancer - in addition to revealing fundamental answered questions in cancer biology. The team is pursing the hypothesis that human cancer, being a polygenic heterogeneous disease, often involves simultaneous dysregulation of multiple genes and cellular processes -shared among different cancer-types, leading to persistent dysregulation of complementary cancerous processes. Other highlights include a new approach to reveal new facets of p21-activated kinases (PAKs) - a group of hyperactivated kinases in human cancer and other diseases, using an integrated strategy involving a new algorithm of kinome, regulatome, structural biology, and neighborhood genomic landscape. Here we identified a set of diverse kinases, activation of which coincides with representative orphan phosphorylation sites; identified potential new substrates; and validated the prevalence of representative new modifiers and substrates of PAK pathways in human tumors. The lab envision that these on-going studies will provide new molecular pathways and tools for the detection and development of novel cancer therapeutic strategies.



TEAM / Rajesh Raju, Deivendran S, Aswathy Mary Paul, Bijesh George

TO SPICE GENOMICS

Black pepper known as the 'King of Spices' or 'Black Gold' is used worldwide as a natural food additive with a unique pungent flavour. *Phytophthora capsici*, an oomycete, causes blight and quick wilt in black pepper. Our laboratory focuses on the stress responsive genes and small RNAs (sRNAs) in pepper. For this, the analysis of high-throughput sRNA deep sequencing, transcriptome and metabolite profiling was done. In an infected plant, differential expression of resistance (R) genes indicated suppressed immunity. Genes involved include nucleotide binding site (NBS) and leucine rich repeat (LRR) genes as well as its two sub-families Toll/interleukin-1 receptor - TIR) and coiled coil –CC. Elevated level of abscisic acid (ABA), a plant hormone suggests its role during infection. The metabolome of pepper was integrated with transcriptome and microRNA profiles to identify and functionally validate the genes and critical regulatory agents for bioactive compound production. In addition, possible involvement of Simple Sequence Repeats (SSRs) in shaping the Splicing Regulatory Elements to undergo alternative splicing events for producing miRNA isoforms was also explored. Specific ribosomal RNA derived fragments (rRFs) from sRNA libraries of P. nigrum were analyzed (Figure). The 5' end of the putative long form of 5.8S rRNA was identified as the site for biogenesis of highly abundant srRNAs that are unique in the Piperaceae family. Comparative analysis of sRNAomes in different plant lineages detected the existence and precise cleavage of unique rRF signature sRNAs upstream of a novel 5' consensus sequence of the 5.8S rRNA. The potential role of rRFs in RNAi silencing was studied by analyzing their occurrence in the AGO complexed sRNAome. tRNA derived fragments (tRFs) targeting developmental and defence related genes were also observed. The non-coding sRNAs and transcriptomes of *P. nigrum, P. capsici* and infected *P. nigrum* were also comparatively analyzed and characterization of *P. capsici* RNAi genes to elucidate the mechanism of RNA interference and generation of sRNAs is to be done.

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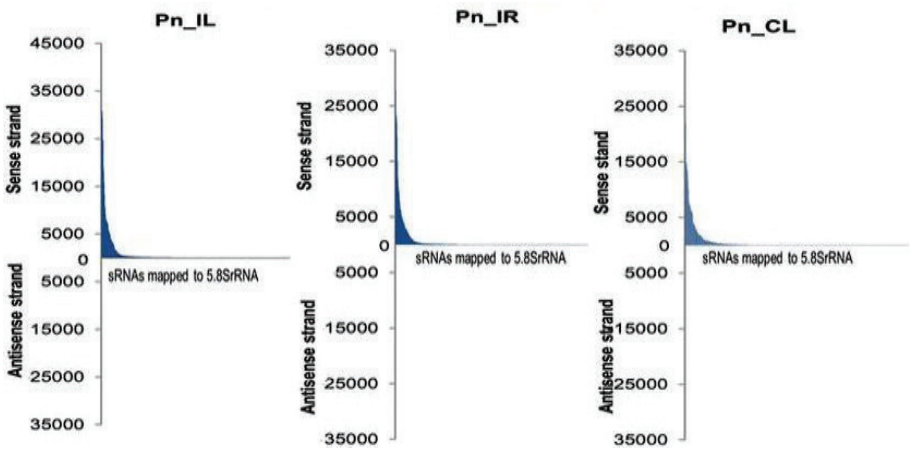
Figure legend

The mapped srRNAs to 5.8S rRNA: The 5'5.8S rRFs were the most abundant category of srRNAs in *Piper nigrum*.



Relevant Publication

A deeper view into the significance of simple sequence repeats in pre-miRNAs provides clues for its possible roles in determining the function of microRNAs. ***[BMC Genetics, 2018, 19(1):29. doi: 10.1186/s12863-018-0615-x.]*** Nisha Joy, Maimoonath Beevi Y P and **E V Soniya**

The sRNAome mining revealed existence of unique signature small RNAs derived from 5.8SrRNA from Piper nigrum and other plant lineages. ***[Scientific Reports, 2017. 7:41052. doi: 10.1038/srep41052].*** Asha Srinivasan and **E V Soniya**

TEAM / Nisha Joy. Mallika. V, Divya Kattupalli, Maimoonath Beevi Y. P, Aswathi U, Sweda Sreekumar, Thulasi R, Sinsha Prakashan, Lakshmipriya. P, Kalapriya V.S

E SREEKUMAR MVSc, PhD
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Relevant Publication

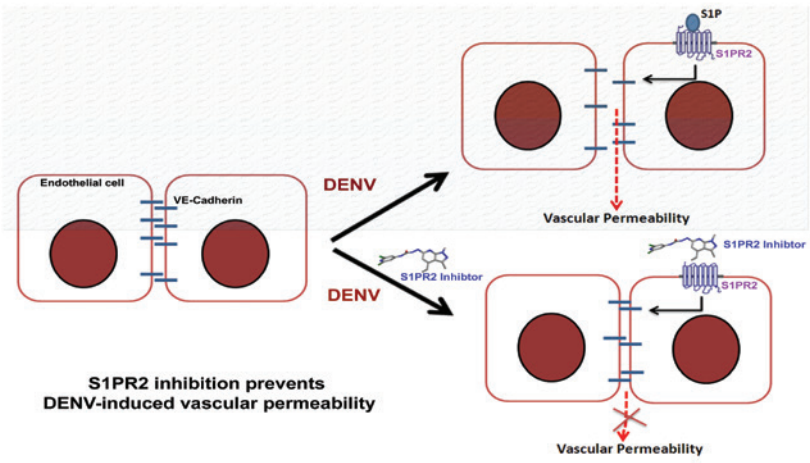
Sphingolipid signaling modulates trans-endothelial cell permeability in dengue virus infected HMEC-1 cells. ***[Prostaglandins & Other Lipid Mediators 2018, 136: 44–54].***
M.G. Anupriya, Sneha Singh, Neha Vijay Hulyalkar, **Easwaran Sreekumar**

GETTING A GRIP ON DENGUE-

A major theme pursued in our laboratory is to identify methods to alleviate the severe complications of dengue disease. We focus on the molecular mechanisms that regulate trans-endothelial cell permeability, alterations in which can result in dengue shock syndrome. We identified that a direct dengue viral infection of cultured Human Microvascular Endothelial cells (HMEC-1) results in increased trans-endothelial cell permeability. Further, in DENV-infected HMEC cells, a microarray analysis indicated modulation of Sphingosine signaling pathways with significant upregulation of Sphingosine-1-phosphate receptor 2 (S1PR2) and S1PR5. We also observed an internalization and cytoplasmic translocation of VE-Cadherin, a component of adherens junctions (AJ), upon infection indicating AJ disassembly. Using JTE-013, a specific inhibitor for S1PR2, we could reverse the increased trans-endothelial cell permeability in these cells. The treatment also decreased cytoplasmic S1PR2 levels and prevented VE-Cadherin internalization, further establishing that SIPR2 signaling has direct links with DENV-induced increase in permeability in HMEC-1 cells. The results give a functional basis to the earlier clinical observations on the significance of low S1P levels in severe dengue patients and reinforce the role of sphingolipid pathway alterations in severe dengue. These observations have been recently published in a key journal in lipid biology (Anupriya et al, Prostaglandins & Other Lipid Mediators 2018, 136: 44–54). The study points out possibility of specific pharmacological targeting of SIPR2 as an attractive option for preventing vascular leakage in dengue (Figure. 1). We are currently exploring these options using Fingolimod (FTY720), an FDA approved S1P analogue, in in vitro and in vivo models of dengue infection.

Figure legend

Up-regulation of the high-affinity Sphingosine-1-phosphate (S1P)-receptor, S1PR2, in dengue virus–infected endothelial cells coupled with low-level of S1P in circulation preferentially activates S1PR2 signalling over S1PR1 signalling resulting in vascular leakage. This could be prevented by inhibiting S1PR2 using specific inhibitors or by promoting the protective S1PR1 signalling through supplementing S1P levels in the circulation.



S1PR2 inhibition prevents DENV-induced vascular permeability

AND CHANDIPURA

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Chandipura virus (CHPV) is an arthropod borne virus belonging to the family Rhabdoviridae and genus Vesiculo virus. First isolated from Chandipura village in Maharashtra, it gained much significance after a large outbreak in 2003 in the state of Andhra Pradesh with a reported 329 cases of which 183 were fatal, predominantly due to encephalitis. Since this outbreak, there have been sporadic outbreaks in different places mortality rates ranging from of 55% to 80%.

Complement-virus interactions maybe pictured as a system ever on the alert marauded by legions of viruses with the outcome of the tussle deciding the victor and the vanquished. Although this area has garnered much interest over the years, the nature of virus-complement interaction with its intricate complexities remains unclear. Thus the over-arching goal of this project is to understand the complex mechanisms of interaction of CHPV with the human complement system and its modulation by CHPV. Marked neutralization (>50%) was observed when CHPV was treated with 1/5 to 1/20 dilutions of normal human serum (NHS) and not heat inactivated NHS. Time course experiments showed that CHPV was highly sensitive to NHS (~75% plaque reduction by 5 min) suggesting susceptibility to heat labile components in NHS. The central molecule of the complement cascade is C3 and neutralization assays with C3 depleted serum showed that CHPV could be neutralized upon C3 reconstitution that confirmed complement dependency. No neutralization was observed when CHPV was treated with EGTA-NHS or C1q depleted serum confirming that C1q and thereby the classical pathway is important. Western blotting of sucrose gradient fractions of CHPV+NHS showed a shift in fractions compared to CHPV-NHS due to complement deposition and aggregation. That, C8 deficient serum could neutralize CHPV supported the aggregation finding. We have thus demonstrated that complement acts as a potent barrier against CHPV and also elucidated the mechanism of neutralization. Insights into this interaction will help understand CHPV pathogenesis and offer a rationale to target this virus or exploit it for various positive applications.

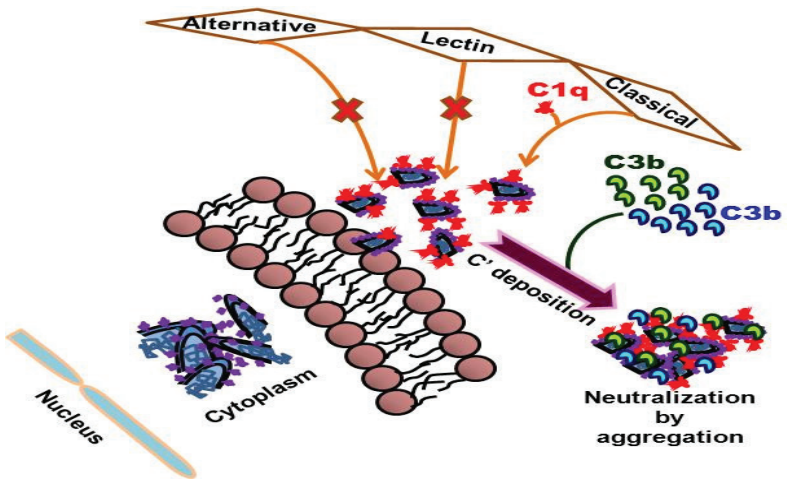

Figure legend

Schematic diagram depicting the mechanism of representation of Chandipura virus by the human complement system. Neutralization of Chandipura virus is by the classical pathway and is largely dependent on C1q. On activation of complement, deposition of components like C3b and C4b mediate viral aggregation that prevents virus infection by blocking viral attachment.

TEAM / Umerali K., Joydeep Nag, Nisha Asok Kumar, Reshma K.M.

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Relevant Publication

Proteomic profiling of β-hCG induced spheres in BRCA 1 defective triple negative breast cancer cells. ***[Journal of Proteome Research, October 13, 2017; DOI: 10.1021/acs.jproteome.7b00562]***. Kumar SS, Rajan A, Sreelatha K H, Revathy N, Jaleel A and **Srinivas P.**

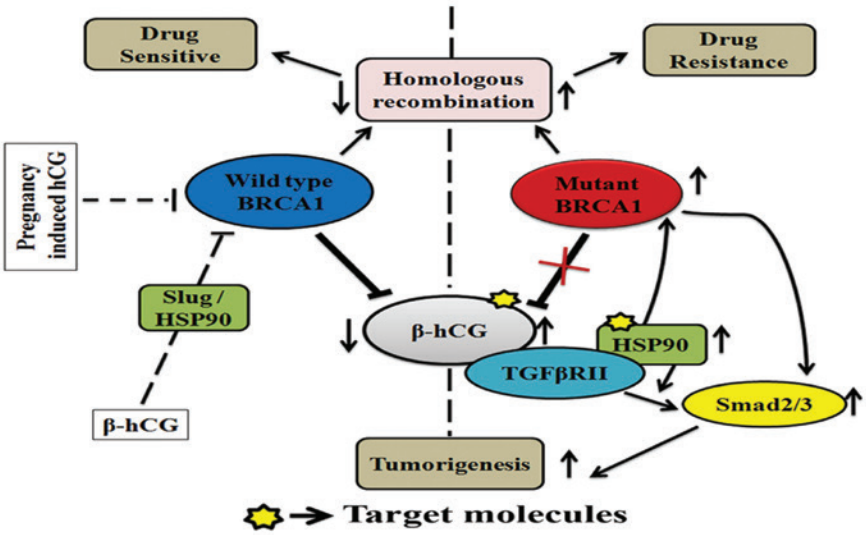
BRCA1 regulation on β-hCG: A mechanism for tumorigenicity in BRCA1 defective breast cancer. ***[Oncogenesis, 2017 Sep 4;6(9):e376. doi: 10.1038/oncsis.2017.75]***. Kumar SS n, Revathy N, Nair RS, Sreelatha KH, Somasundaram V, Reshma RS, Rajan A, Neetha R L, Varghese GR, Thankappan R, Jerald MaheshKumar J, Arkadiusz C, Anilkumar TV, **Srinivas P.**

BREAST CANCER BETA HCG-

BRCA1 has both ligand dependent and independent transcriptional control over estrogen receptors. However, tumor progression in BRCA1 defective condition cannot be controlled by inhibiting estrogen receptors. Apart from estrogen and progesterone, β-hCG is thought to be critical for the development and differentiation of breast tissue. Therefore, we hypothesized that a possible reason for selective tumourigenesis by BRCA1 might be the influence by β-hCG which has not been analyzed till date. Human chorionic gonadotropin β (β-hCG) is a highly controversial molecule as certain studies suggest it has anti-tumor properties while others have found it to be pro-tumorigenic. We identified for the first time that β-hCG expression was linked to BRCA1 status and it's over expression is seen in BRCA1 mutated breast cancers. An inverse correlation has been observed between BRCA1 and β-hCG in human breast cancers (Figure). We also demonstrate that the cancer cells with wild-type but not mutant BRCA1 directly repress the expression of β-hCG by binding to its promoter. Further, β-hCG promotes migration and invasion predominantly in BRCA1 mutant breast cancer cells. Also, stable over expression of β-hCG in BRCA1 mutant (HCC1937 β spheres) but not wild-type breast cancer cells results in the formation of spheres even on monolayer cultures which expressed higher levels of EMT and stem cell markers. Interestingly, hemoglobins were identified at both cellular and secretory level in HCC1937 β spheres and experiments after treating with ROS inducers revealed that β-hCG induces hemoglobin and protects the cancer cells during oxidative stress. We found that β-hCG can bind and phosphorylate TGFβRII, irrespective of LHCGR status and induce proliferation in BRCA1 defective cells. Our results confirmed that there exists a transcriptional regulation of BRCA1 on β-hCG and BRCA1 mutation promotes β-hCG mediated tumorigenesis through TGFβRII signalling. Thus, inhibiting β-hCG-TGFβRII could prove an effective treatment strategy for BRCA1 mutated tumors.

Figure legend

Summary of regulation between β-hCG and BRCA1 and possible tumorigenesis in BRCA1 defective breast tumors. (* indicates the possible targets for effective inhibition of tumorigenesis in BRCA1 mutated cancer cells)



TEAM / Ratheeshkumar T, Satheesh Kumar S, Revathy Arathi Rajan, Geetu Rose Varghese, Neetha RL, Dipyaman Patra, Neethu Krishnan, Arya Nagendran

AND PROGESTERONE SHIFTS

Progesterone is a biphasic hormone whose response in breast cancer cells is an initial proliferative burst, followed by sustained growth arrest. We recently described the role of progesterone in regulating calcium signaling. In endometrial cells the ability of progesterone to deplete Ca 2+ store, has an important role in cell proliferation, migration, invasion, and cell death. We demonstrated TOB-1 as a target for progesterone-mediated signaling and further that ROS can modulate and trigger the function of TOB-1, promoting crosstalk in a time and dose dependent manner. Further, we demonstrated that progesterone could activate the tumor suppressor p53 and PTEN in a time dependent manner. Recent studies have highlighted the importance of p53 and PTEN in calcium signaling and its associations with endoplasmic reticulum and mitochondria associated membrane (MAMs). We further analyzed the proteome profile of progesterone treated MCF-7 cells. LC/MS/MS analysis of ER+ breast cancer cells identified 1628 proteins, among which 212 and 191 proteins were up regulated and down regulated respectively with compared to control. Bioinformatics data analysis and functional classification of proteins revealed a role for progesterone in calcium signaling. Additionally, FRET analysis of calcium cameleon probed cells upon progesterone treated MCF-7 supports efflux of calcium. The current study provides evidence for calcium dependent signaling involving calcium pumps and calcium binding proteins as a trigger for endoplasmic stress. These early events contribute for increased ROS and may modulate cell death and cell proliferation depending on the threshold. The order of events cannot be ascertained yet, since ROS induction and calcium efflux are closely interlinked. This finding indicates survival mechanism of progesterone in ER positive breast cancer through calcium signaling. The exact mechanism and the order of events still need further elucidation. These insights may lead to the development of innovative "Ca2+-signaling hormonal drugs that could enhance Ca2+ fluxes in cancer in hormone positive cells.

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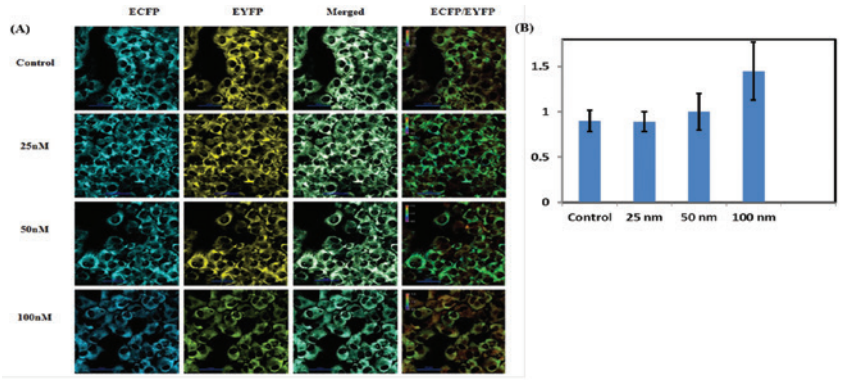
Figure legend

Progesterone induces calcium efflux in MCF-7 cells: Cells were stably transfected with ER-localized calcium probe, D1ER cameleon were treated with progesterone at different concentrations, 25nM, 50nM,100nM for 24H. The treated and untreated cells were imaged using Laser Scanning confocal microscope A1R (Nikon). Both Enhanced cyan fluorescent protein (ECFP) and enhanced yellow fluorescent protein (EYFP) emission were collected using NIS element software. ECFP/ EYFP ratio clearly indicated that higher concentration of progesterone (100nM) induces calcium efflux.



Relevant Publication

VDAC1 and SERCA3 mediate progesterone triggered Ca2+ signaling in breast cancer cells. ***[Proteome Research, 2018 17(1): 698-709]***.
Viji Remadevi, Arun Surendran, Abdul Jaleel, T.R. Santhosh Kumar and **Sreeja Sreeharshan**

TEAM / Lakshmi M. L, Juberia MA, Vini Ravindran, Viji Remadevi, Anjana, Savitha

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Relevant Publication

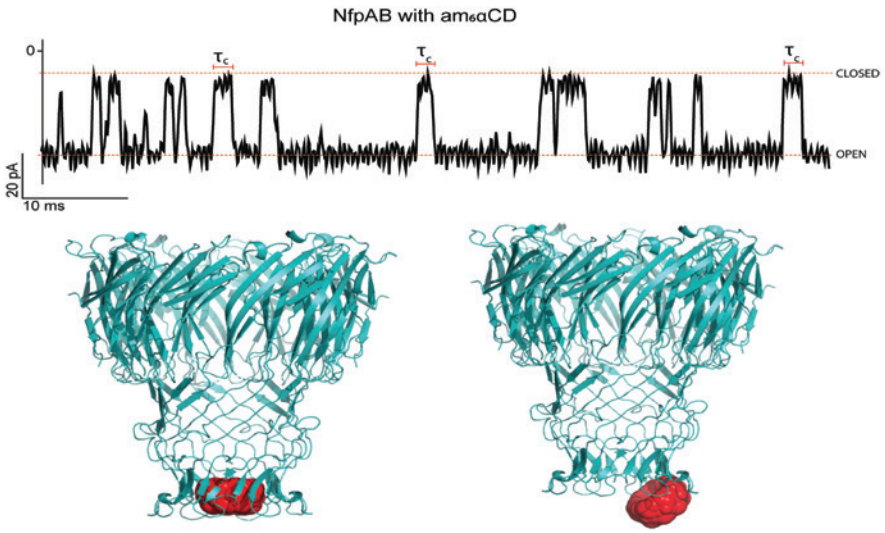
Controlling Interactions of Cyclic Oligosaccharides with Hetero-oligomeric Nanopores: Kinetics of Binding and Release at the Single-Molecule Level. ***[Small, 2018 (DOI: 10.1002/smll.201801192)]***
Remya S, Smrithi Krishnan R, **Mahendran KR.**

FROM CELLULAR ENGINEERING -

My laboratory focuses on understanding the structural assembly of membrane pores such as pore-forming toxins, antimicrobial peptides and ion channels. Further, we engineer and build membrane pores for applications in nanobiotechnology. Single molecule electrical sensing with protein nanopores were developed to identify size and chemical composition of macromolecules. This method can be applied to analytes ranging from peptides, polysaccharides to nucleic acids. Despite the rapid development of single-molecule techniques, the underlying mechanisms in molecular transport through nanopores are poorly characterized. Here, we use a novel approach to control the transport of cationic cyclodextrins (CDs) across the asymmetrically shaped and charged hetero-oligomeric protein pore NfpAB derived from Nocardia farcinica. We examined the interaction of differently sized and charged cationic CDs with NfpAB to elucidate the structural asymmetry of the pore by measuring the ion current blocking during the binding of CDs (Figure). To elucidate the influence of charge, we studied the interaction of cationic octasaccharide am8γCD and cationic heptasaccharide am7βCD with NfpAB. Our experimental data suggests that the relative binding strength of the CDs with NfpAB is as follows am8γCD > am7βCD > am6αCD. Binding kinetics obtained by the asymmetrical addition of CDs to the pore confirms the asymmetrical shape and charge distribution. Accordingly, we proposed a molecular model based on the kinetics of CD release from the NfpAB. Our study clearly established role of negatively charged residues in the hetero-oligomeric NfpAB in capturing and releasing the molecules via electrostatic attractions and repulsions in a controlled manner. Applications in nanobiotechnology are emerging for membrane protein pores in sensing, sequencing, cell permeation, etc. Hetero-oligomeric nanopores described in this work will allow a far greater range of proteins to be used for such applications.

Figure legend

Relesae of am6αCD from NfpAB at 1M KC1. Top: Ion current recordings showing release of attached am6αCD from trans side of NfpAD at -15mV. Bottom: Schematic model showing controlled release of attached am6αCD from trans side of the pore at different voltages.



TO CELLULAR BIOIMAGING

Mitophagy, the selective elimination of mitochondria is an important cellular process required for maintaining functional mitochondria. Mitophagy has received increased attention because of its role in neurodegenerative diseases, hypoxia-mediated cell survival or cell death in cancer and aging-related diseases. Owing to its clinical and biological importance, there have been several attempts to develop assays for the detection of mitophagy. Since mitophagy is a highly dynamic temporally regulated process, live cell approaches with increased throughput are critical in addressing the complex mechanism of mitochondrial removal as well as to identify small molecule modulators of mitophagy.

We developed two separate live cell approaches to specifically detect mitophagy in cancer cells. The first approach, using stable cells expressing both EGFP-LC3 and Mito-DsRed, is sensitive for image-based detection of early events of mitophagy, marking of mitochondria with LC3 aggregates. Conventional imaging and software-based co-localization analysis after proper segmentation allow quantification of the mitophagy process. A major advantage of this system is its ability to monitor mitophagy with high temporal resolution if single cell clones are used.

In the second method, we used stable cells expressing the lysosomal membrane protein LAMP1-RFP and Mitochondria with EGFP. Since the approach is real-time compatible, even steady-state imaging can visualize snapshots of mitophagy. A selected compound screening revealed highly heterogenic degradation pattern of Mito-EGFP signal within lysosomes. Interestingly we observed that increased mitophagy alters the ratio of cellular lysosomal to mitochondrial mass. This gradual change in lysosomal and mitochondrial mass helped us to render the assay quantitative. We have successfully identified several new mitophagy inducers with potential clinical utility using these methods.

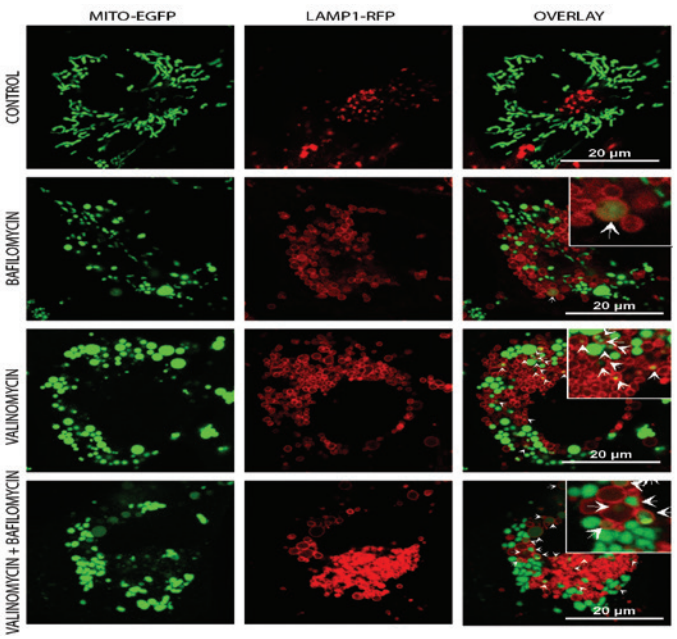


Figure legend

Confocal imaging of cells expressing Mito-EGFP and LAMP1-RFP reveals diverse stages of late mitophagic events OVCAR-8 cells stably expressing Mito–EGFP and LAMP1-RFP were treated with valinomycin for 24 h or 21 h valinomycin followed by 3 h with bafilomycin or bafilomycin alone for 3 h. The representative images of Mitochondria EGFP and Lamp1 RFP are shown. The lysosomes with engulfed mitochondrial EGFP are indicated with arrows. The increased lysosomal accumulation of mitochondrial EGFP is evident in Bafilomycin pretreated mitophagic cells. The inset shows a portion of the image zoomed to visualize mitophagy.

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Relevant Publication

Strategies for imaging mitophagy in high-resolution and high-throughput. ***[Eur J Cell Biol. 2018 Jan;97(1):1-14]*** Indira D, Varadarajan SN, Subhasingh Lupitha S, Lekshmi A, Mathew KA, Chandrasekharan A, Rajappan Pillai P, Pulikkal Kadamberi I, Ramachandran I, Sekar H, Kochucherukkan Gopalakrishnan A, **TR Santhosh Kumar**

TEAM / Asha Lekshmi, Shankara Narayanan V, Santhik SL, Mydhily Nair, Leena Chandrasekhar, Sanoj Namdev Patil, Minsa M, Prakash R, Aneesh Chandrasekharan, Devi Chinmayee M

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Relevant Publication

Preparation of an efficient and safe polymeric-magnetic nanoparticle delivery system for sorafenib in hepatocellular carcinoma. ***[Life Sciences, 2018, 206: 10-21]***.
Greeshma Tom, Sheena Philip, Rimal Isaac, P.K. Praseetha, S.G. Jiji, **VV Asha**

USING DRUG MINIATURES-

Sorafenib is the only FDA approved agent against unresectable hepatocellular carcinoma (HCC). Unfortunately, its use is limited by undesirable characteristics like poor aqueous solubility and systemic toxicity resulting in decreased bioavailability. Nanoparticulate technology is among the several approaches suggested to eliminate toxicology concerns and improve efficacy. Superparamagnetic iron oxide nanoparticles (SPIONs), as drug delivery vehicles, offer an alternative to address concerns associated with hydrophobic anti-cancer agents.

The current study was intended to fabricate a SPION based delivery system for sorafenib that can simultaneously enable targeted delivery of sorafenib and expand its therapeutic index against hepatocellular carcinoma (HCC). Co-precipitation and physical entrapment methods were employed for the synthesis of sorafenib loaded PVA coated SPIONs. The superior activity of nanoconjugate was demonstrated by AO/EB staining, FACS, immunofluorescence and Western blot. The safety of the sorafenib-conjugated nanoparticles was verified in Wistar rats. The synthesized nanoparticles were in the size range of 5-15nm.

The adsorption of PVA to the SPIONs and the conjugation of sorafenib to the nanocarrier were confirmed by XRD, FTIR and Raman spectra analyses. VSM study ascertained the superparamagnetic nature of the nanoconjugate. Cellular uptake studies suggested its efficient entrapment in HepG2 cells. MTT assay showed that the cytotoxicity of sorafenib loaded PVA/SPIONs was comparable or higher than free sorafenib. The activation of apoptosis and autophagy pathways in HepG2 by the nanoconjugate was demonstrated. Concurrent with these studies, activation of autophagy accompanied by apoptosis was evident in HepG2 cells exposed to sorafenib loaded PVA/Fe3O4, through confirmation of the lipidation of LC3 protein present on autophagosomes by immunofluorescence and immunoblotting. Acute toxicity testing in Wistar rats supported the safe administration of the nanoconjugate and established its localization in animal tissues by Perl's Prussian Blue reaction. The percentage of iron administered as the empty PVA/Fe3O4 was also monitored. The entry of sorafenib loaded PVA/Fe3O4 into the animals' body was conclusively proven through visualization of these nanoparticles as blue dots in the tissue sections. The test compound did not cause any abnormalities in the animals throughout the period, which suggests its pharmacological safety.

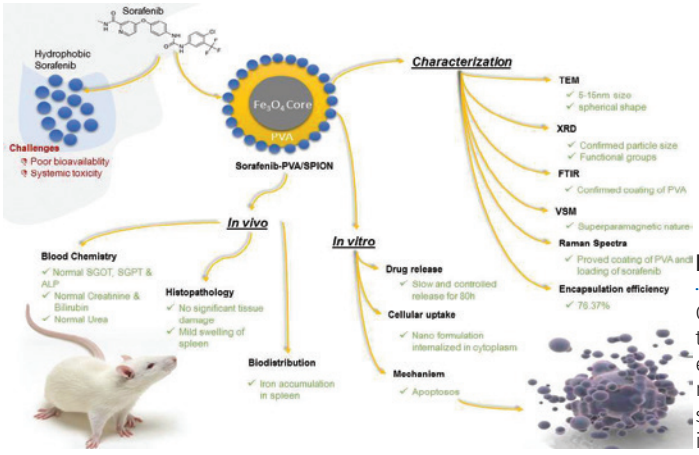

Figure legend

Graphical Summary of the preparation of an efficient polymeric-magnetic delivery system for Sorafenib in HCC.

TEAM / Greeshma Tom, Sheena Philip
Collaborators / Rimal Isaac, P.K. Praseetha; Department of Nanotechnology, Noorul Islam Centre for Higher Education, Kumaracoil, Tamil Nadu

AND CARRIERS FOR CANCER

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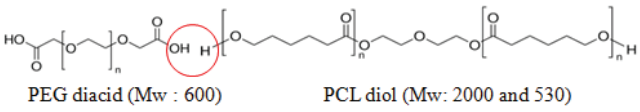
Our laboratory mainly focuses on development of novel drug releasing systems for cancer. Among the central nervous system neoplasms, gliomas are the most common anaplastic tumors seen in children and adults. Even after intensive therapy many glioma patients suffer from aggressive recurrence.

By use of an implant system as regional chemotherapy technique, we expect direct delivery of a drug into the surgical site of a tumor and timely release of required amount of drug; thus eventually decreasing peripheral toxicity. The present study designs biodegradable drug *implants*, studying the release kinetics *in-vitro* and *in-vivo*, toxicity testing and enhancing the targeted drug delivery rate. Combination of drugs can be implanted at a single instance. Sustained release of drugs for a wide span of time can inhibit recurrent glioblastoma without causing damage to other parts of the brain. Advantages of developing such technique are mainly to surpass the blood-brain barrier and to make the drug available in the appropriate amount to decrease the nonspecific cytotoxicity along with other side effects of chemotherapy.

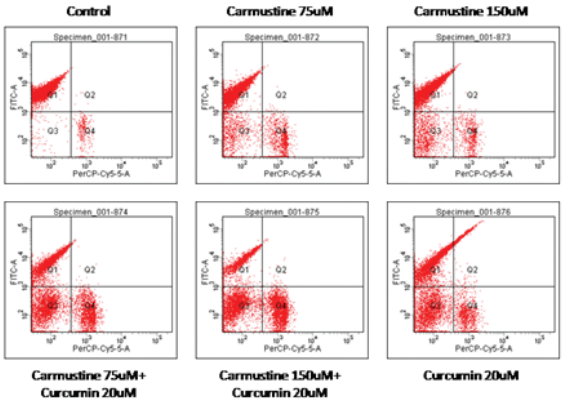
We developed a polymer-based hydrogel polycaprolactone (PCL) with polyethyleneglycol (PEG) copolymer purified and gelation was studied. The hydrogel was found at the concentration range of 100-300 mg/ml that was stable from 37^{0}C to 47^{0}C. Curcumin was used as a model drug and entrapped in the hydrogel successfully. We used carmustine as a chemotherapeutic agent along with curcumin as an adjuvant to bring down the quantity of drug required to exhibit cytotoxic effects. The action of curcumin as an adjuvant to carmustine was analyzed by cell cytotoxicity (MTT assay) and confirmed by Live dead assay flow cytometry analysis (Figure).



PEG diacid (Mw : 600) PCL diol (Mw: 2000 and 530)

Poly-condensation reaction

Polymer gel formation



Live Dead Assay using Flow cytometry

Figure legend

Preparation and characterization of copolymer system

TEAM / Vivek R, Meenu Vasudevan S, Mrunal Vitthal Wanjale, Teena Jacob Chirayil, Akhil K Mohan, Nanditha CK, Shilpasree MT

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Relevant Publication

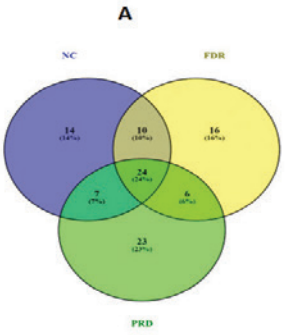
Distinct Predictors and Co-morbidities in Early Onset Type 2 Diabetes Mellitus Among Asian Indians. ***[Metabolic Syndrome and Related Disorders 2017; 15(9):458-64]***
Vijayakumar G, Sreehari GK, Vijayakumar A and **Jaleel A.**

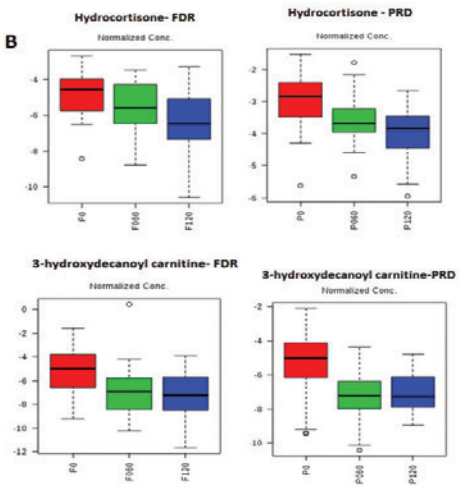
DIABETES DISEASE DEVELOPMENT-

Along with the raising prevalence of type 2 diabetes (T2DM), the age of onset of the disease is falling and more and more young people (below the age of 45 years) are becoming diabetic patients, termed as Early Onset T2DM. Our recent study on a population (age 20 years and above) in central Kerala showed that 48.4% of diabetic patients belong to early onset T2DM category, which is extremely alarming. The study also found that early onset T2DM patients have not only adverse cardiovascular risk profiles and poor glycemic control but also a higher chance of getting micro-vascular and macro-vascular complications compared with usual onset T2DM patients. A way to know how metabolic changes facilitate the onset of diabetes is by studying the altered metabolism of healthy people who are at risk of getting diabetes. To explore the molecular mechanisms behind the early onset T2DM, we initiated an investigation on a selected population of normal healthy people, between the age of 18 and 40 years in central Kerala. All healthy study subjects were grouped them into normal control (NC), first-degree relatives of patients with diabetes (FDR), overweight, and pre-diabetes (PRD) subjects were taken as positive controls. Biochemical measurements show the existence of metabolic risk in the diabetes risk groups in terms of glucose metabolism and its regulators. Mass spectrometry based plasma metabolomics analysis showed significant alteration in hydrocortisone and 3-hydroxydecanoyl carnitines in pre-diabetes and FDR samples, indicating hyperglycemia-induced inhibition of hydrocortisone secretion and deregulation of fatty acid β -oxidation pathway. This study promises to bring a valuable tool in the early detection of disease onset, development and progression. Thus, if such metabolic alterations are detectable in a healthy population, early interventions can be utilized for prevention of disease.

Figure legend

Postprandial metabolic alterations in normal control, FDR, and pre-diabetes subjects. Venn diagram (1A) showing the significantly altered metabolites identified in normal control (NC), first-degree relatives of patients with diabetes (FDR), and pre diabetes (PRD) subjects by one-way ANOVA (FDR <0.05%). Box and whiskers plots (1B) show commonly altered metabolites in FDR and pre diabetes group. Statistical analysis was performed with MetaboAnalyst 4.0



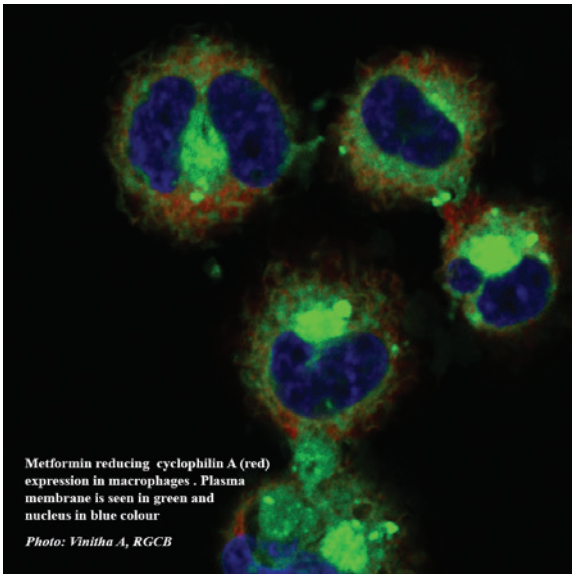


TEAM / Mahesh Krishna, Kalaivani V, Aneesh Kumar A, Vineetha A, Anusree VR, Gopika Satheesh, Akhila Suresh

AND PROGRESSION BIOMARKER

Hyperglycemia drives inflammation and dramatically accelerates atherosclerosis, a major macro-vascular complication of diabetes mellitus. High glucose in circulation can activate monocytes to secrete proteins that can signal and accelerate atherosclerotic lesion formation. Our search for such monocyte secreted proteins using proteomic analysis of high glucose-primed monocytes first identified higher levels of Cyclophilin A in plasma of patients with diabetes and coronary artery disease in comparison with plasma obtained from healthy volunteers.

We found that cyclophilin A accelerates atherosclerosis in hyperglycaemia by modulating monocyte to macrophage differentiation and reducing oxidized lipoprotein uptake. It is possible that targeting Cyclophilin A activity using inhibitory agents or molecules may retard progression of atherosclerotic lesions in diabetes. In this context, cyclophilin A gains clinical significance as a target for treatment strategy in preventing vascular complications in patients with diabetes. Our mission was to find inhibitors/drugs that can reduce Cyclophilin A levels so that the pro-inflammatory stimulus can be repressed. Given the known effects of metformin in reducing vascular complications of diabetes, we measured the effect of metformin on cyclophilin A expression, lipid accumulation, expression of scavenger receptors, plasma cytokine levels and AMP-activated protein kinase (AMPK) activity in macrophages using an *ex vivo* model of cultured macrophages isolated from patients with type 2 diabetes with and without coronary artery disease (CAD). In addition, the effects of metformin on migration of monocytes, reactive oxygen species (ROS) formation, lipid uptake in the presence of cyclophilin A inhibitors and comparison with pioglitazone were studied using THP-1 monocytes. Metformin reduced cyclophilin A expression in human monocyte-derived macrophages. Metformin also decreased the effects of cyclophilin A on macrophages such as oxidized low-density lipoprotein (oxLDL) uptake, scavenger receptor expression, ROS formation and secretion of inflammatory cytokines in high-glucose conditions. Metformin reversed cyclophilin A-induced decrease in AMPK-1α activity in macrophages. We therefore infer that Cyclophilin A inhibition using AMPK activators such as metformin is a possible preventive strategy for limiting progression of atherosclerosis in diabetes. This could also pave the way for developing newer drugs to repress atherosclerosis by targeting cyclophilin A.



Metformin reducing cyclophilin A (red) expression in macrophages . Plasma membrane is seen in green and nucleus in blue colour

Photo: Vinitha A, RGCB

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Relevant Publication

Metformin attenuates effects of cyclophilin A on macrophages, reduces lipid uptake, secretion of cytokines by repressing decreased AMPK activity. ***[Clinical Science 2018, 132(6):719-738]***. **Ramachandran S**, Vinitha A, V Raman Kutty, Ajit Mullasari, M Radhakrishna Pillai, C C Kartha.

TEAM / Vinitha A, Jayalekshmi VS, Thushara P; **COLLABORATORS /** Dr Ajit Mullasari, Madras Medical Mission, Chennai and Professor V Raman Kutty, Sree Chitra Institute of Medical Sciences & Technology

MALINI LALORAYA PhD
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Relevant Publication

Impaired Arginine Metabolism Coupled to a Defective Redox Conduit Contributes to Low Plasma Nitric Oxide in Polycystic Ovary Syndrome. ***[Cell Physiol Biochem. 2017 Oct 20;43(5):1880-1892. Epub 2017 Oct 20].***
Krishna MB, Joseph A, Thomas PL, Dsilva B, Pillai SM, **Laloraya M**

INFERTILITY

PCOS BIOLOGY-

Polycystic ovarian syndrome (PCOS) is a common metabolic disorder of young women that negatively affects fertility. The manifestation of the disorder is highly heterogeneous comprising hyperandrogenemia, oligo/ anovulation and polycystic ovaries. Recurrent miscarriages contribute to subfertility - a major co-morbidity associated with PCOS, which is thought to be due to compromised endometrial decidualization. Regulatory T (CD4+CD25+ CD127-) cells maintain immune homeostasis and suppress the maternal responses targeted against the fetus. We previously identified lowered regulatory T (CD4+CD25+ CD127-) (Tregs) in PCOS due to diminished STAT5B phosphorylation as a consequence of IL2 hypo-responsiveness resulting in lowered FOXP3 expression. Treg generation is known to be affected by NO levels as NO induces formation of a new class of Tregs - CD4+CD25+Foxp3- regulatory T cells (NO•-Tregs) via p53, IL-2, and OX40. Interestingly NO administration in PCOS women increases pregnancy rate in PCOS women. The status of NO metabolites is controversial in PCOS. Earlier work has suggested reduced arginine as a possible biomarker in PCOS women. Arginase 1 (ARG1) the enzyme responsible for Arginine conversion to ornithine was elevated in our patient study population suggesting that it depletes L-arginine thereby limiting its bioavailability for NOS. Our work showed that Dimethylarginine dimethylaminohydrolase 2 (DDAH2) responsible for ADMA clearance was reduced while protein arginine methyltransferase 1 (PRMT1) involved in ADMA synthesis was high leading to ADMA accumulation. Any feeble NOS activity is kept in check by increased ADMA.

Our finding of altered expression of genes involved in arginine bioavailability culminates in sub-optimal levels of NO and consequent failure of NO-Treg generation. Low NOx would result in compromised Treg numbers at implantation resulting in immune rejection of the implanting embryo with its paternal set of genes. Thus, NOx insufficiency needs to be taken care of at an early stage in PCOS patients by L -arginine supplementation directly or by alternative approach of PCOS specific diet including L-arginine rich foods (peanuts and walnuts, meats, seafood and legumes such as soybean and chickpeas).

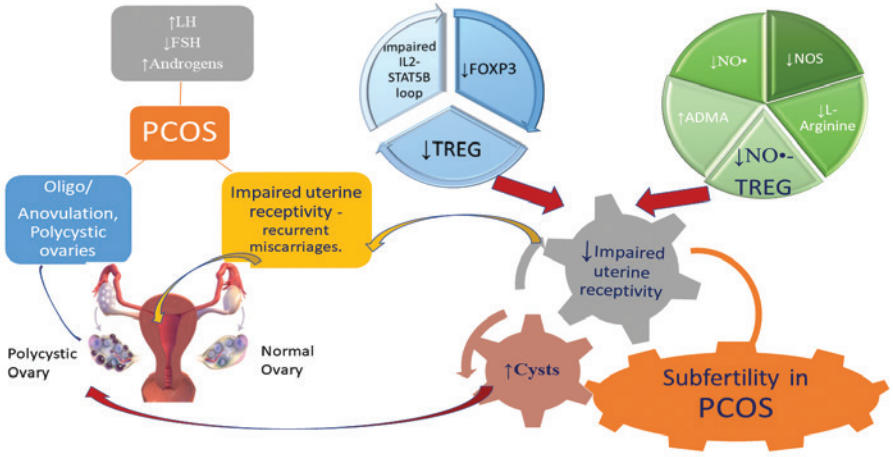

Figure legend

Impaired IL2-STAT5 loop and reduced NO levels result in reduced TREG generation, which is the epicenter for embryo rejection and ovarian cysts formation in subfertility associated with PCOS.

TEAM / Renjini AP (RA-DST), Betcy Susan Johnson, Selin Joseph, A.R.Krishnaindhu

AND SPERM PROTEOMICS

We are building networks of miRNA, mRNA, proteome and eipgenome in a germline stem cell differentiation landscape in adult testis. As we discovered that miR34c and miR449a are key players in the process, we examined the effect of altering the levels of these two molecules in downstream gene expression regulation and the resulting germ cell fate. Possibilities of directed differentiation of GSCs into somatic cells are also being explored.

Using differential display proteomics of spermatogenic cells from fertile and infertile men, our laboratory identified 19 molecules which appear to be critical for the production of functional spermatozoa. We have enhanced the search for finer proteome-level changes in spermatogenic cells from these subjects by employing high-resolution LC-MS/MS technology. We are in the process of designing a protein chip for identifying molecular defects associated with spermatozoa which might help the clinician to attempt the best possible Assisted Reproductive Technology (ART) intervention in male factor infertility cases. We are currently evaluating the functional significance of 6 of the critical molecules (TDP-43, AIRE, CNNM1, DYNLT1, NPHP1 and PCDH11Y) identified in our laboratory which are associated with spermatogenic impairment.

We profiled raft-associated proteins (RAPs) of spermatozoa at various stages of their maturation process, and this dataset was used for in silico network biological identification of potential sperm RAP-oocyte protein interactions. A total of 130 proteins were found up-regulated during sperm maturation, of which 108 proteins were present in RaftProt database. The interactomes of each raft protein was selected from STRING network prediction tool and the entire interactome list was screened for their association with oocyte or cumulus or both by using REPRODUCTION-2DPAGE database. The immediate interacting partner identification of 130 proteins under the set parameters resulted in 619 proteins interacting with 55 sperm RAPs (Figure a). The analysis of interacting partners on the oocyte or cumulus proteins yielded 183 proteins that can interact with 53 sperm RAPs (Figure b). These 183 oocyte associated proteins when evaluated for any interactions among themselves showed multiple small networks of interactions. The major families involved in network interactions include chaperones such as Hsp, Cct and Atp6v1 indicating the significance of these families in sperm raft-oocyte interactions. The networks denote the complexity of sperm raft-oocyte interactions and predict the importance of chaperones in regulating the fertilization process.

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Relevant Publication

Expression levels of Protocadherin 11Yb (PCDH11Y) in the germ cells in the semen correlate with fertility status in men. ***[Reprod. Fertil. Dev. 29(11): 2100-2111, 2017].***
Anilkumar TR, Devi AN, Pillai SM, Jayakrishnan K, Oommen OV and **Kumar PG**

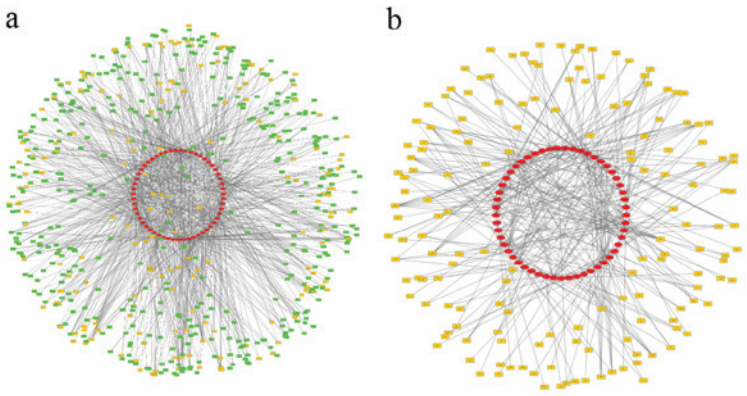

Figure legend

The sperm raft-oocyte protein interaction network. a) The network showing sperm raft proteins and its interacting partners. The red ellipses denote sperm raft proteins and rectangular nodes denote the interacting partners (green = not associated with the oocyte and orange = oocyte associated. b) Sub-network showing sperm raft proteins and its potential interactions with oo cyte proteins. Red ellipses and orange ellipses denote sperm raft and oocyte associated proteins respectively.

TEAM / Nomesh Yadu, Soumya A, Devi AN, Mahitha Sahadevan, Irfan Khan P, Aswathy JR, Jeeva SE, Vysakh G, Shabith Raj

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Relevant Publication

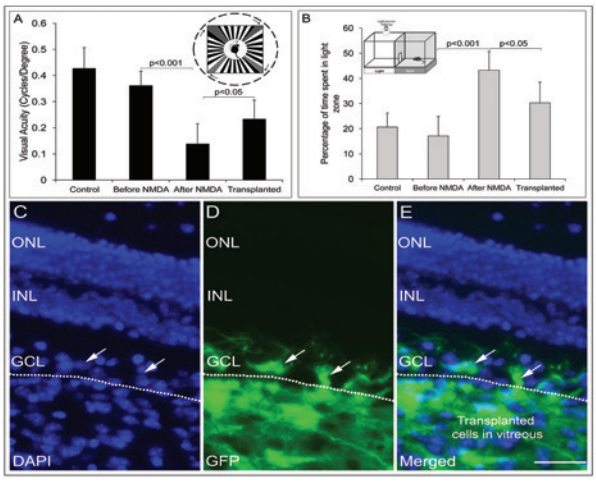
Intraocular injection of ES cell-derived neural progenitors improve visual function in retinal ganglion cell-depleted mouse models: ***[Frontiers in Cellular Neuroscience, 11 (2017) e 295, doi: 10.3389/fncel.2017.00295]*** Divya MS, Rasheed VA, Schmidt T, Lalitha S, Hattar S, and **James J**

STEM CELLS TREATMENT STRATEGY-

Retinal ganglion cells (RGC) transplantation is a promising strategy to restore visual function resulting from irreversible RGC degeneration occurring in glaucoma or inherited optic neuropathies. Here, we evaluated possible improvement of visual function by transplantation of ES cell derived neural progenitors (ES-NP) into NMDA injected, RGC-ablated mouse models and a pre-clinical glaucoma mouse model (DBA/2J) having sustained higher intra ocular pressure (IOP). Significant improvement in visual acuity was observed in transplanted animals as evidenced from optokinetic response (Fig-A). In the light avoidance test, animals after transplantation spent less time in the light zone compared to those prior to transplantation, indicating a significant improvement in light responsiveness (Fig-B). Further the integration of the transplanted cells into the GCL and RGC lineage was confirmed (Fig-C-E). Expression of c-Fos, an immediate early gene upon light stimulation in the transplanted cells indicated formation of functional neural circuits with the photoreceptor expressing cells. These results are suggestive that the transplanted cells are capable of functionally integrating into the host retinal circuitry and partial recovery of vision. Although, partial restoration of vision is observed we still do not observe any extension of nascent axons into the brain visual centers of the host. This is challenging and needs to be addressed since the adult retina is devoid of all the cues for axon guidance. Therefore, it is important to first understand and identify the molecules that are involved in axonal guidance during early retinal development. For this we have narrowed down on the master regulator gene Pax6 that is involved in RGC fate specification but its expression persists till adulthood and could be involved in axonal guidence. With Pax6 cKO mouse models we have observed that KnocKout of Pax6 in developing retina alters the expression of axonal guidance molecules. Further *in vitro* and *in vivo* experiments are also being carried out to understand this regulation.

Figure legend

GFP-expressing ES-NPs showed extensive integration and functional connectivity in transplanted NMDA-injected mouse models. (A): visual acuity of transplanted, NMDA-injected animals is significantly increased compared to that of NMDA-injected animals prior to transplantation; (B): transplanted, NMDA-injected animals also showed improved light avoidance behavior compared to that of NMDA-injected animals prior to transplantation; (C-E): transplanted cells extensively integrated into host retina.



TEAM / Lalitha S, Riya Ann Paul, Parvathy S, Meera V, Budhaditya Basu, Surya S, Biju S Nair
COLLABORATORS / Samer Hattar, Johns Hopkins University, Baltimore, MD, USA

AND DISEASE DEVELOPMENT

Mammalian development involves a complex network of different signaling pathways modulated by a intricate coordination between transcription factor and epigenetic factors. Answer to different deadly diseases might lie in how the normal pathway progress during mammalian development. Our laboratory focuses on epigenetic factors in development that could eventually generate cues for studying diseases. Embryonic stem cells or induced pluripotent stem cells and their differentiation to different lineages constitutes the in vitro model for studing development. Similarly regulatory pathways manifested in animal (mouse/rat) during pre-implantation or post-implantation embryo constitutes in vivo development model. Finally, we focus on the implication of these studied pathways in the context of human diseases involving patient tissue. Recently, we identified how downregulation of histone chaperone Aprataxin-PNK like factor (APLF) could enhance the kinetics and efficiency of cellular reprogramming. Downregulation of APLF in embryonic fibroblasts could induce the expression of E-cadherin associated with Mesenchymal-to-epithelial transition (MET). This cellular transition is involved in cancer metastasis. Hence upon investigation of invasive ductal breast carcinoma tissue, APLF levels were significantly enhanced as compared to the negligible presence in normal tissue sections. We demonstrated that downregulation of APLF abrogated the invasive, tumorigenic and metastatic behaviour of metastatic triple negative breast cancer cell line. To understand why APLF is less in normal tissue we are again looking back into development. Finally, we also demonstrated that a histone chaperone (APLF) could regulate both development and disease.

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Relevant Publication

Enhanced expression of histone chaperone APLF associate with breast cancer. ***[Mol Cancer. 2018 Mar 26;17(1):76]*** Majumder A, Syed KM, Mukherjee A, Lankadasari MB, Azeez JM, Sreeja S, Harikumar KB, Pillai MR, **Dutta D**

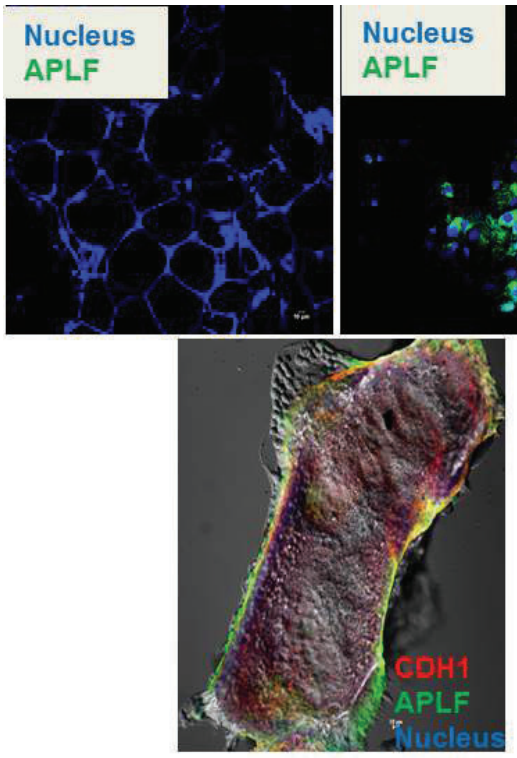

Figure legend

APLF in development and disease. (Top) IF analysis for expression of APLF in normal and invasive ductal carcinoma. (Bottom) APLF in developing embryo.

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CARDIAC FAILURE BIOLOGY- MITOCHONDRIA

Cardiac failure is a progressive condition in which weakened contractility of the muscle contributes to inadequate blood supply to the demanding organs and an impaired oxygen supply/demand ratio. The major drugs for management of heart failure unload the heart, decrease blood pressure and maintain the systolic or diastolic function of a compromised heart. These treatment strategies only aid to attenuate cardiac dysfunction and do not reverse the diseased heart to a healthy condition. Despite therapeutic interventions, mortality and re-hospitalization after treatment are 15 and 35 % respectively in patients with heart failure.

Mitochondrial dysfunction is widely recognized as a major accompaniment of heart failure. Alterations in mitochondrial dynamics (fission, fusion, autophagy), membrane potential, ion homeostasis, switch in substrate metabolism and increase in reactive oxygen species (ROS) and other free radicals (nitric oxide, hydroxyl) are distinct features of mitochondrial dysfunction. We examined the metabolic changes associated with long term cardiac hypertrophy induced by pressure overload, related the alterations to transitions in mitochondrial transporters and investigated the mechanistic link between mitochondrial dysfunction and fluctuation in mitochondrial transporter ABCB7.

Pressure overload hypertrophy was induced in 3 months old male Wistar rats (n=20) by constriction of aorta using titanium clips. H9C2 cells were used for studies relating mitochondrial transporter deficiency or over expression in the mitochondrial function. Cardiac tissues from rats with left ventricular (LV) hypertrophy had a significant decrease in the expression of ABCB7 and mitochondrial oxidative phosphorylation (mt-OXPHOS) enzymes. There was also an increased level of lipid metabolites and elevated levels of free iron, ROS and autophagy related proteins in LV of these animals. Knockdown of ABCB7 in H9C2 cells and stimulation with angiotensin II resulted in iron overload in both mitochondria and cytoplasm. A decrease in mRNA and protein levels of mt-OXPHOS specific enzymes, dynamics and autophagy clearance and activation of IGF-1 signaling were also seen in these cells. ABCB7 over expression rescued all these changes. ABCB7 was found to co-localize and interact with mitochondrial complexes IV and V. ABCB7 deficiency in chronic pressure overload results in iron overload and mitochondrial dysfunction, contributing to heart failure.

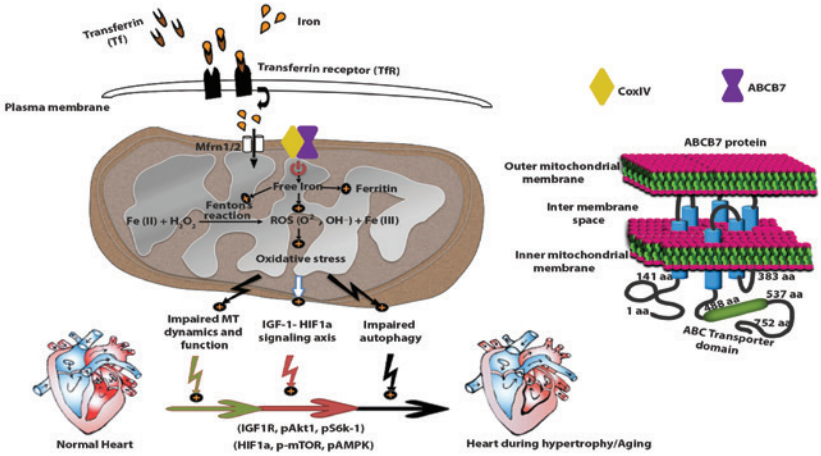

Figure legend

Schematic diagram of the role of ABCB7 in the heart and the proposed mechanisms which may promote cardiac dysfunction in chronic pressure overload. ABCB7 interacts with COXIV and regulates cellular iron homeostasis and cellular ROS levels in cardiomyocytes. Down regulation of ABCB7 results in impaired iron homeostasis, oxidative stress, mitochondrial dysfunction, altered autophagy and activation of HIF1α-IGF1 signaling pathway in the hypertrophied heart

TEAM / Vikas Kumar, Jaya Mary Thomas, Jithin Dev, Ciji Varghese, Dhanya R, Sumi S and Surya Ramachandran

TO RNA BIOLOGY

All eukaryotic mRNAs (except those encoding histones) harbor poly(A) tail at the 3'-end that is required for the stability and efficient translation of the mRNA. There are two major poly(A) polymerases (PAPs) in the nucleus involved in general mRNA polyadenylation - canonical PAPα/γ and Star-PAP. We are interested in understanding the mechanism of PAP specificity, regulation of alternative polyadenylation, processing of ncRNAs and mRNAs, and cellular implications in cardiovascular disease (CVD) and cancer. We demonstrated a mechanism of PAP specificity using Star-PAP as an example that is influenced by phosphorylation(s) and association with unique co-regulators. We identified a unique Star-PAP associated factor - RNA binding motif 10 (RBM10) with enriched expression in the heart as a regulator of cardiac hypertrophy (CH) and heart failure (HF). We confirmed RBM10 association with Star-PAP and showed that RRM2 domain on RBM10 interacts with catalytic domain on Star-PAP. This binding directs Star-PAP function towards polyadenylation of overlapped RBM10-Star-PAP targets. Microarray analysis demonstrated ~30% of RBM10 regulated genes are common with that of Star-PAP, one fifth of which were related to heart diseases/conditions including cardiac hypertrophy (CH) and heart failure (HF).

RBM10 binds mRNA 3'-UTR along with Star-PAP that is required for the assembly of Star-PAP polyadenylation complex and guides Star-PAP complex to specifically regulate 3'-end processing of mRNAs critical for CH/HF. Accordingly, extension of this study in physiologically relevant model in rat cardiomyoblast (H9C2) for hypertrophy and animal (Wistar rat heart) for CH and subsequent progression to HF demonstrated down regulation of both RBM10 and Star-PAP. Ectopic re-expression of RBM10 attenuated cardiomycyte hypertrophy. Consistently, knockdown of either RBM10 or Star-PAP in H9C2 cell line generated hypertrophic response. Our results establish RBM10 as a new regulator of CH, and reveal a novel Star-PAP/RBM10-mediated anti-hypertrophy mechanism directly linked to HF (Figure).

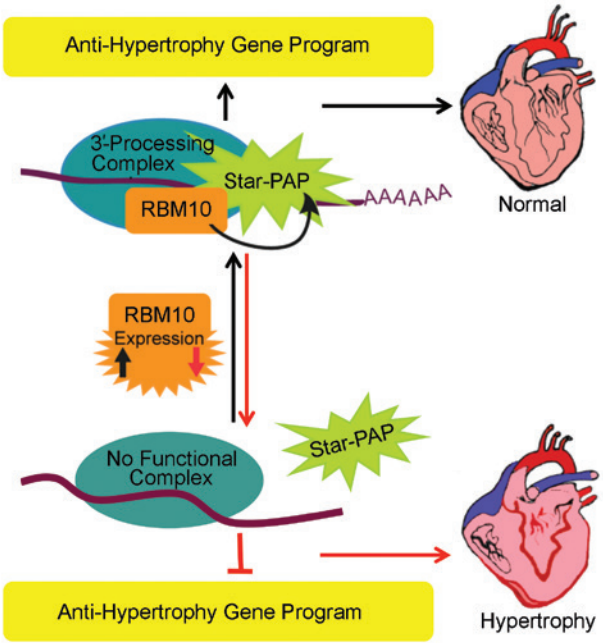

Figure legend

Model showing RBM10-Star-PAP nexus as an anti-hypertrophic mechanism.

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PEPTIDE ANTIBIOTICS
STOPPING MRSA-

Prospecting of frogs *Clinotarsus curtipes and Hylarana temporalis* that live in microbial pathogen opulent hostile environments of the Western Ghats, Kerala, identified forty-nine pharmacologically important mini-proteins termed as CABPAs. Majority of them possess an N-terminal hydrophobic region with a proline hinge middle region and a positively charged C-terminal region. They exist as non-interacting alpha helices in membrane mimicking solvents showing they preferentially adopt helical conformation upon binding with bacterial membrane. They showed broad-spectrum bactericidal activity against both Gram positive and negative bacteria with minimum inhibitory concentration (MICs) ranging from 1-100 µg/ml and prevent biofilm formation. Brevinin peptide amide B1CTcu3 destroyed drug resistant superbug MRSA below 12 µg/ml but showed haemolytic properties at high concentration. B1CTCu5, which is non-toxic to macrophages, showed potent in vitro anti – *M. tuberculosis* activity and eliminating intracellular mycobacterium growth within THP1 derived activated macrophages in a concentration dependent manner. CABPAs could not induce complete membrane depolarization of *E. coli* cells at their MICs even after 3h, showing that the membrane depolarization cannot always lead to the bacterial killing. Structure-activity analysis using Systematic and Modular Modification and Deletion (SMMD) analogous showed that although the presence of C-terminal rana box enhanced hydrophobic character, its removal can seriously disturb bactericidal potency and haemolytic nature. This amphiphilic region provides the required conformational stability to CABPAs, reduced sensitivity to proteases and low bacterial membrane binding. The nature of the amino acid present in this region is very important for its preferential interaction with Gram-negative bacteria. The pharmacophore region of CABPAs lies near the N-terminal region and any change in their cationicity or hydrophobicity by single amino acid substitution or deletion can seriously affect their bactericidal nature. Sequential removal of amino acids from N-terminal brought down its bactericidal potency and haemolytic nature. These results showed that integrity of both C- and N-terminal regions of CABPAs are very important for bactericidal activity and an optimum balance between the cationicity and hydrophobicity is required the initial interaction with anionic bacterial membrane phospholipids and the negatively charged lipopolysaccharides. Bactericidal nature of D-peptide amides showed that peptide-membrane interactions are non-stereospecific. Efficacy of CABPAs as antibiotic agent is hindered by their poor *in vivo* half-life due proteolytic degradation and the high intracellular uptake by reticuloendothelial system. PEGylation/higher fatty acid acylation improved their solubility and therapeutic index though to a small extent it affected their bactericidal potency. CABPAs can be used as antiseptic/anti-inflammatory drugs for human or veterinary use or adjuvant/s in personal care products or even as anti-invective agents along with classical antibiotics.

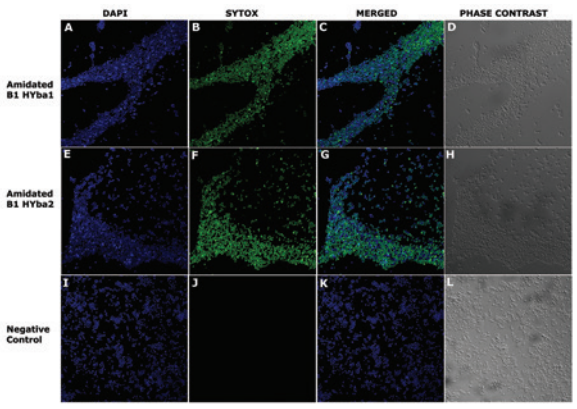
TEAM / Neethu Ajayakumar, Pratibha Narayan, Ms. Anju Krishnan, Manu, Smitha Devi, Aswani Kumar

AND KILLING VIBRIO CHOLERAE

We previously reported two new brevinin1 peptides (brevinin1 HYba1 and brevinin1 HYba2) identified from the skin secretion of the fungoid frog *Hydrophylax bahuvistara* from the Western Ghats of India. Antimicrobial, hemolytic and cytotoxic properties of brevinin1 peptides and their synthetic analogs (amidated C-terminus) were investigated. The peptides (except the acidic forms) had antimicrobial activity against all tested Gram-positive and negative bacteria with MICs in the range 1.5–100 micromolar. C-terminal amidation increased activity of the peptides against the tested microbes without altering their hemolytic and cytotoxic properties.

Being novel, an understanding of the mode of action of amidated peptides (B1/1CONH2 and B1/2CONH2) will provide insights into their therapeutic potential. Fluorescent probing along with SEM and AFM was performed to monitor changes in the bacterial membrane (*S. aureus and V. cholerae*) under peptide challenge. Influence of divalent cations on membrane interaction of the peptides was also evaluated.

Double staining (DAPI and SYTOX green) was used to investigate the bacterial membrane permeation by the amidated peptides. Confocal analysis revealed that the primary targets of these peptides are bacterial membranes and they alter the membrane permeability of bacterial cells (Figure). Results of flow cytometric analysis demonstrated that the extent of membrane disruption increases with increasing peptide concentration and leads to bacterial death through significant disruption of the membrane structure. Detection of SYTOX green signal at a sub- MIC concentration of the peptides was an interesting observation that is an indication of membrane rupture. The ability of the peptides to depolarize the membrane of *S. aureus* and *V. cholera* was investigated using the voltage sensitive fluorescent dye DiBAC4. Results showed that both the peptides are capable of inducing membrane depolarization before permeabilization. Scanning electron microscopy and AFM analysis revealed a drastic change in surface morphology of the bacteria tested in the present study. AFM results further confirmed the findings of SEM observations. AFM analysis of *V. cholerae* with both the peptides at MIC showed roughening of the surface compared to control and appearance of ghost-like structures and fused cells as previously reported. Mode of action of amidated frog skin peptides showed that peptide-bacteria interaction initially causes depolarization of the bacterial membrane followed by pore formation with the appearance of cellular debris and thread-like structures, which terminates in aggregation and appearance of 'ghost-like structures' as evident from the SEM and AFM analysis. Cationic peptides displace Ca2+ and Mg2+ ions from their binding sites on the gram-negative bacterial membrane during membrane permeabilization.



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Relevant Publication

Studies on the mode of membrane interaction of C-terminally amidated Brevinin1 HYba1& 2 peptides against bacteria. ***[Int J Pept Res Ther, 2018, 24:117–129]***. Vineeth Kumar T.V, Asha R, Shyla Gopal and **Sanil George**

Figure legend

Amidated brevinin1 peptide induced an influx of SYTOX green into S. aureus. First vertical panel (A, E, I) shows DAPI signal where all the bacterial cells could be visualized. Images B, F and J represents SYTOX signal; only membrane-damaged cells emit the green signal (B and F). Merged images (C, G and K) show a combinatorial signal of DAPI and SYTOX. D, H and L represent phase contrast images.

TEAM / Shyla Gopal, Kiran S Kumar, Anoop V.S

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STEM CELLS

ACCELERATING TUMORIGENESIS-

A small subset of heterogeneous cancer cells having self-renewal ability called cancer stem cells (CSCs), influence the prognosis of cancer. CSCs reside in a special microenvironment called "CSC niche", and its disruption will be an effective way to target CSCs. Our major focus is to understand the signaling pathways and molecules CSCs (Figure). Signaling pathways are the means of communication between cells and their environment. A ligand is a molecule that sends signal and receptor is a molecule that receives it. We used sphere culture to enrich CSCs, and used ALDH1A1 to mark them. "Phosphoproteomic analysis" was employed to find the molecules and pathways supporting self-renewal. The relevance of the data generated from cell lines and mouse models were evaluated in patient-derived oral cancer tissues. Among the 110 pathways identified, some were studied in depth while others are being evaluated.

The Eph/Ephrin signaling is a bi-directional pathway where both the interacting cells receive signals. Deregulation of this pathway leads to cancer progression and poor prognosis. Of 22 molecules involved in the pathway we identified that only EphA2 and EphrinB1 regulate oral cancer "CSC niche". Our FACS and immunofluorescence data revealed that CSCs express EphA2 while surrounding cells express EphrinB1, confirming that reverse signaling is not required to maintain CSCs. The EphrineB1+ cells could be initiating a forward signaling to the ALDH1A1+ cells to maintain self-renewal. Here, for the first time, we demonstrate that Eph/Ephrin pathway regulates the self-renewal property of CSCs in oral cancer.

Hippo signaling is a way by which cell communicates with its neighbor. Integrin signaling, on the other hand, is a way of communication with its surrounding substratum. Upon activation, the key molecule of Hippo pathway, YAP/TAZ localizes to nucleus. Active Integrin signaling mediated by Integrinα5/Integrinβ1/Fibronectin was evaluated. Using Integrinα5-siRNA and YAP-over-expression, we conclude that cooperation of Integrin and Hippo signaling under TGF-β regulation has an implication in the regulation of self-renewal ability of CSCs.

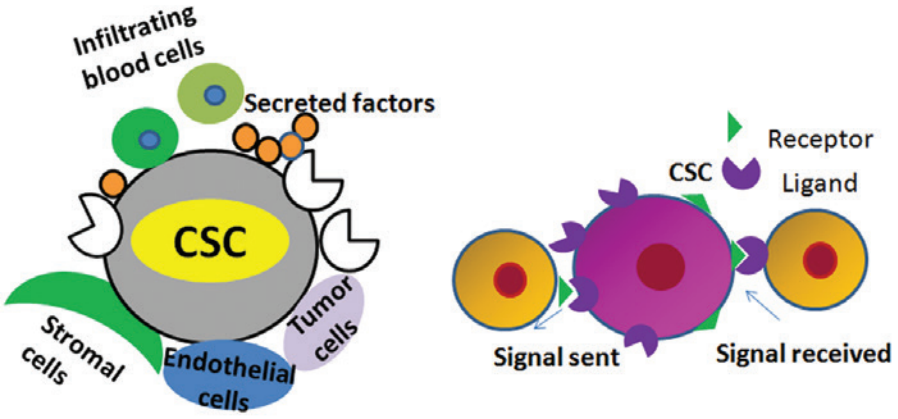

Figure legend

Diagrammatic representation of "CSC niche" Soluble secreted factors in the substratum (extracellular matrix) or cell-cell contact initiates signaling pathways. A CSC can receive a signal through its receptors present on the cell surface. It can also send signals to neighboring cells through secreted factors or surface ligands.

TEAM / Amrutha Mohan, Geetha S, Anitha Vimal

AND CANCER METASTASIS

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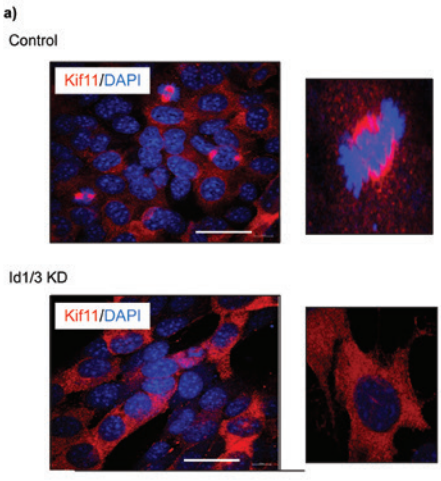
Metastasis or the spread of cancer from the primary site to other parts of the body is a silent killer in breast cancer, with 90% mortality rate for women with metastatic disease. A major hurdle in understanding metastasis is in modeling the complexity of the process. With a view to understand the cell intrinsic mechanisms involved in the spread of breast cancer, studies looked at Id1, a negative bHLH transcriptional factor. The main aim of this work was to delineate key molecular players involved in the cell autonomous control of metastatic cells. Evidence points to breast cancer following a hierarchical model, with Cancer Stem Cells (CSCs) driving critical phenotypes of the bulk tumor.

We previously demonstrated that the bHLH transcription factor, Inhibitor of Differentiation 1 (ID1), has an important role in maintaining the CSC phenotype of proliferation and self renewal in the Triple Negative breast cancer (TNBC) subtype (Figure a, b, c). There are strong indications that proliferation via the cell cycle process is disrupted when Id1 is depleted in the TNBC subtype. A genetic screen revealed that the cell cycle genes Kif11and Aurka were significantly affected in TNBC models of Id1 depletion and expression. We took this work forward by investigating how alteration in the cell cycle genes Kif11 and Aurka via Id1 promotes the CSC phenotype in TNBC. We determined that Id1 acts at multiple points of the cell cycle by alteration of key molecules, in addition to Kif11 and Aurka, to hold the cells poised in the G0/G1 phase till conditions are favorable for the tumor cells to proliferate again. Intriguingly, Kif11 and Aurka also contribute to the self-renewal phenotype affected by Id1 through novel cell cycle independent mechanisms.



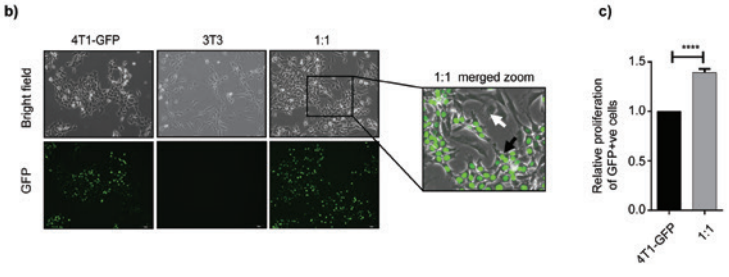


Figure legend

Understanding the role of cell intrinsic and extrinsic factors that contribute to breast cancer metastasis. (a) Id1/3 knockdown significantly affected the cell cycle in 4T1 tumor cells as immunofluorescence staining revealed non-dividing phenotype in tumor cells depleted of Id1/3 (20x magnification). (b) Direct co-culture of 4T1-GFP cells with 3T3 cells in 1:1 ratio for 48 hours (Phase contrast and fluorescence microscopy images 10x). Inset where the white arrow shows fibroblast cell and black arrow shows 4T1-GFP tumor cell. (c) There is a significant increase in tumor cells in co-culture. The relative increase in GFP+ve cells was analyzed using flow cytometry

Relevant Publication

The role of cancer stem cells in tumor heterogeneity and resistance to therapy ***[Can J Physiol Pharmacol. 2017 Jan; 95 (1):1-15]***. Konrad C, Murali R, Varghese AB, **Nair R.**

TEAM / Archana PT, Bintha Anu Varghese, Reshma Murali, Nitheesh Karthikeyan

RASHMI MISHRA PhD
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Relevant Publication

Extracellular Proton Concentrations Impacts LN229 Glioblastoma Tumor Cell Fate via Differential Modulation of Surface Lipids. ***[Frontiers in Oncology. 7:2, pages 1-23.]***. Sebastian John, KC Sivakumar and **Rashmi Mishra**

MECHANICAL STRESS AIDING TUMORS-

Cells often encounter macropinocytotic osmotic changes, shear pressure from the circulating body fluids as well as rigidity stresses from the extracellular matrix stiffening, acidification and galectin-glycocalyx clustering. The plasma membrane in eukaryotes acts as the prime interface at which mechanical micro-environmental forces are sensed and relayed to the intracellular controller for an effective adaptive response. We look to understand the link between specialised plasma membrane assemblies called the lipid rafts and biomechanical force homeostasis in physiology and pathologies with a special attention on brain, vascular and cerebrovascular ailments. Lipid rafts are dynamic cholesterol and sphingolipid enriched signalling units, broadly comprising of planar and curved caveolar sub-types. In brain, caveolae are particularly enriched in the neural stem cell (NSC) populations lining the ventricles. Caveolin-1 (CAV1) protein is indispensably required for sculpting caveolae and loss of CAV1 has been evidenced to upregulate proliferation, however the mechanism underlying this observation was not clear. The ventricular zones in brain are highly susceptible to mechanical forces from the cerebrospinal fluid and rigidification of the extracellular matrix (ECM) bed. Intriguingly, the most aggressive forms of brain tumors, the glioblastoma multiforme (GBM), mark their origin from this zone. This would mean that caveolae depleted NSC or caveolae low NSC that normally reside in the heterogeneous lateral ventricular zone can turn tumorigenic on enhanced ECM stiffness and stretch forces. Hence, the lead emerging hypothesis was that the loss of caveolae from the human neural stem cell populations of the lateral ventricles, due to enhanced stiffening ECM, can be a seed to the origin and progressive of brain tumors. Results suggest that upon stretch, the caveolae disassemble and its resident IGFR receptors undergo SUMOylation by SUMO2 isoform that enables the receptor translocation to the nucleus. The nuclear IGFR acts as a transcription factor for upregulation of proliferation associated genes such as cyclinD1, TCF/LEF1 and beta catenin. Inhibition of SUMO2 alone or in combination with EGFR receptor inhibition promoted significant GBM cell death. The human protein atlas data shows high nuclear expression of both SUMO2 and IGFR in several other tumor types and future efforts may bring forth the inhibition of SUMOylation, especially SUMO2 as an efficient universal anti-tumor therapy.

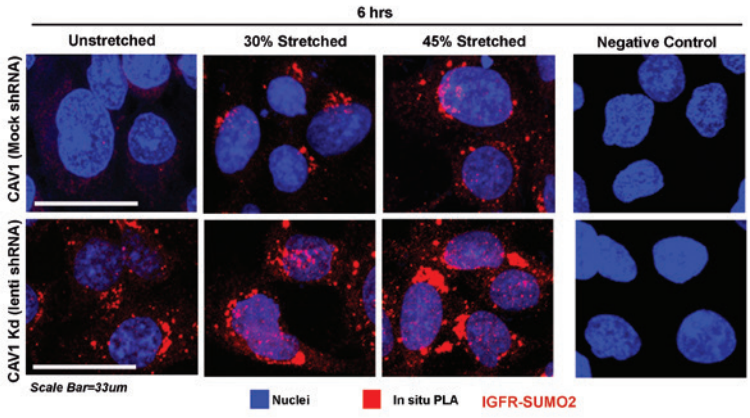

Figure legend

In situ PLA assay for detection of direct protein-protein interaction shows positive nuclear interaction between IGFR1 and SUMO2 upon mechanical loss of caveolae In Neural Stem Cells

TEAM / Sebastian John, Gayathri KG , Meera R. Nair

Varicose veins are enlarged and twisted veins with an impaired blood flow. They are no longer considered simple, unpleasant cosmetic issue. Complications of this disease range from throbbing pain and cramps to skin pigmentation and chronic unhealing ulcers. The risk factors for developing this disease are not well understood as the causes and the disease progression is yet unknown. Varicose veins have a recurrence rate of 26% to 60% after corrective surgery. This is attributed, at least partly, due to the lack of understanding of the etiology and pathogenesis of this condition.

are currently studying the role of altered hemodynamic shear stress induced endothelial dysfunction in the pathogenesis of varicose veins (Figure).

We performed studies to identify shear stress sensitive genes and their regulators in endothelial cells that play important roles in mechano-sensing and signal transduction. Human Umbilical Vein endothelial cells (HUVEC) were exposed to uniform and non- uniform shear stress mimicking earliest venous flow pattern and analyzed to delineate its specific molecular signature.

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AND VARICOSE VEINS

We focus on the genetic and molecular determinants in the pathogenesis of varicose veins. Our initial studies to understand the genetic basis of this disease led to the finding of key mutations in FoxC2 gene in patients with varicose veins. Further, we demonstrated that there is an abnormal arterialization of saphenous veins in patients with varicose veins. Recent reports suggest a significant role for FoxC2 in downstream signaling of hemodynamic shear stress in the lymphatic vasculature. Vascular developmental studies suggest that common signaling pathways are involved in venous and lymphatic system formation. We

We also examined the proteomic profile of vein tissues from patients and control subjects to understand disturbed flow induced changes in venous endothelium. LC-MS/MS analysis revealed 201 proteins to be up regulated and 52 proteins were down regulated in varicose veins compared to healthy controls. These differentially expressed proteins include proteins associated with shear stress pathway, endothelial function and inflammatory markers.

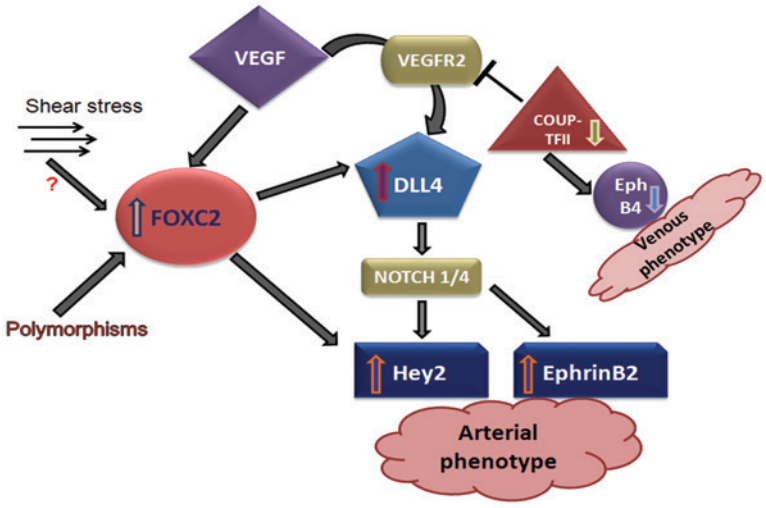

Figure legend

Thematic representation of molecular signalling in the remodelling of saphenous veins in patients with varicose veins.

COLLABORATORS / Ravi Kumar B.L (Kempegowda Institute of Medical Sciences, Bangalore); Kalpana, G Kamalapur (Sri Jayadeva Institute for Cardiovascular Sciences & Research, Bangalore), C.C. Kartha (RGCB)

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Relevant Publication

Are two doses of human papillomavirus vaccine sufficient for older girls aged 15-18 years? Results from a cohort study in India. ***[Papillomavirus Research, 2018, 5: 163-171]*** Bhatla N, Nene BM, Joshi S,. Esmy PO, UR Reddy Poli, Joshi G, Verma Y, Zomawia E, Pimple S, Prabhu PR, Basu P, Muwonge R, Hingmire S, Sauvaget C, Lucas E, Pawlita M, Gheit T, Jayant K, Malvi SG, Siddiqi M, Michel A, Butt J, Sankaran S, Kannan TR, Varghese R, Divate U, Willhauck-Fleckenstein M, Waterboer T, n Müller M, Sehr P, Kriplani A, Mishra G, Jadhav R, Thorat R, Tommasino M, **Pillai MR**, and Rengaswamy Sankaranarayanan, for the Indian HPV vaccine study group.

HPV VACCINATION STRATEGIES-

An estimated 528,000 new cervical cancer cases and 266,000 deaths due to cervical cancer were estimated in 2012. In low resource settings such as India, cervical cancer represents almost 12% of all female cancers. HPV infections are primarily transmitted through sexual contact. A bivalent and a quadrivalent HPV vaccine are currently available that are highly efficacious in preventing infection with HPV types 16 and 18 that together account for almost 70% of all cervical cancer cases. Since an increase in worldwide HPV vaccination could be facilitated if fewer than three doses of vaccine would be as effective as three doses, a multicentric cluster-randomized trial was initiated in India. The untimely suspension of vaccination due to events unrelated to the study gave rise to a single dose group. The primary outcomes defined for this study were immunogenicity in terms of L1 genotype-specific binding antibodies and incident and persistent infections after vaccination for the vaccine-targeted HPV types 16, 18, 6, and 11. We have previously demonstrated that two doses of the quadrivalent HPV vaccine were non-inferior to standard three doses. Further, the study indicated that the short-term protection afforded by one dose of HPV vaccine against persistent infection with HPV 16, 18, 6, and 11 is similar to that afforded by two or three doses of vaccine.

An increase in worldwide HPV vaccine implementation and coverage, particularly in low-middle resource settings such as India, will be significantly facilitated should a single dose of the vaccine be as effective as three doses. To address this question, we examined vaccine efficacy in terms of immunogenicity, incident and persistent HPV infections and HCII based HPV genotyping of the screen-eligible women. As immunological end points, the concentration of binding antibodies against the major capsid protein L1 and neutralizing antibodies specific for neutralizing-epitopes in HPV-L1 protein of vaccine targeted types were tested. To test for non-inferiority of antibody concentrations in different dose groups, log-transformed mean MFIs in linear regression models were used to obtain MFI ratios and their corresponding 95% confidence intervals (CI). Antibody titres at months 0, 7, 12, 36 and 48 were compared and non-inferiority was inferred when the lower bound of the confidence interval of the ratio of the immunogenicity measures exceeded 0.5. Cervical samples for HPV genotyping were collected from the participants initially at 18 months after marriage or 6 months after first child-birth (whichever was earlier) and yearly thereafter. . HPV type-specific E7 PCR bead-based multiplex genotyping was performed to detect 19 high-risk or probable high-risk types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68a, 68b, 70, 73, and 82), and two low-risk HPV types (6 and 11). An age-matched cohort of unvaccinated married women was recruited from the

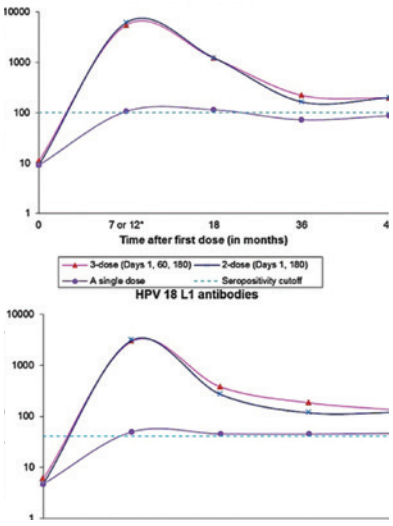

Figure legend

Mean median fluorescent intensity (MFI) values for HPV 16 and 18 L1 antibodies at different time points among girls who completed 3-dose, 2-dose or single dose of vaccination.

TEAM / RGCB Team: Priya R Prabhu, Kannan TR, Rintu Varghese, Edwin S, Subha Sankaran, Divya Jayalakshmi, Aparna GJ, Vivek Ashok Kumar, Jinu Austin

TO STOP A DEADLY CANCER

different study sites as the reference group. Of the 17,7294 vaccinated girls, 4,348 (25%) girls received three doses on days 1, 60, and 180 or later (three-dose group); 4,979 (28%) received two doses on days 1 and 180 or later (two-dose group); 3,452 (19%) received two doses on days 1 and 60 by default (two-dose default group); and 4,950 (28%) received one dose by default (one-dose default group). HPV infection outcomes were reported as frequencies of cumulative incident and persistent infections of vaccine-targeted and non-targeted high-risk HPV types accumulated during the seven year follow-up. Cumulative incident infections included all detectable infection at any visit up to year 7. Persistent HPV infection was defined by the presence of type-specific HPV DNA on repeated cervical samples over a 12 month interval. Albeit inferior to that of 3- or 2-doses, the one dose recipients demonstrated a robust and sustained immune response against HPV 16 and 18 over a 4 year period (fig 1). The proportion of persistent infections against HPV 16 and 18 infections was similarly low in all the vaccinated study groups throughout the 7 year follow-up period compared to the age-matched unvaccinated cohort. The frequencies of HPV 16 and 18 infections were higher in 1,481 unvaccinated women (6.2%) than 0.9% in 1,180 three-dose, 0.9% in 1,179 two-dose, 1.7% in 1,473 two-dose (default) and 1.6% among 1,823 one dose recipients. Importantly, the frequencies of vaccine non-targeted HPV types were similar between three-dose, two-dose (including the default group), one-dose groups and unvaccinated control women indicating similar HPV exposure in all study participants. There were no persistent HPV 16 infections among the 2,989 vaccine recipients as opposed to 14 (1.2%) among 1,141 unvaccinated control women. These results indicate that a single dose of the quadrivalent HPV vaccine is similar to the three- and two-dose vaccine schedules. HPV infection and cervical precancerous lesion data are warranted before policy guidelines regarding a single dose can be formulated or implemented (Vaccine. 2018, S0264-410X (18), pg 30286-X).

The current WHO recommendation for HPV vaccination schedule is dependent on the age of the recipient at the time of vaccine administration. While a 2-dose schedule (0, 6 months) is recommended for girls <15 years at the time of first dose, a 3-dose schedule (0, 1-2, 6 months) is recommended for girls ≥15 years at the time of first dose. Extending two-dose recommendations of HPV vaccine to girls between 15-18 years will reduce program cost and improve compliance. To address this, we examined the immunogenicity outcomes of L1 binding antibody titres, neutralizing antibody titres and antibody avidity against the targeted HPV types in 1795 girls aged 15-18 years receiving two doses, 1515 15-18 year old girls receiving three doses of the vaccine with the 15-18 year old three dose recipients (standard of care) and the 2833 10-14 year old three dose recipients (best response group). Immunologic non-inferiority was inferred when the lower bound of the confidence interval of the ratio of the immunogenicity measures exceeded 0.5. Vaccine targeted HPV infection outcomes were also compared in these groups as the early efficacy end points. The seven month L1-binding antibody titres of 15-18 year old two-dose recipients were non-inferior to 15-18 year old and 10-14 year old three-dose recipients. Frequency of incident infections from vaccine-targeted HPV types in the 15-18 year old two-dose recipients is similar to the three dose recipients. None of the girls receiving two or three doses had persistent infection from vaccine-targeted types. These findings support that two doses of HPV vaccine can be extended to girls aged 15-18 years (Papillomavirus Res. 2018, Vol 5, pg 163-171).

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Relevant Publication

Can a single dose of human papillomavirus (HPV) vaccine prevent cervical cancer? Early findings from an Indian study. ***[Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.02.087]***

Sankaranarayanan R, SJoshi S M, Basu P, Esmy PO, Prabhu P, Muwonge R, Bhatla M, Nene BM, UR Reddy Poli, Geeta Joshi, Verma Y, Zomawia E, Pimple S, Shaw J, Hingmire S, Lucas E, Sauvaget C, Pawlita M, Gheit T, Jayant K, Sylla G Malvi SG, Siddiqi M, Michel A, Butt J, Sankaran S, Kannan TR, Varghese R, Divate U, Willhauck-Fleckenstein M, Waterboer T, Müller M, Sehr P, Kriplani A, Mishra G, Jadhav R, Thorat R, Patel R, Chiwate A, M Tommasino M, **Pillai MR** for the Indian HPV vaccine study group.

TEAM / International Team: R. Sankaranarayanan, M. Tomassino, Gheit T (France), Pawlita M (Germany)
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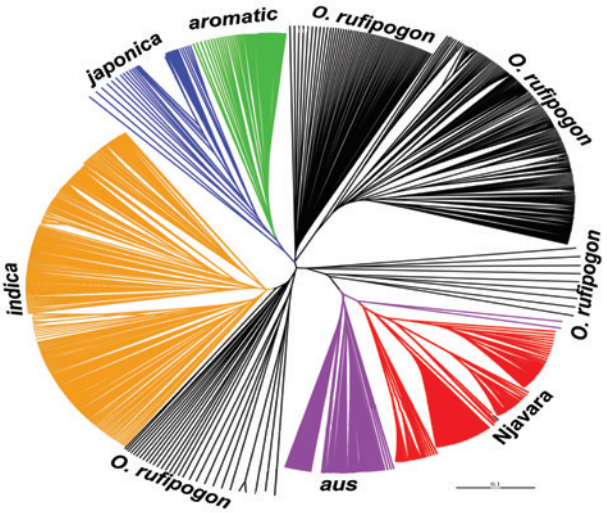
GENETICS

MEDICINAL RICE ANCESTRY-

A fast-growing 60 days rice strain is referred in Indian subcontinent since Vedic (1900-500 B.C.) period. The medicinal and nutritive properties of this rice strain called *Shashtika* (Sanskrit) or *Njavara* (Dravidian etymology), whose cultivation is currently limited to Kerala state, is extensively described in seminal Ayurveda compendia Charaka Samhita and Sushruta Samhita (circa 660 - 1000 B.C.). Although *Njavara* grains are used for acclaimed Ayurveda treatments since time immemorial, little is known about its phylogenetic position in global rice pool and its centre of domestication. We analyzed over 600 samples including *Njavara* individuals, traditional cultivars belonging to the known ancestral sub-groups indica, japonica, aromatic and aus in global rice gene pool and the populations of the progenitor species *Oryza rufipogon* form Southeast Asian countries using microsatellite markers and gene genealogical methods. Based on neutral microsatellite markers, *Njavara* produced a major clade distinct from the clades produced by the ancestral sub-groups. In the phylogenetic analysis also, based on sequences retrieved from 19 unlinked EST-based sequence tagged site (STS) loci the *Njavara* genotypic classes were clearly separated from the cultivar belonging to the ancestral sub-groups. In genealogical analysis *Njavara* shared haplotypes with the *O. rufipogon* populations originating from Central India–Southeast Asia region. Results signify that *Njavara* is genetically distinct in global rice gene pool. Further, from the phylogenetic characteristics and morphological features, it is likely that *Njavara* is a still cultivated early domesticate in Indian rice gene pool. Possibly *Njavara* rice reached Kerala from Northern India concomitant with Ayurveda in late B.C or early *A. D. Njavara* represent a rare example of mankind preserving a cultivar in pure form over millennia by the traditional prudence in on-farm selection, because of its medicinal applications.

Figure legend

Dendrogram of genetic relationships between rice cultivars and the progenitor *O. rufipogon* based on microsatellite markers showing the genetic distinctness of *Njavara* in relation to known ancestral sub-groups in rice.



TEAM / Sayuj K. P, Vishnu. S. Nath, Smini Varghese, Lesly Augustine, Vinitha M. R, Teena Elizabeth Alex

AND IMMUNITY IN PEPPER

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Plant immunity is a highly dynamic molecular surveillance mechanism critical for the existence of plants. The tropical non-model spice crop, *Piper nigrum* (black pepper) has long been under severe threat by the 'quick wilt' disease, caused by the hemi-biotrophic oomycete pathogen, *Phytophthora capsici*. Based on recent observations using a unique integrated transcriptome-based proteomics strategy, we hypothesize that innate immunity could be a key mechanism targeted and manipulated by the hemibiotroph, *P. capsici*, facilitating its growth and proliferation within the susceptible host. To validate our hypothesis, we performed a high throughput comparative transcriptomics strategy in *P. nigrum* leaves subjected to *P. capsici* infection or infiltrated with classical elicitors of innate immunity viz. flg22 and modified chitosan.

Receptor-like kinases (RLKs) are surface localized, transmembrane receptors comprising a large family of well-studied protein kinases. We identified 808 *P. nigrum* specific protein kinases that could be categorized into nine sub-groups. The most significant representation of the protein kinase groups was found for Receptor-like kinase-Pelle (RLK-Pelle). These are RLKs involved in immunity and are designated as the pattern-recognition receptors (PRRs) that detect pathogen-associated molecular patterns (PAMPs). The complete protein-coding gene and corresponding protein sequence of 17 potential PRRs were identified from P.nigrum, which is the first report from this species.

Time scale gene expression analysis of these PRR genes was performed by qRT-PCR that has helped to identify their critical role in pathogen surveillance (Figure). These observations support our claim that innate immunity is the dominant player in the disease resistance mechanism of *P. nigrum*. We propose that biotechnological manipulation of innate immunity exploiting PnRLKs could be a most favorable strategy for deployment of strong broad-spectrum disease resistance in black pepper. Our integrated multi-omics approach not only enables the discovery of new genes/proteins but also will generate an improved reference for studying plant immunity of spice crops in general.

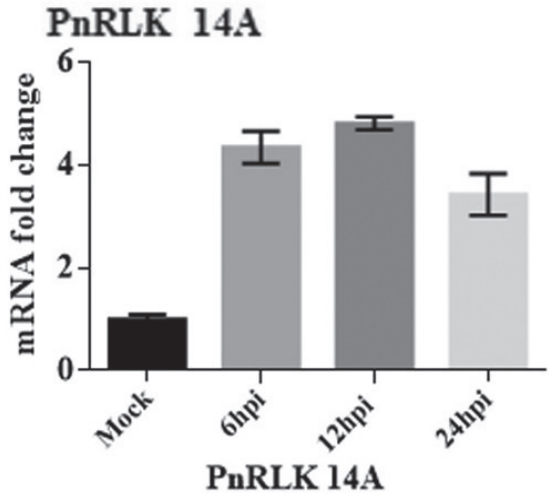

Figure legend

Time-course (0-24 hpi) Real Time expression analysis of a representative receptor-like kinase (PnRLK 14A) identified from *Piper nigrum*.

TEAM / Chidambareswaran M, Gayathri GS

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Relevant Publication

Fodrin as a regulator of microtubule nucleation. ***[Mol. Biol. Cell 2017 P1150, 28:26 3727; doi:10.1091/mbc. E17-10-0618]***. J.S. Sreeja, R.K. Nellika, **S. Sengupta;** ASCB-EMBO MEETING December 2017 Philadelphia USA.

REVEALING MITOTIC SECRETS-

Fodrin, a non-erythroid homologue of spectrin, plays a pivotal role in the maintenance of cytoskeletal structure integrity of plasma membrane.
We have earlier shown that fodrin disappears from centrosomes in brain derived cells as the cells enter the prometaphase stage and comes back after cytokinesis. To further elucidate its functional involvement in mitosis, fodrin was down regulated by shRNA treatment that gave mitotic defects as multipolar and broken spindles were observed. In these cells, chromosomes were uncongressed. Further by live cell imaging, a high percentage of cells displayed mitotic delay. The mitotic defects and mitotic delay indicates increase in the checkpoint protein functions as confirmed by the addition of MPS1 inhibitor, Reversine that could recover the cells from mitotic delay. Further the checkpoint defect was detected as an increase in the checkpoint protein BubR1 in cells with fodrin down regulation. We found that loss of fodrin gave rise to lesser number of kinetochore-attached microtubules that was a cause for increase in the check point protein attachment.
Further, we detailed the presence of fodrin as a component of the γ-TuRC (gamma tubulin ring complex) derived from neuronal tissue and neuronal lineage cells. γ-TuRC is a complex association of proteins, utilised in the cells as a major tool for microtubule formation and organisation. Centrosome, being the major hub of microtubule nucleation in mammalian cells, is rich in γ-TuRCs. Towards understanding the contribution of fodrin in γ-TuRC mediated functions in the cells, we employed both in vitro and in vivo approaches. Fodrin was downregulated by targeted shRNA treatment and centrosomal microtubule nucleation in mitotic cells was analysed by the astral microtubule intensity around the centrosomes in these cells.

Fodrin downregulated cells showed significant reduction in astral microtubule intensity in comparison to the control. For understanding the significance of the direct association of fodrin with γ-TuRC, *in vitro* microtubule polymerization was monitored turbidometrically. There was an increase in the nucleation time when fodrin was added to nucleation competent γ-TuRC derived from HEK293. Electron microscopic analysis also showed a reduction in the number of microtubules formed by neuronal γ-TuRC which contained fodrin when compared to HEK 293 derived γ-TuRC.

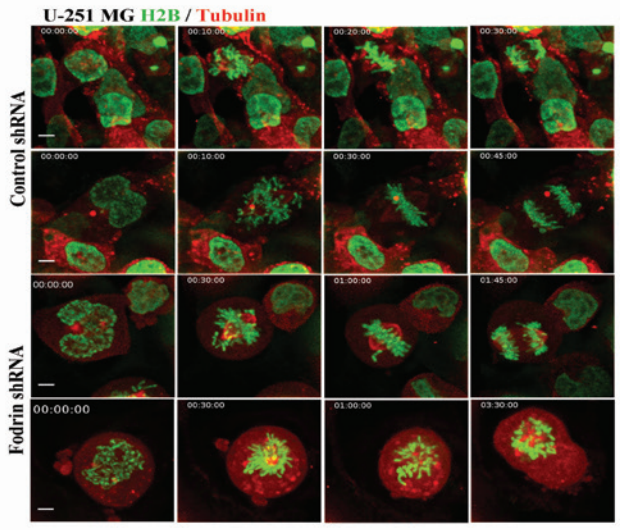

Figure legend

Fodrin depletion causes delayed mitotic progression. Cells were transfected with either control or fodrin shRNA and post 96 hours, live cell imaging was performed. Time taken for progression from nuclear envelope breakdown (NEB) to onset of anaphase was considered as the mitotic time.

TEAM / Rince John, Rohith Kumar, J.S. Sreeja, Dhrishya Dharmapal, Viji S.

AND DRUG REPOSITIONING

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Autophagy is a process by which essential building blocks of the cells are recycled to promote its survival. Efforts to inhibit autophagy so as to improve cancer therapy have thus attracted great interest. Mutations in p53 gene is a hallmark of tumor development, making it an attractive target for cancer therapeutics. In our exploration to develop specific targeting of mutant p53, destabilization of mutant p53 protein in SW480, MiaPaCa and MDAMB231 cell lines upon treatment with a thiazole antibiotic thiostrepton (THSP) was studied. THSP traditionally has been employed in veterinary medicine to treat dermatological disorders but in recent years has also emerged as a potential molecule for inhibiting Forkhead box Transcription factorM1 (FOXM1-a master cell cycle regulator). Autophagy process delivers cytoplasmic materials to lysosome for degradation through the formation of an autophagosome. LC3B I to LC3B II conversion was evident from our studies indicating the existence of autophagy induction upon THSP treatment. In order to elucidate the mechanism of thiostrepton triggered mutant p53 degradation, we explored the impact of proteasome inhibition on activation of autophagy. Combined treatment of thiostrepton and cycloheximide/chloroquine prevented the degradation of mutant p53 protein, reinforcing autophagy as the means of mutant p53 destabilization. Our initial studies suggested that mutant p53 degradation post THSP treatment was carried out by BAG3 mediated autophagy, based on the evidence of BAG1 to BAG3 switching. Subsequent interactome analysis performed post thiostrepton treatment revealed an association of p53 with autophagosome complex associated proteins such as BAG3, p62 and HSC70. Re-accumulation of p53 was seen in BAG3 silenced cells treated with thiostrepton, thereby confirming the role of BAG3 in destabilization of this molecule. Further, localization of p53 into the lysosome upon THSP treatment substantiated our findings that mutant p53 was degraded by an autophagic process.

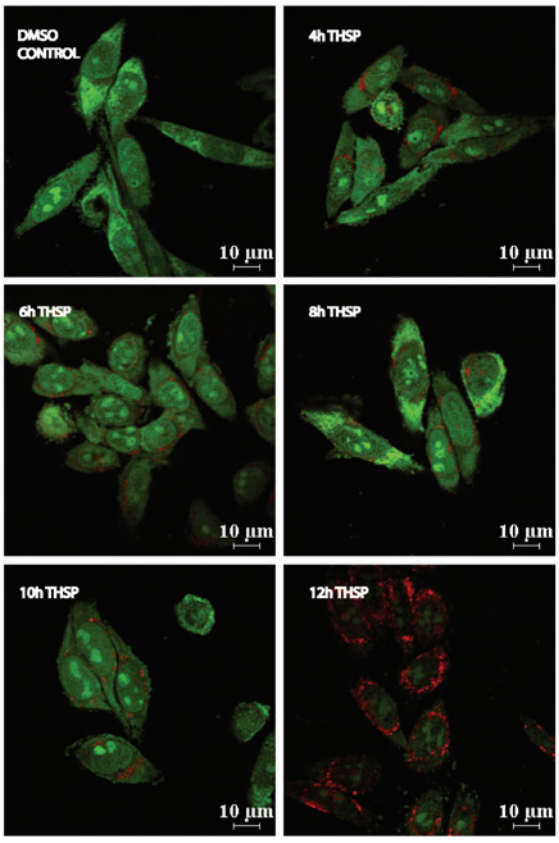

Figure legend

Acridine orange staining showing evident autophagosome formation in THSP treated cells compared to that of control (60×)

Relevant Publication

Thiostrepton degrades mutant p53 by eliciting an autophagic response in SW 480 cells. ***[J Cell Physiology 1-13, (2018) DOI: 10.1002/jcp.26601.]***
Dhanya K, Manu M, Maharrish C, John Samu, **Nair Asha**.

TEAM / Betsy M, Tapas Pradhan, Samu John, Anjana Soman, Ketakee Mahajan, Rajshree R Nair, S K Vijyalakshmi

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UNDERSTANDING EXCITOTOXICITY BIOLOGY-

In many neurodegenerative diseases glutamate induced excitotoxicity has been implicated as one of the causes of neuronal death. Calcium signaling influences growth cone responses to guidance cues and also guidance signaling. Semaphorin family of guidance molecules mainly act as chemorepellants. Semaphorin 3A expression is reported to be upregulated during ischemic condition and also in some neurodegenerative diseases.

Excitotoxicity model was been established in 9DIV rat primary cortical neurons by glutamate treatment. Microtubule associated protein -2 (MAP2), which is a neuronal marker was reduced upon glutamate treatment of primary neurons. Hence, MAP2 can be used as a marker for neuronal death in excitotoxicity. Cell death was also assessed by Hoechst staining. Semaphorin 3A showed altered expression in glutamate treated cortical neuronal cultures. Neuropilin 1, the receptor for semaphorin which stabilizes the semaphorin-plexin interaction was also found to be upregulated in the glutamate treated primary cortical neurons.

The expressions of the signal transducing receptors of semaphorin, plexin A1 and plexin A4 were upregulated in the glutamate treated primary cortical neurons. Semaphorin binding to different receptors will elicit different response in the cells. Immunocytochemistry analysis of glutamate treated primary cortical neurons showed enhanced expression of semaphorin 3A. The implication of these findings point that in excitotoxicity, semaphorin, binding to these receptors and successive signaling may be inducing regressive events. These findings warrant further analysis on semaphorin signaling during excitotoxicity.

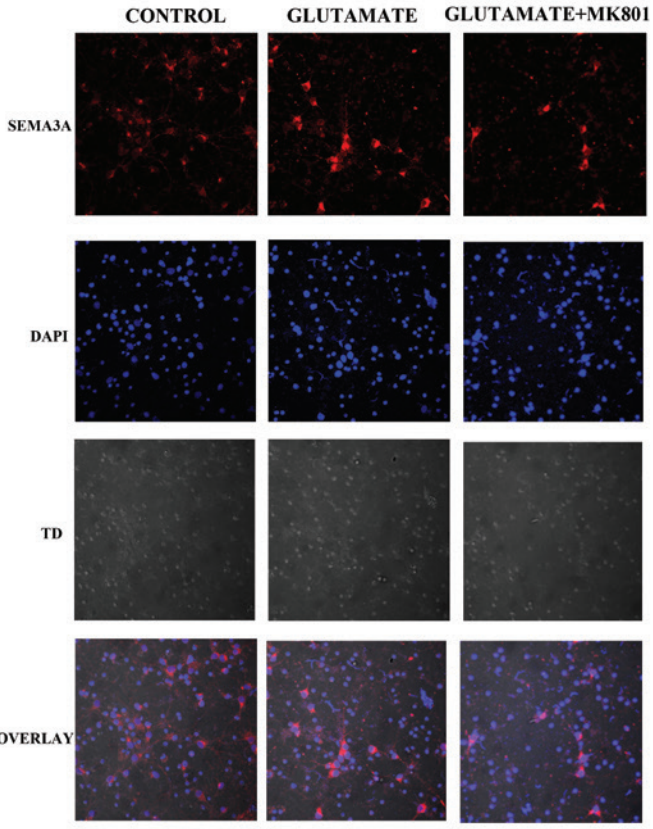

Figure legend

Primary cortical neuronal cells showing increased expression of semaphorin upon glutamate treatment. In excitotoxicity excess glutamate causes cell death.

AND CALCIUM DETECTION

Variations in intracellular concentrations of calcium regulate many of the neuronal functions, development, survival and death. The entry of extracellular calcium through the calcium channels and the calcium released by the intracellular organelles contribute to the changes in the intracellular calcium. Techniques that are real time, fast and sensitive are thus required for observing the transient changes in calcium in the cell.

A simple end point assay was developed based on the interaction of Calcium/calmodulin dependent protein kinase (CaMKII) with GluN2B subunit of the N-methyl-D-aspartate receptor. Exogenous GFP-α-CaMKII expressed in the cytosol of HEK-293 cells translocates to GluN2B, also exogenously expressed in the mitochondria or endoplasmic reticulam, upon calcium stimulation. This resulted in the formation of green fluorescent punctate appearance which can serve as a signal for calcium release. Calcium sensor cell line developed in our laboratory also gives fluorescent punctae in response to calcium that can be used for high throughput screening of calcium channels. The punctae is stable even after calcium removal and fixing and hence can be viewed without real time imaging. This also makes it possible to have multi field imaging of the same sample.

Genetically-encoded Ca2+ indicators (GECI) based on a single fluorescent protein such as GCaMP6m can respond to transient changes in the intracellular calcium. GCaMP6m shows variations in fluorescence intensity with changes in intracellular calcium. Hence these can be used for live cell imaging of neuronal activity. We made a comparative study on the stability of fluorescence upon calcium removal and upon sample fixing, steps that are involved in an end point assay, between our assay and the GCaMP6m fluorescence based assay. The fluorescent punctae in our endpoint assay does not fade away with EGTA washes or paraformaldehyde fixing. The enhanced fluorescent intensity of GCaMP6m decreases with the removal of calcium or upon fixing of the sample. Due to this drawback, it cannot be used as an endpoint assay. Moreover, multi field imaging of the same sample is also not possible with GCaMP6m.

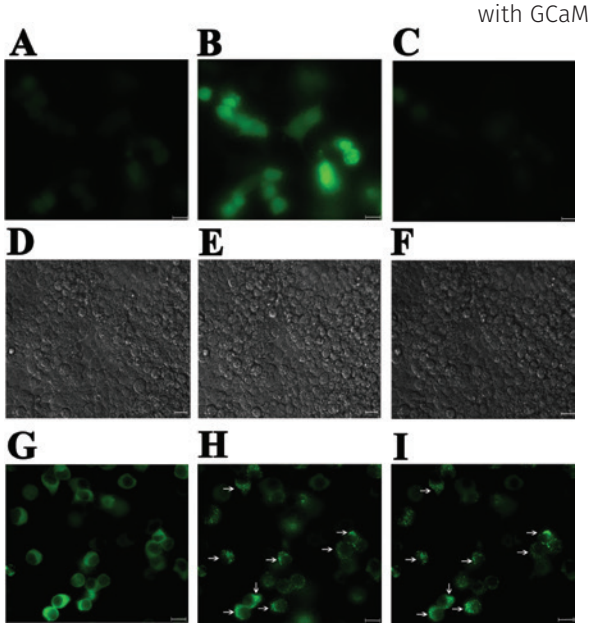

Figure legend

Calcium sensing by the end point assay was compared with that by a GECI, GCaMP6m. A, B and C show fluorescence of GCaMP6m transfected HEK-293 cells, before and after treatment with Ca2+ and after fixing, respectively. G, H and I show fluorescence images of the calcium sensor cells expressing GFP-α-CaMKII and MLS-NR2B, before and after Ca2+ treatment and after fixing, respectively. The white arrows indicate cells with punctate pattern.

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Relevant Publication

A Simple End-point Assay for Calcium Channel activity. ***[Cell Calcium, 2018 https://doi.org/10.1016/j.ceca.2018.05.009]***. Arunkumar, R. C., Steephan, M., Rajeevkumar, R., Suma Priya, S. D., Kumar, M., Paul, M., Mayadevi, M., and **Omkumar RV**.

TEAM / Arun Kumar R.C., Ramya. R. Prabhu, Mantosh Kumar, Lakshmi, K., Sowmya Gunasekharan, Reena Sarah Jacob, Sethu Lakshmi **COLLABORATORS /** Remya Chandran and C. Sadasivan, Kannur University, Kerala

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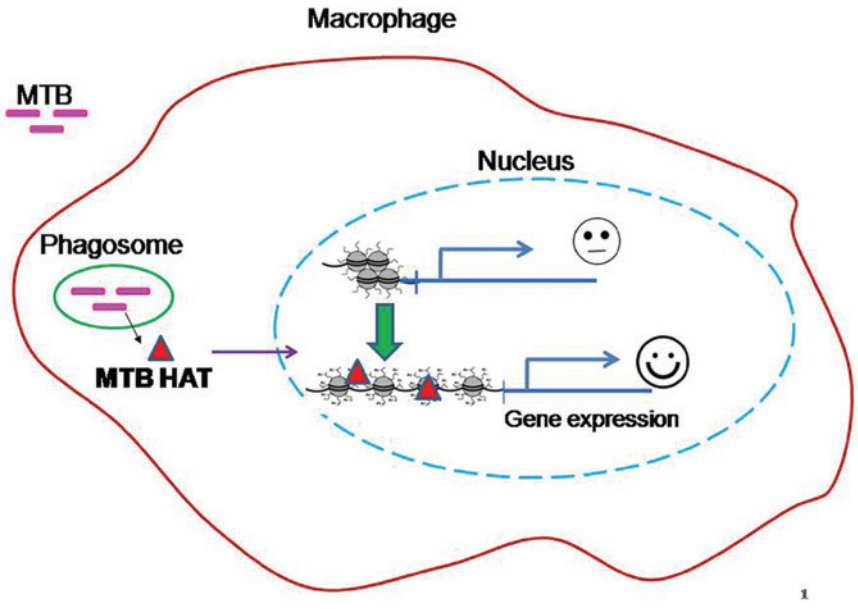
PATHOGENS PATHWAY ELUCIDATION-

Down-regulation of expression of genes that modulate host immune responses is one of the many strategies employed by successful intracellular pathogens. We showed that during MTB infection the levels of host histone deacetylase 1 (HDAC1) goes up significantly with a concomitant reduction in the levels of histone H3-acetylation in macrophages. We further demonstrated that HDAC1 is recruited to the promoter of IL-12B in macrophages infected with virulent MTB, and the subsequent hypo-acetylation of histone H3 suppresses the expression of this gene that plays a key role in initiating Th1 responses. IL-12 is a key cytokine in the Th1 responses. Its production is up regulated when a healthy person is infected with MTB and this leads to a cascade of events that finally eliminates the invading bacteria. By interfering with the formation of functional IL-12, MTB succeeds in surviving in the host. Interestingly knockdown of HDAC1 in macrophages reduced the survival of intracellular MTB significantly. Our recent findings indicate that it is the phosphorylated form of HDAC1 that is recruited to the promoter of IL-12B. We have identified certain host and bacterial proteins that interact with phosphorylated HDAC1 to bring about repression of gene expression in infected macrophages.

Conversely, we have discovered an interesting counter phenomenon also in MTB-infected macrophages. We identified and characterized a novel 8 KDa histone acetyltransferase (MTB HAT, Rv3423.1) of mycobacterial origin that acetylates histone H3 at Lysine 9/14 positions. We have shown that a few macrophage genes get up regulated in infected macrophages due to the recruitment of this HAT to their promoters. We have also generated a knockout strain of MTB deficient in Rv3423.1 gene.

Figure legend

Diagram depicting the probable mechanism by which histone acetyltransferase secreted by *Mycobacterium tuberculosis* (MTB HAT) effects host gene expression by acetylating histones at the promoter region.



TEAM / Krishna Kurthkoti, Aravind Madhavan, Arun B, Laiza Paul, Ranjit Ramachandran Sajith Raghunandanan, Akhil Raj, Balaji M, Jijimole, Leena Desai Rajkumar Sreejith R

AND BIOFILM GENOMICS

Bacterial biofilms pose a serious problem for wound healing in chronic infections. Chronic wound biofilm is composed of diverse polymicrobial communities and rapid high-throughput genomic approaches have revolutionized the ability to identify and quantify the microbiome associated with wound infections. Bacterial diversity of 100 chronic diabetic ulcer samples were profiled via culturing and metagenomic analysis. Results showed that *Enterococcus, Pseudomonas, Proteus, Staphylococcus* and *Streptococcus* were the predominant biofilm forming genera. The establishment of bacterial biofilm over wound tissues was proved using fluorescent in situ hybridization and scanninfg electron microscopy (SEM) imaging (Figure). Whole genome sequencing of *Enterococcus faecalis*, a good biofilm former, revealed presence of mobile genetic elements including phages and genomic islands, a sex pheromone responsive plasmid and other aggregation substances which contributes to its biofilm forming potential. Genome analysis in comparison with non-biofilm forming strains yielded a pan-genome of 4209 genes, of which 1357 were core genes (32.2%). Clusters of Orthologous Genes (COG) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis revealed that the genes unique to biofilm formers involve those associated with defense mechanisms, polysaccharide metabolism, phosphotransferase system and two-component systems. Comparative genomics signifies the role of fsr (*Enterococcus faecalis* quorum-sensing locus) two-component system and a polysaccharide lyase in biofilm formation. Several adhesion associated factors, putative transcriptional regulators, phosphotransferase system and certain phage-associated proteins are found exclusively in biofilm formers.

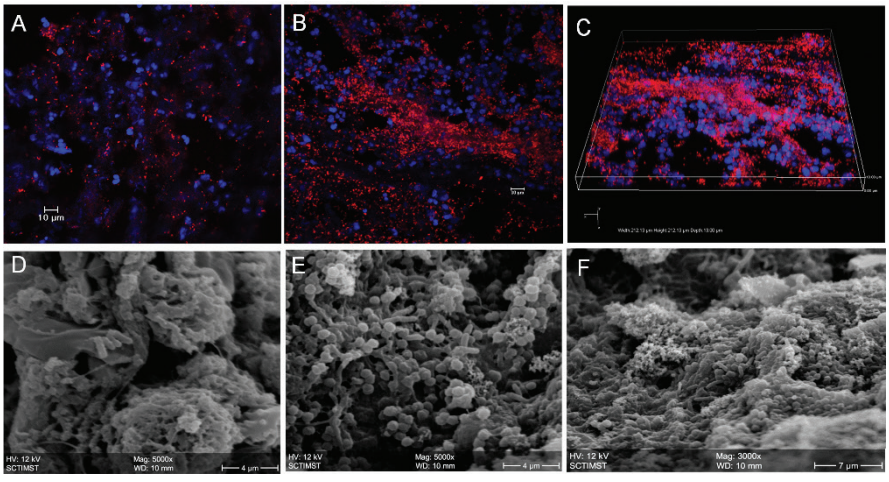


Figure legend

In-situ visualization of biofilm in wound tissue. Fluorescent *in situ* Hybridization shows bacterial cells (red) attached to the host wound debridement tissue (blue -DAPI). A) Acute wound, B) Chronic wound with bacterial biofilm, C) Isometric view of biofilm. SEM images of (D) Acute wound with planktonic bacterial cells, 5000x, (E & F) Chronic wound with clustered bacterial biofilm, 5000x & 3000x respectively.

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Relevant Publication

Metataxonomic approach to decipher the polymicrobial burden in diabetic foot ulcer and its biofilm mode of infection. ***[International Wound Journal 2018, 15(3): 473-481]***.
Karthika S, Joby John, Megha P.R, George.S and **Sabu Thomas**

TEAM / Divya M.P, Karthika. S, Lekshmi. N, Sudha B Nair, Devika Das J, Megha P.R, Merin Paul, Saritha K.L
COLLABORATORS / Joby John, Department of Surgery, Government Medical College Hospital, Trivandrum

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Relevant Publication

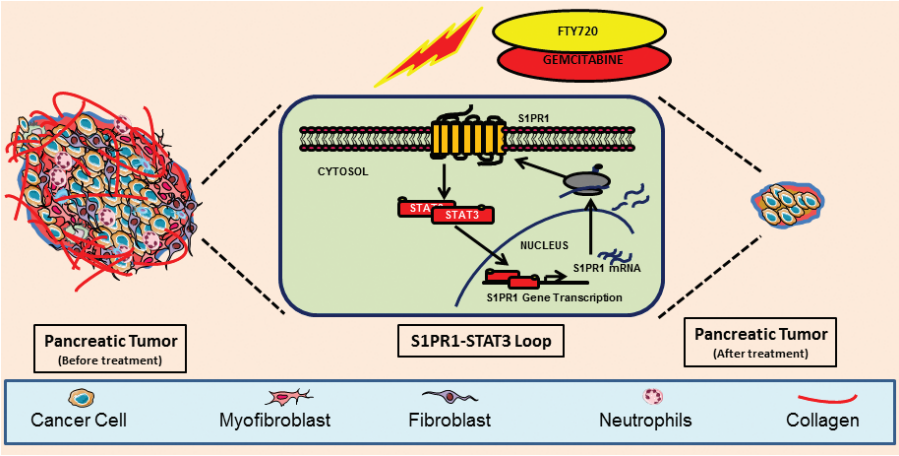
Targeting S1PR1/STAT3 loop abrogates desmoplasia and chemosensitizes pancreatic cancer to gemcitabine. ***[Theranostics 2018; 8(14): 3824-3840]***. Lankadasari MB, Aparna JS, Mohammed S, James S, Aoki K, Binu VS, Nair S, **Harikumar KB.**

DECIPHERING CHEMOSENSITIZATION-

Sphingosine 1-Phosphate (S1P) is a pleiotropic lipid molecule present inside cells and acts either intracellularly or through cell surface G protein-coupled receptors (S1P receptor, S1PR 1-5). S1PR1 has been reported to be a key factor responsible for persistent STAT3 activation in different tumor types. However, the precise role of S1PR1 in pancreatic cancer is not clear. Fingolimod (FTY720) is the first FDA-approved oral drug for the treatment of the relapsing form of multiple sclerosis. FTY720 also acts as a functional antagonist to S1PR1. Our results established FTY720 as a molecule that increases the efficacy of gemcitabine and is a promising agent in the management of pancreatic cancer mainly through inhibition of S1PR1/STAT3 loop. We observed that FTY720 treatment reduced the expression of S1PR1 in pancreatic cancer tissue. This was related to p-STAT3 levels whose expression was abolished by treatment with FTY720 and gemcitabine. To understand how S1PR1/STAT3 pathway regulates desmoplasia and subsequently inhibition of pancreatic cancer progression, the role played by Shh signaling was evaluated. We observed that mRNA transcripts of both Shh and Gli-1 were significantly upregulated while Gli-3, a known suppressor of desmoplastic changes, was considerably downregulated in the group treated with gemcitabine alone. Collectively, these data suggested that inhibition of S1PR1/STAT3 loop resulted in inactivation of Shh pathway and desmoplasia, reduced resistance to gemcitabine, and improved the delivery of gemcitabine to tumor sites.

Figure legend

Graphic illustration showing that by targeting S1PR1/STAT3 loop in pancreatic cancer leads to reduction in desmoplastic content resulted in increased accumulation of gemcitabine and decrease in the growth of pancreatic cancer.



TEAM / Asha P, Sabira Mohammed, Manendra Babu L, Yadu Vijayan, Shirley James, Sreesha S Kumar, Anu B, Prameela Kumari TK

AND NON-CODING RNAs

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P- element induced Wimpy testis (Piwi) proteins, a subfamily of argonaute proteins, mediate their function by interacting with a specific class of small non-coding RNAs called piRNAs. The Piwi-piRNA pathway plays a critical role in germ cell formation and germ stem cell maintenance by transposon silencing. Increasing evidence indicate that Piwi proteins are inevitable for maintenance of stem cells and can act as guiding signals for many epigenetic factors. Since expression levels of Piwi proteins and associated piRNAs showed aberrant expression patterns in various cancers and their expression is majorly confined to stem cells, we hypothesised that they may have a regulatory role in the maintenance and self-renewal of cancer stem cells (CSC). We therefore investigated involvement of Piwi proteins in CSC maintenance cervical cancer cells. There are four Piwi homologs in human: PiwiL1-4 and all were present in cervical cancer cells. Among them, PiwiL1 homolog showed significant expression and exhibited differential sub-cellular localization in response to human papillomavirus (HPV) infection. The observation that PiwiL1 expression was significantly high in the presence of HPV oncogenes, suggested that a correlation with these oncogenes. To further analyze this, we performed an in silico docking analysis with PiwiL1 protein and HPV oncogenes, E6 and E7. PiwiL1 has three main domains: PIWI, PAZ and MID (Figure A). *In-silico* docking experiments predicted a possible interaction of E6/E7. E6 of HPV-16 showed interaction with PAZ domain (Figure B) whereas that of HPV-18 showed a weak interaction (Figure C), as indicated by the binding energy values. On the other hand, E7 showed an interaction with PAZ domain (Figure D & E). Whether this has any influence on the differential cellular localization of PiwiL1 that was observed with respect to presence of HPV oncogenes has to be further validated.

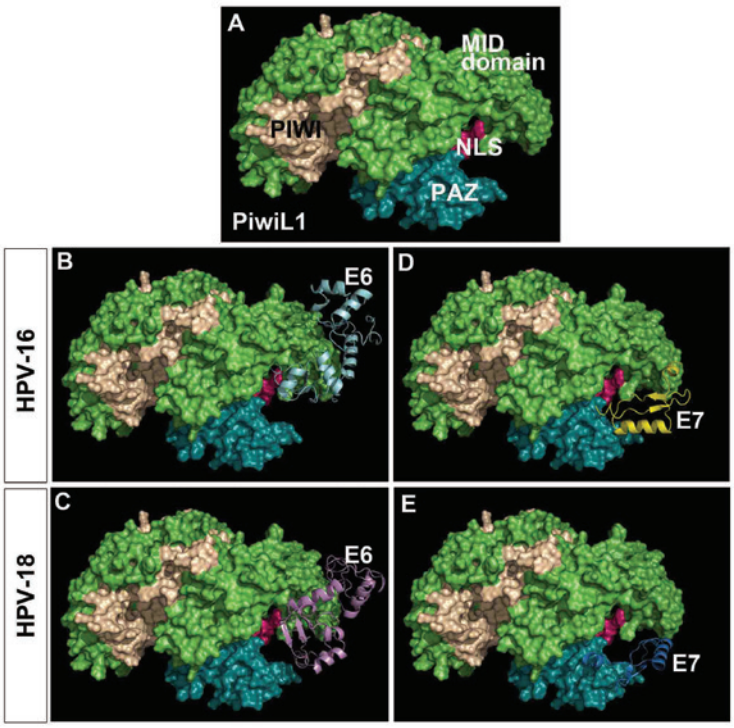

Figure legend

PiwiL1 could be interacting with HPV oncogenes. (A) Crystal structure of PiwiL1. (B-C) Interaction with E6 proteins from HPV-16 and -18. (D-E) Interaction with E7 proteins from HPV-16 and -18. Both E6 and E7 have been represented as ribbon structure.

TEAM / Midhunaraj K, Mary Angelin

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Relevant Publication

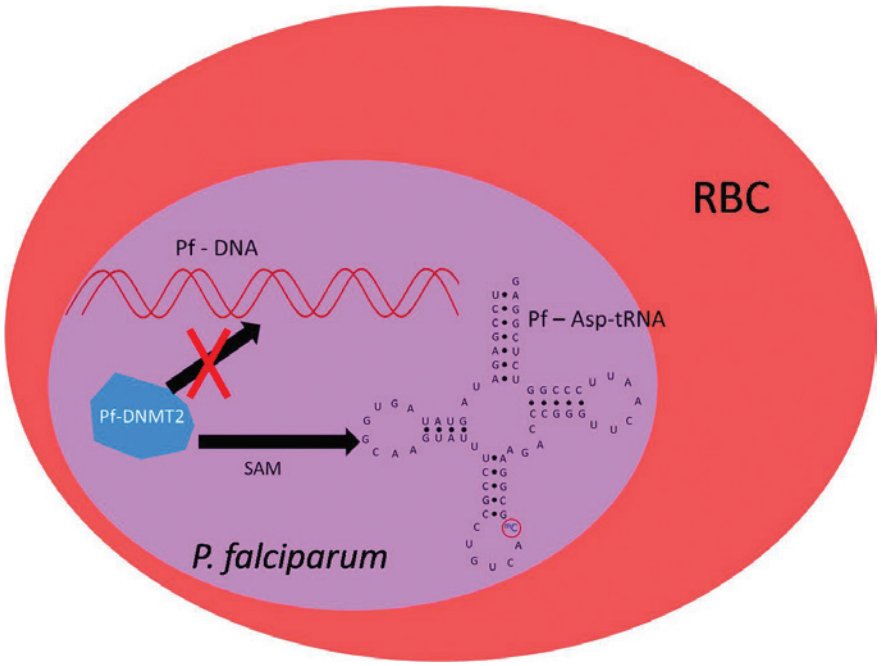
DNA methyltransferase homologue TRDMT1 in Plasmodium falciparum specifically methylates endogenous aspartic acid tRNA. ***[Biochim Biophys Acta – Gene Regulator Mechanisms. 2017 Oct; 1860(10): 1047-1057]***. Govindaraju G, Jabeena CA, Sethumadhavan DV, Rajaram N, **Rajavelu A**

FROM PLASMODIUM EPIGENETICS-

The parasite *Plasmodium falciparum* has a complex life cycle with a complex genetic make-up. The gene regulatory mechanisms are poorly studied and there is lack of clarity on DNA methylation. Importantly, DNA methylation is absent in other apicomplexan group of protozoan parasites such as Toxoplasma and Cryptosporidium. Genome sequencing of the parasite revealed presence of a putative C5 methyltransferase, a homologue of DNMT2 called TRDMT1 (tRNA Aspartic acid Methyltransferase 1). However it was unclear whether *P. falciparum* TRDMT1 methylates DNA and/or tRNA. We investigated the presence of cytosine methylation in the nucleic acids *P. falciparum* and found that parasite carries TRDMT1, a conserved homolog of DNA methyltransferase DNMT2. We also found that TRDMT1 did not methylate DNA in vitro (Figure). TRDMT1 mediated C38 methylation of aspartic acid tRNA could thus play a critical role by translational regulation of important proteins and modulate the pathogenicity of the malaria parasite. The highlights of the work thus includes a first report on the tRNA methylation in any apicomplexan group of parasites (*Plasmodium, Toxoplasma, Cryptosporidium, Isospora* and *Babesia*) and that *P. falciparum* proteome is enriched for proteins with polyAsp repeats which are functionally important and methylation of aspartic acid tRNA could modulate *P. falciparum* pathogenicity through translational regulation of functionally important proteins.

Figure legend

Schematic representation of Pf DNMT2 activity in *P. falciparum*. The TRDMT1 (DNMT2) specifically methylates tRNA asp and does not prefer DNA as substrates.



TEAM / Gayathri G, Jabeena CA, Devadathan VS, Nivethika R

TO SCHIZOPHRENIA EPIGENETICS

Epigenetics refers to interaction of gene and environment. Impact of environment on genome is studied based on patterns of alterations in methylation, chromatin modifications and microRNA. Our laboratory has been investigating the significance of epigenetics in Schizophrenia. We earlier reported that genetic variants in DNA methyltransferases are themselves associated with Schizophrenia. This is crucial since the threshold of environmental insults will be determined by these genes. This findings prompted us to evaluate all historical data on alteration in methylation, chromatin modifications and microRNA in Schizophrenia. We found that majority of the data presented was on post mortem samples or patients from conventional treatment protocol. This further prompted us to question whether the reported patterns of epigenetic alterations are for the disease (Schizophrenia) or whether it is influenced by antipsychotic drugs. By evaluating these historical data from various published articles we presented our perspective which indicates that the reported alterations in host epigenome might be influenced by antipsychotic drugs ie whether antipsychotic drugs can modulate the human epigenome and if so, whether the drug induced epigenetic modulation can explain the heterogeneity in drug response. To resolve this issue the global DNA methylation, expression status of epigenetic genes and their crosstalk with microRNAs were studied first in an *in-vitro* system followed by validating the observations in patients. *In-vitro* data demonstrated that antipsychotic drugs induce epigenetic response by downregulating microRNA that target DNA methyltransferases, resulting in global hypermethylation. A similar trend was observed in patients as well and alterations were markedly associated with drug response rather than disease pathogenesis.The study demonstrates an epigenetic mode of action for antipsychotic drugs and suggests for a careful interpretation of epigenetic alteration in pathogenesis of schizophrenia.

Subsequently, it was imperative to differentiate the role of host epigenetics from pharmacoepigenetics in resolving therapeutic response. Here too the pharmacoepigenetic response of haloperidol, clozapine and olanzapine was first investigated in-vitro by monitoring the alterations in expression of ABCB1,CYP1A2 and CYP3A4, promoter methylation and their target microRNA expression studies. Critical observations were then followed up in patients. In-vitro antipsychotic drugs enhanced expression of ABCB1,CYP1A2 and CYP3A4 which seems to be regulated by miR-27a and miR-128a and not methylation. A similar pattern was observed in patients as well in regard to ABCB1. This study too demonstrates that antipsychotic drugs can influence miRNA mediated epigenetic response in pharmacogenes resulting in modulating therapeutic response.

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Relevant Publication

Pharmacoepigenomic response of antipsychotic drugs on pharmacogenes is mediated by microRNAs. ***[Epigenomics, 2017, 9(6):811-821]***. B Swathy, KR Saradalekshmi, IV Nair, CM Nair, **Moinak Banerjee**

Haloperidol induces pharmacoepigenetic response by modulating miRNA expression, global DNA methylation and expression profiles of methylation maintenance genes and genes involved in neurotransmission in neuronal cells. ***[PloS one 2017, Sep 8;12(9): e0184209]***. B Swathy, **Moinak Banerjee**

TEAM / Aswathy PM, Ann Mary Alex, Shafeeque CM, Sindura KP, Binithamol K Polakkattil, Bindu Asokan, Sheela G

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Relevant Publication

Characterization of a novel asparaginase from soil metagenomic libraries generated from forest soil. ***[Biotechnol Lett. 2018, 40(2):343-348]***. Arjun J K, Aneesh B, Kavitha T and **Hari Krishnan K**

MICROBES PROVIDING CANCER DRUGS-

Microorganisms are key sources for several novel biomolecules beneficial to mankind. But most of these resources are inaccessible, since majority of them are recalcitrant to cultivation. The potential of these uncultivable fractions can be explored through the culture independent metagenomic approach which solely depends on the analyses of genetic information available in their collective community DNA. Through this approach, we generated metagenomic DNA libraries from forest soil and their functional screening revealed a potential clone harboring L- asparaginase gene. The gene was subcloned and generated a recombinant system overproducing asparaginase and the specific activity of the novel purified enzyme (200 IU/mg) was much higher compared to commercial *Escherichia coli* L-asparaginase.

L-asparaginase of bacterial origin is one of the principal components for the treatment of acute lymphoblastic leukemia, derived from a very small fraction of cultivable bacteria and evokes several side effects during therapy. Considering the demand for asparaginases with improved therapeutic potential and immune-compatibility, the novel asparaginase obtained was characterized, which showed significantly better cytotoxicity against leukemic cell lines. The IC50 of the recombinant protein on HL-60 cell line was 0.78 µg/ml and that of MOLT-3 and MOLT-4 cell lines was 0.39 µg/ml (Fig.1), which is better than that of the commercial E. coli asparaginase (1.4 µg/ml). The enzyme showed optimum activity at pH 7 and 35oC and the presence of Mg2+, Ca2+and K+ enhanced the activity indicating its suitability for human use. The cytotoxicity of the recombinant asparaginase was further confirmed by DNA fragmentation assay. The toxicity of recombinant asparaginase was further evaluated in healthy mice and the histopathology analysis did not reveal any lesions suggesting that the enzyme has no toxic effect on normal tissues. Moreover, the in-vitro studies with human serum and blood samples revealed the enzyme is highly stable and hematocompatible. All these characteristics represent an excellent background to develop this enzyme as a potential antileukemic therapeutic agent.

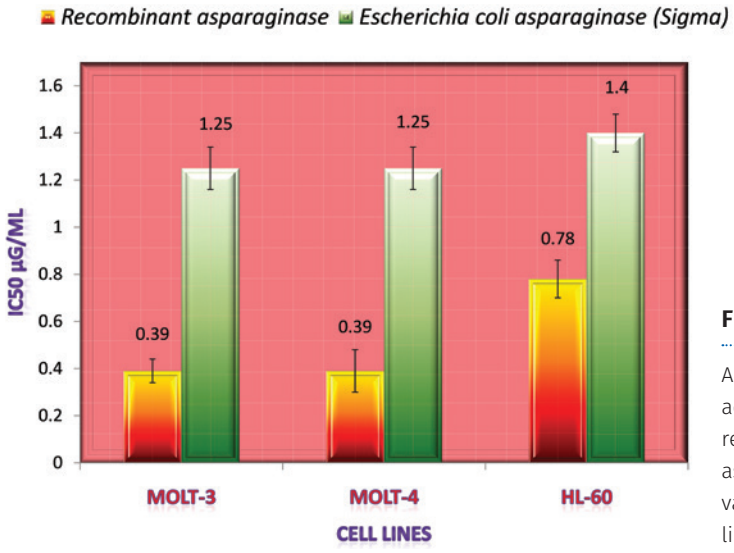

Figure legend

Antiproliferative activity of recombinant asparaginase against various leukemic cell lines.

TEAM / Arjun. J.K, Aneesh. B , Kavitha T, Geetha. S. L

TO BECOMING DRUG RESISTANT

By focusing on microbial genome evolution, the emphasis of our current research is on reconstructing the evolutionary history of antibiotic resistant microbial pathogens whose genomes are completely sequenced. Methicillin-resistant strains of *S. aureus* (MRSA) is now a problem worldwide and is increasingly recovered from both hospital and community settings. *Staphylococcus aureus* acquired the ability to be resistant to multiple antibiotics including penicillin, methicillin, vancomycin etc. The mecA gene encodes for a penicillin-binding protein (PBP2) that has a low affinity for most of the semisynthetic and most cephem agents. The MecA and its regulators are encoded in a transposable element called SCCmec and widely spread across the *S. aureus* strains. A better understanding of the origin and evolutionary route of antibiotic resistance genes encoded from the transposable element is not yet clear. We performed a detailed phylogenomic analysis of 152 *S. aureus* genomes from different hosts with reference to 7,251 bacterial genomes available in the NCBI database. Our results show that crucial genes that are responsible for the maintenance and functioning of the SCCmec cassette (mecA, mecR1, mecI, orfX, IS431, tn554, ccrA1, ccrB2 cad, cop and ars genes) were universally or nearly universally distributed within Staphylococcus species level (Figure). There are 6 Staphylococcus species including *S. sciuri, S. pseudointermedius, S. lutrae, S. epidermidis, S. argenteus* and *S. haemolyticus* showing a high sequence similarity (>90%) with SCCmec elements of S. aureus. By analyzing the distribution pattern and maximum-likelihood phylogenies of SCCmec genes of *S. aureus* with its homologs from different taxonomic levels, we hypothesize that SCCmec elements in *S. aureus* might have been assembled in one of the common ancestors of *Staphylococcus aureus* and spread across multiple species via vertical and lateral evolution. In another phylogenetic study, we observed that MRSA strains circulating in India are forming a monophyletic clade with reference to globally circulating ones. This gives the clue that, Indian strains have a single origin of type IV MRSA which is under current circulation.

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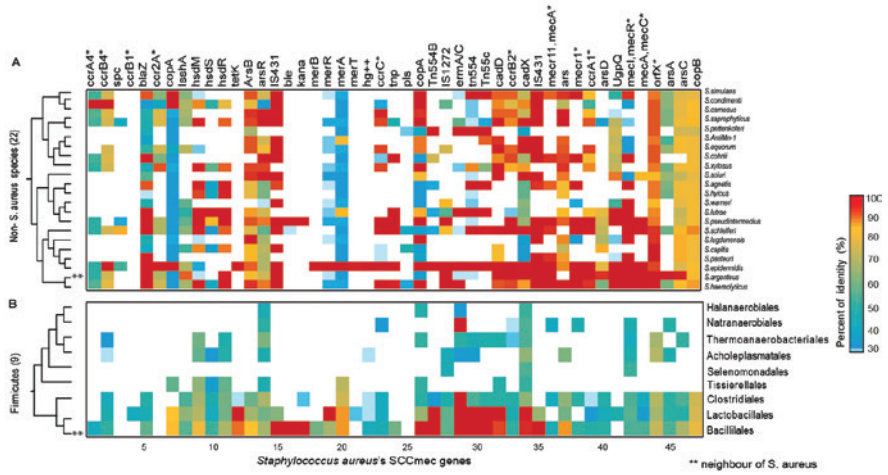

Figure legend

Distribution of SCCmec gene families in non-S. aureus species: X-axis labelled with 47 SCCmec gene families and Y-axis is representing the 16srRNA tree. A Matrix cells are representing the BLAST identity percentage of SCCmec gene families in 22 non-S. aureus species. B depicts presence of homologous sequence to SCCmec genes in 10 firmicutes order level.

TEAM / Jiffy John, Sinumol George, Sabrina Rayen, Govind Krishnadas

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Relevant Publication

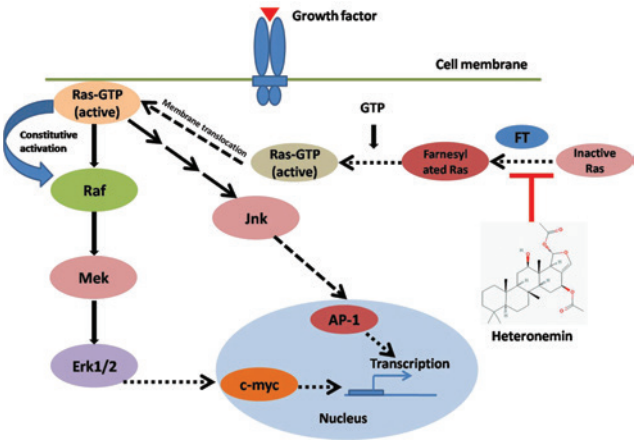
Heteronemin, a marine natural product, sensitizes acute myeloid leukemia cells towards cytarabine chemotherapy by regulating farnesylation of Ras, ***Oncotarget, 2018, 9, 18115-18127***
Saikia M, Archana P.R, Shabna A, NP Anto, Mittal R, Shabna S, Pillai KS, B S.Vinod, V. Peter, Thomas R and **Ruby John Anto**.

BIODIVERSITY PROVIDING LIFE SAVERS-

We demonstrated that heteronemin, a marine natural product, sensitizes acute myeloid leukemia cells towards cytarabine chemotherapy by regulating Ras. Constitutively active Ras has been implicated in several malignancies, most importantly hematological malignancies. Acute Myeloid Leukemia (AML) is a hematological malignancy implicated by the abnormal clonal proliferation of myeloid progenitor cells in bone marrow and peripheral blood for which currently cytarabine is a front line chemotherapeutic. However, cyatarabine exhibits several toxic side effects including immune-suppression and chemoresistance. In the current study, we have used heteronemin, a sesterterpene isolated from marine sponges, for sensitizing AML cells towards the action of cytarabine. Heteronemin is reported to have farnesyl transferase inhibitory action. Since farnesylation is a crucial event in the activation of Ras, induced by the chemotherapeutic drug, cytarabine, we hypothesized that heteronemin can act as an effective chemosensitizer for AML chemotherapy. Our studies showed that heteronemin sensitizes HL-60 AML cells towards cytarabine, without causing significant toxicity towards peripheral blood mononuclear cells isolated from healthy volunteers. Ras pull down assay showed that heteronemin significantly inhibited the expression of cytarabine-induced active Ras (Ras-GTP), in HL-60 cells. Further, pre-treatment with heteronemin caused significant inhibition of cytarabine-mediated activation of various MAPK proteins (ERK, JNK and p38) instigated by Ras signaling. Moreover, cytarabine-induced nuclear translocation of AP-1 and NF-κB the downstream effector molecule of MAPK pathway was almost completely inhibited by heteronemin as assessed by electrophoretic mobility shift assay (EMSA). Further, cytarabine induced-c-myc over-expression is significantly down regulated by heteronemin in the cells treated with their combination.

Figure legend

Heteronemin sensitizes acute myeloid leukemia cells to Cytarabine, by down-regulating the expression of active Ras (Ras-GTP) and MAPK signaling. Heteronemin binds to the active site of farnesyl transferase (FT), inhibiting the addition of farnesyl moiety to inactive Ras, thus preventing the translocation of Ras to the plasma membrane from cytoplasm. This in turn prevents the activation of Ras, by inhibiting the formation of Ras-GTP. This further abrogates MAPK signaling, and cytarabine-induced nuclear translocation of AP-1 and NF-κB, the downstream effector molecules of MAPK pathway. Cytarabine induced-c-myc over-expression is significantly down-regulated by heteronemin in the cells treated with their combination.



TEAM / Archana.P.R, Liju.V.B, Haritha H. Nair, Minakshi Saikia, Mohan Shankar G, Shabna A, Shabna S, Swetha M, Aiswarya U.S, Vijay Alex, Jannet S

In 2010, the *Chlorella* genome was decoded and presence of various classes of genes was discovered in this micro alga. The question we address is whether hormone biosynthesis and signaling genes can be utilized for generating *Chlorella* lines which have high efficiency of photosynthesis, improved ability to absorb toxic metals and increased accumulation of biomass. We previously reported a total of 305 genes related to hormone biosynthesis and signaling that could be annotated using homology based search and reciprocal BLAST. A gene related to cytokinin (CRG), one related to jasmonic acid (JARG) and one related to auxin (ARG) were selected for further functional characterization. The growth phases of *Chlorella* can be clearly demarcated into LAG, LOG and Stationary phases. The expression of the selected genes was checked during these phases using RT-PCR. CRG and JARG have higher expression during LAG and LOG phase whereas their expression decreases during stationary phase. ARG on the other hand has higher expression during stationary phase. It thus appears that CRG and JARG may have a role during active cell division and cell growth phase. Subcellular localization of the three selected proteins was studied in onion epidermal cells where CRG was seen to localize in both nucleus and cytoplasm whereas JARG and ARG were seen as punctate fluorescence in the cytoplasm which maybe in one of the organelles. CRG is a cytokinin riboside 5'-monophosphate phosphoribohydrolase which helps in the release of cytokinin nucleobase and ribose 5'-monophosphate. This enzyme hydrolyzes only cytokinin riboside 5'-monophosphate but not AMP, suggesting that it is specifically involved in cytokinin activation. Stable overexpression and silencing transgenics for CRG gene were prepared and confirmed by PCR. Overexpression of CRG led to a longer stationary phase of these lines whereas the counterpart wild type had already entered the death phase as is visible from the difference in the intensity of green colour of chlorophyll (Figure A). Further there was a marked difference in the cell size between CRG OX and WT as is visible from the photographs which was also confirmed by measuring the diameter of these cells (Figure B, C). The CRG OX lines had almost 3 times more chlorophyll as compared to the WT. There was no visible phenotypic difference between CRG RNAi lines and WT. This is evidence for the CRG protein functioning in the cytokinin pathway as the cells were alive for a longer period than the wildtype. It is well known that cytokinin positively affects chloroplast development and in the CRG OX lines the chlorophyll content was higher than the wild type.

AND ENERGY SOURCES

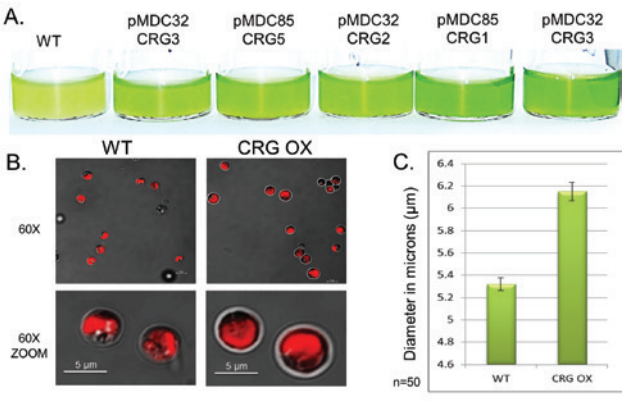


Figure legend

Functional characterization of a cytokinin related gene (CRG) in *Chlorella*; (A) Overexpression (OX) phenotype of CRG (B) Comparison of wildtype Chlorella and CRG OX cells (C) Comparison of diameter of the wild type Chlorella and CRG OX cells.

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Relevant Publication

A survey of MIKC type MADS-box genes in non-seed plants: Algae, Bryophytes, Lycophytes and Ferns. **Front Plant Sci. 9,1-13** Thangavel G and **Nayar S.** (2018).

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DISEASE CHOLESTEROL RHYTHMS-

We investigate how compartments and components of endocytic machinery co-ordinate uptake, sensing and integration of various signals and nutrients. Aberrations in this process are hallmarks of cancer, metabolic and neurological diseases. Furthermore, viruses and intracellular pathogens hijack endocytic machinery for cellular entry and dissemination. Hence understanding this process is of utmost importance. Endocytosis plays a major role in signal integration by transporting and processing signals in membrane-bound compartments (endosomes and lysosomes) and by recruiting sensors and integrators on their limiting membrane. However, underlying molecular mechanisms remain elusive. Our investigations focus on delineating these mechanisms in physiological and pathological states. For this, we use cell biological, biochemical and genetic approaches in cultured cells and vertebrate model, zebrafish. Currently, we are focussing on two kinases that are associated with endocytic compartments. One is a novel, uncharacterized kinase, termed BMP-2 inducible kinase (BMP2K) that localizes to endocytic clathrin-coated pits on plasma membrane. Ectopic expression of BMP2K in zebrafish embryos results in developmental defects. Currently we are generating gene knockouts and mutants to delineate the functional part of BMP2K in cells and zebrafish embryos. To further unravel the mechanism, we are identifying potential substrates and interacting partners of BMP2K using high throughput screens. Another kinase is mTOR, the master integrator of growth and metabolism that gets activated on lysosomes in a regulated fashion. Our investigations reveal that cholesterol regulates mTOR signaling on lysosomes. Currently, we are deciphering the mechanisms of cholesterol sensing and mTOR activation on lysosomes by creating knockouts and mutants of cholesterol transporters, LDLR and NPC1. Together, this will help us understand how endocytosis evolved for signal/ nutrient sensing and integration in eukaryotes and how it goes awry during diseases.

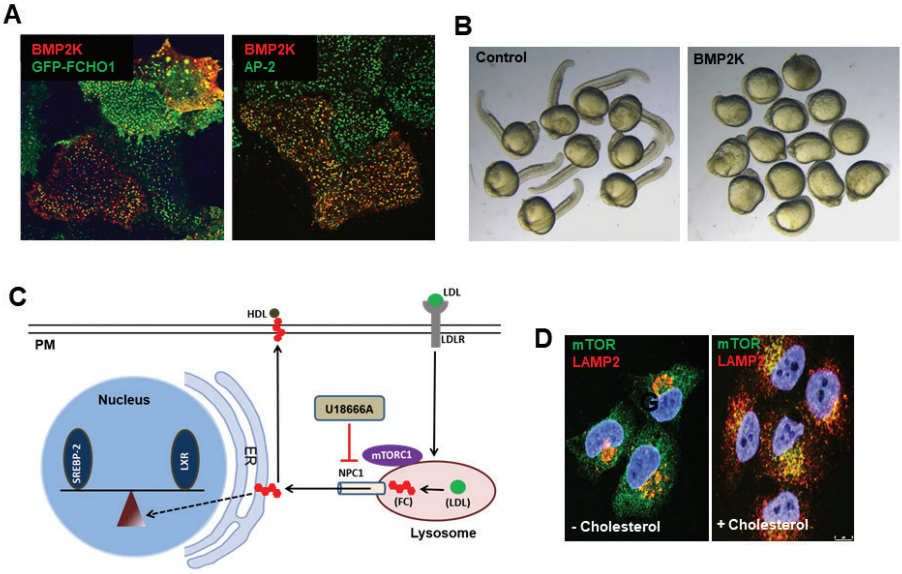

Figure legend

Confocal sections of cells showing co-localization of BMP2K with GFP-FCHO1 or AP-2 in surface clathrin -coated pits revealed by immunofluorescence. B. Morphology of zebrafish embryos at 24 hours post fertilization expressing control or BMP2K mRNA microinjected at one-cell stage. C. Cartoon depicting cholesterol uptake, transport and signaling in cells. D. Cholesterol-mediated recruitment of mTOR on lysosomes.

TEAM / Nishada Qathoon, Reshmi P B

AND BROWN FAT DYNAMICS

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Adipose tissue is classified into two main categories: white adipose tissue (WAT) and brown adipose tissue (BAT). Both play a crucial role in regulating energy homeostasis. The transition from a white to brown fat phenotype (brown-like/beige cells) is associated with protection against metabolic disease. However, the brown adipose tissue (BAT) and/or beige fat function decline with age; the underlying molecular link between aging impaired thermogenesis and its impact on metabolic complications are not studied yet. Our research interest centers on the impact of brown and/or beige fat function on age related obesity and insulin resistance. As reported previously, Early B cell factor 2 (EBF2) is a major transcription factor in brown fat development. However, several unanswered questions relating to lineage commitment and the mechanism by which transcription factors regulate brown and beige fat size, functionality, number and maintenance of pre-adipose stem cells under various metabolic conditions remain elusive. We thus identified and validated molecules that interact with EBF2 in brown fat and their deletion constructs for further analyses. For domain mapping experiment, we generated a set of EBF2 variants by altering/deleting an N-terminal DNA binding domain (DBDΔ, 1-246aa) and a point mutant (237-239SKHΔ), helix-loop-helix and C-terminal transactivation domain (HLH-CTDΔ, 338-575 aa) and CTD required for transactivation functions (CTDΔ, 382-575aa) respectively. Further, we implemented CRISPR/Cas9 and sh-RNA mediated knock out/down of EBF2 to obtain Ebf2 knockout (KO) cells. The wild type and KO cells were tested for their efficacy in adipogenesis and thermogenesis (Figure). We also examined the pioneering function of EBF2 and its interacting molecule at BAT-selective gene regulatory elements.

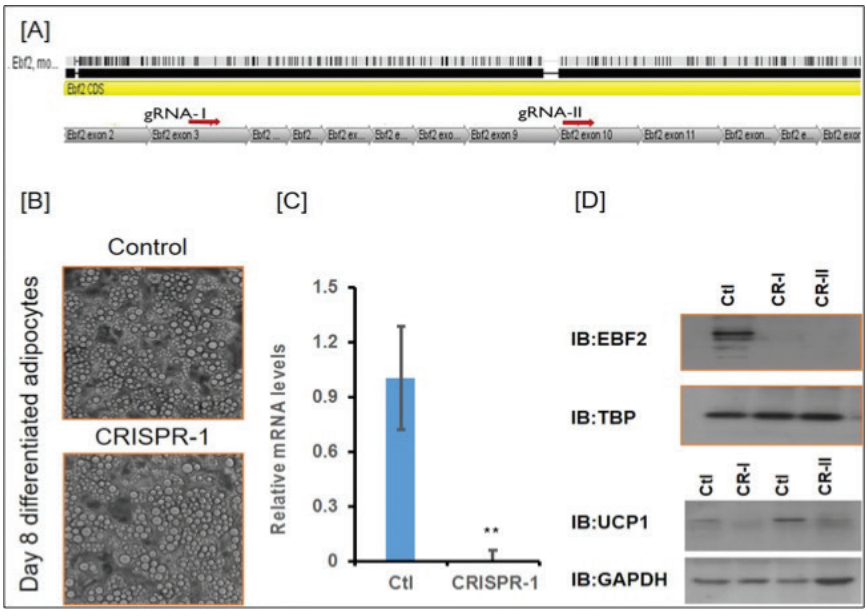

Figure legend

CRISPR-Cas9 mediated knock down of EBF2 in brown pre-adipocytes. A: To generate EBF2 knockdown cells, specific gRNAs were designed to target EBF2 coding sequence. B: EBF2-CRISPR cells differentiated into mature adipocytes. C: qPCR analysis showing relative levels of Ebf2 mRNA and D: Immunoblot for EBF2 and UCP1 expression.

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MEASLES VACCINATION FAILURE-

Measles is a global public health problem, and a leading cause of death in children world-wide. Widespread use of measles containing vaccine (MV) resulted in a dramatic decrease in measles morbidity and mortality. Measles vaccination began in India in the 1980's and the 2-dose schedule was introduced in 2010. Despite these vaccination campaigns, India experiences hundreds of outbreaks yearly. In 2005, 92,000 children died from measles in India, and in 2010 that number had dropped to ~65,000, but still accounts for nearly half of all global measles mortality. Even though the second dose of measles vaccine has further decreased the number of cases, outbreaks still occur in India. Measles vaccine (MV) failure clearly plays a role in global outbreaks, where between 10-50% of cases occur in individuals who had been previously immunized. Even after two doses, measles vaccine has a 2-5% primary failure rate. In India, vaccine failure is likely to be an even greater problem as sero-protection rates < 75% have been documented. Our preliminary data indicates that two doses of measles vaccine is still associated with a failure rate of >6% in southern Indian children. This rate of failure may be high enough to interfere with control and eradication efforts of the most transmissible human virus known. Our objective is to identify key differences between vaccinated children who subsequently become infected (vaccine failure) and vaccinated children who are immune (vaccine success). In turn, this data may contribute to the improvement of vaccination schedules, identification of biomarkers of vaccine efficacy, development of new vaccines, and the evaluation of therapeutic and/or supportive care during measles infection.

Figure legend

Prevalence of IgG antibodies in children (Cohort 1, 4-12 years who received 2-dose vaccination) against Measles by Gender. (A) Female (B) Male

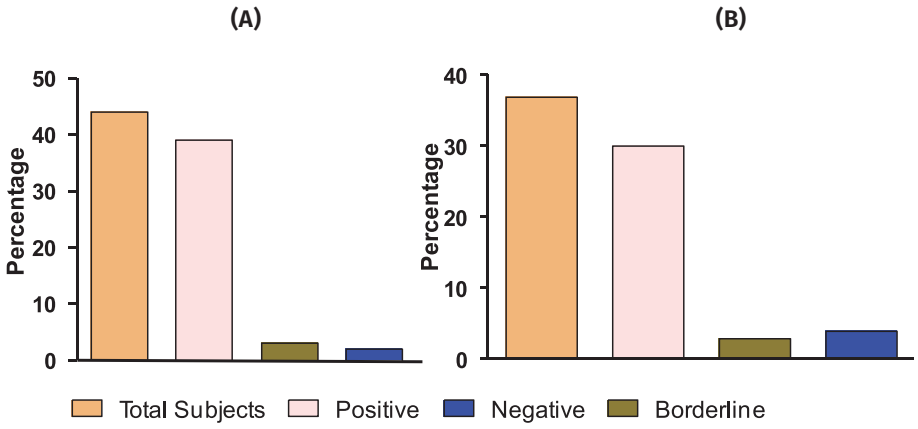

Figure 1

To fulfil the above mentioned objective, the study was divided into 3 cohorts. In Cohort 1 (n=1000), we collected a single blood draw from children (4-12yrs) who have already received two doses of measles vaccine (in case of delay in 2nd dose we will keep an interval of 4 weeks). In parallel, blood was collected from child's mother (Cohort III, n=1000). In Cohort II (n=800), children who were diagnosed with measles disease (regardless of vaccine history) were recruited These children and their mothers (Cohort III, n=800) will undergo a blood draw as well as a

children aged 4-12 years who had received 2 dose measles vaccination, representing 44% female and 37% male children (Figure 1). The total IgG antibody positivity reached 59.9%; 4.8% of the results were negative and 4.8% were borderline [Figure 1]. Virus genotyping was based on the 600-nt coding sequence for the carboxyl terminus of nucleoprotein (N) of measles virus. Molecular analysis showed measles genotype D4 and D8 were prominently circulating in Kerala (Figure 2). The study recruitment and molecular and immunological analysis is still ongoing.

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AND SUCCESS

nasal and/or throat swab (children) to determine what type of measles virus the child is infected with. Recruitment of volunteers for the study is multi-centric. To date we have collected 81 samples for Cohort I, 71 samples for cohort II and 152 samples for Cohort III from Trivandrum (2-sites), Palakkad (15-sites) and Trichur (3-sites) regions. The presence of specific IgG antibodies against measles in the sera samples (Cohort 1) was determined by the ELISA method (Novatec Immundiagnostica Gmbh). All determinations were performed in duplicates. The results were evaluated qualitatively as positive (>11NTU), negative (<9NTU) and borderline (9-11NTU). A total number of 81 sera samples were collected till date from

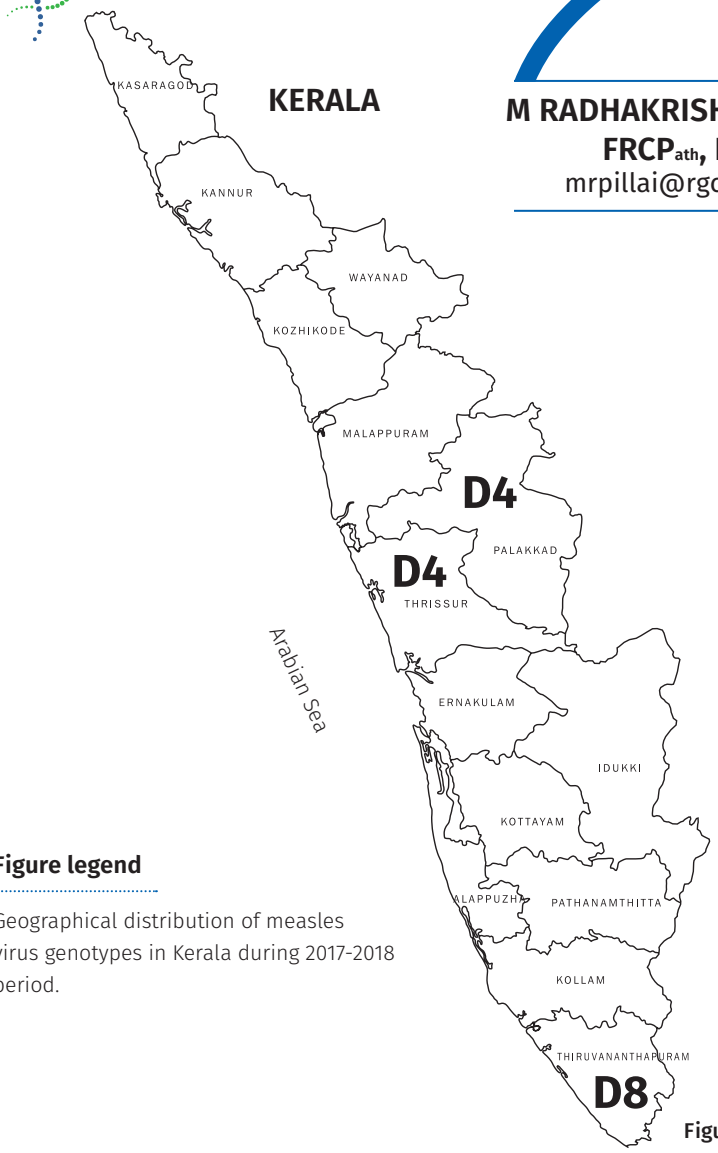

Figure legend

Geographical distribution of measles virus genotypes in Kerala during 2017-2018 period.

Figure 2

TEAM / Mayo Clinic, Rochester, USA: Richard B Kennedy
Emory University, Atlanta, USA: Joshy Jacob

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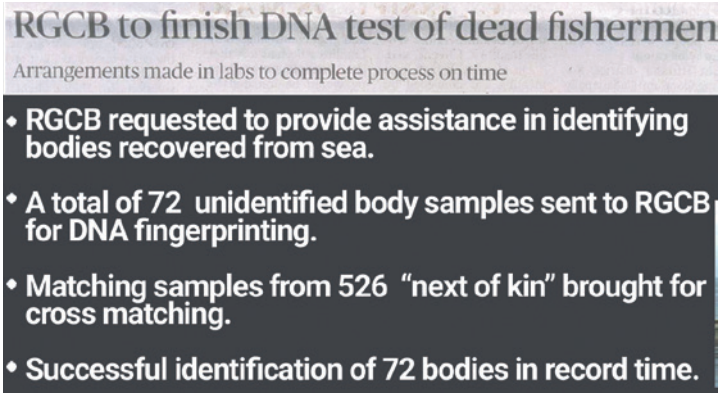
MOLECULAR FORENSICS & DNA FINGERPRINTING (MFDF)

MFDF offers DNA fingerprinting services to legal bodies, crime investigating and law enforcing agencies for maternity/paternity disputes, crime, rape incidents and cases involving persons missing. Species identification in wildlife forensics is yet another service offered by MFDF. Other services offered by this facility include DNA fingerprinting and DNA barcoding of plants, animals and microbes. The facility also offers hands on training on DNA fingerprinting and DNA barcoding techniques.

SERVICES FOR THE PEOPLE-

The MFDF did an outstanding job in helping investigation agencies identify victims of cyclone Ockhi. By comparing with 533 reference samples of relatives of missing persons, a total of 74 victims identified. A total of 165 samples were analyzed for identification, maternity/paternity and relationship disputes forwarded by courts from different districts of Kerala and the Women's Commission. A total of 204 samples forwarded from various forest range offices through courts related to animal poaching were identified. A very large number of support services were also provided including DNA Barcoding/ Fingerprinting/Sequencing analysis to various research institutions, colleges and universities from all over India.

MFDF also received a major research contract from the Kerala Forest Department for "DNA profiling of Asian Elephants (Elephas maximus) in Kerala and establishment of a DNA fingerprint database of captive elephants in Kerala"


RGCB to finish DNA test of dead fishermen

Arrangements made in labs to complete process on time

- RGCB requested to provide assistance in identifying bodies recovered from sea.
- A total of 72 unidentified body samples sent to RGCB for DNA fingerprinting.
- Matching samples from 526 "next of kin" brought for cross matching.
- Successful identification of 72 bodies in record time.


Ockhi aftermath: 33 decaying bodies wait for identification, kin for answers

VISHNU VARMA
KOCHI, JANUARY 2

IT HAS been more than a month since Cyclone Ockhi wreaked havoc off Kerala coast. But, while the stream of bodies of fishermen at hospitals has ceased, at least 33 bodies in extreme stages of decomposition lie scattered across mortuaries in the state, waiting to be identified by their loved ones.

Two of these bodies are in the mortuary of General Hospital in Kochi. Seated in a small office inside the morgue, Dr Biju James, police surgeon at the hospital, has one request: "do justice to the dead, as soon as possible".

"After someone dies, their body must be respected. It must be buried or cremated. Otherwise, it will decay. I have done my work and paid my respects. The state should do its job now," he said.

Mortuary at the General Hospital in Kochi. Vishnu Varma

"For identification, we have taken a bone marrow sample and given it to police. It will be sent to Rajiv Gandhi Centre for Biotechnology in Thiruvananthapuram for DNA sampling. The body has been lying in an ice box for 30 days now. It is a health hazard."

According to him, most of the 13 bodies brought to General Hospital were over a week old and had started decomposing when they were brought in. Dr James said he performed autopsies of eight of the 13 bodies and those which were identified through DNA sampling were immediately handed over to their families.

According to disaster management officials, a bulk of the bodies (16 out of 33) are lying in mortuaries in Kozhikode as most of them were found floating off the coast there. While five bodies are at hospitals in Ernakulam district, mortuaries in Thiruvananthapuram, Malappuram and Kannur districts have three bodies each.

Prashanth S, an emergency medical technician at the General Hospital, said the bodies had bloated when they were brought.

"Many of them had been in the sea for over a week. They had swelled to twice or thrice the size, making physical identification virtually impossible. The anatomy had completely changed. In some cases, the eyes had been nibbled by fish," he said.

At the Rajiv Gandhi Centre for Biotechnology in Thiruvananthapuram, a team of scientists has been working incessantly since the first week of December to identify the decomposed bodies.

Through an intricate process of DNA sampling, they have been tasked with ensuring that the bodies are handed over to the right families. Over the past month, 30 such bodies have been identified, but over three dozen bodies still remain to be matched.

"DNA sampling is a time-consuming process. We got 68 post-mortem samples and 424 reference samples from family members. Sometimes, the samples are contaminated. We have to be very careful," said a scientist.

"They (families) are anxious, but we can't explain the science to them," he said.

The Indian EXPRESS epaper editions Wed, 03 January 2018 epaper.indianexpress.com//c/25070053

Vishnu Varma
@VishKVarma

Also going unreported in most other media is the brilliant work being done by the scientists at the RGCB in Trivandrum trying to identify the bodies through DNA sampling. #Ockhi

LABORATORY MEDICINE AND MOLECULAR DIAGNOSTICS (LMMD)

LMMD is a special purpose vehicle to meet the molecular diagnostic requirements for infectious disease and cancer. It is currently the only molecular diagnostic laboratory in India accredited by both NABL and NABH. LMMD has an established competence of testing 50 diverse and clinically relevant pathogenic virus, in addition to virtually all bacterial identification from an assortment of biological samples. Fungal and parasite identification is performed on demand. This emphasizeS the social commitment of RGCB and has elevated the status of LMMD to the only Government of India testing facility, with these many parameters under one roof. Furthermore, the turn-around time for testing any parameter being under 48 hours after sample receipt has made LMMD the preferred choice in diagnostics by clinicians. The Regional Cancer Centre, Trivandrum has chosen LMMD as its referral laboratory for molecular cancer marker testing this year. LMMD caters to the molecular diagnostic requirements for all government and every major private hospital in and around Thiruvananthapuram. LMMD is also an MCI recognized rotation centre for medical post-graduates with intake from all government medical colleges across the State and has trained over 45 medical postgraduates this year. An ongoing Department of Science & Technology research project on snake species identification from the victim's blood deploying a lateral flow device, has culminated in validated prototype stage. The accreditation of LMMD by NABL has been extended till August 2020 after successfully clearing the external audit process this year.

AND OF THE PEOPLE

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SAJI GEORGE MTech, PhD
Distinguished Scientist and
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GATEWAY TO INNOVATION & BUSINESS DEVELOPMENT

BioNest is a unique facility designed to provide infrastructure and scientific support to enable researchers, investors and entrepreneurs looking to transform biology, medical based technologies and innovations into real and mature big business. Located in Kochi, the commercial capital of Kerala, BioNest is jointly managed by Rajiv Gandhi Centre for Biotechnology (RGCB) and Kerala Start-up Mission (KSUM). Spanning an area of 44,000 square feet, BioNest offers incubation space for individual companies backed up by a state of the art "plug and play" central common instrumentation facility for Analytical Biochemistry, Phytotechnology, Cell & Molecular Biology and Bioprocess Engineering. Through BioNest, hospitals all across the region have access to RGCB's high end NABL and NABH accredited molecular diagnostic facilities for infectious diseases, cancer and cardiovascular diseases. BioNest also offers RGCB's expertise and facilities for bioinformatics & computational analysis; DNA barcoding facilities for plant and microbial material as well as expert advice and assistance on IPR and RA related matters.

BioNest has initialized its current operation into 4 broad business verticals viz. molecular biology, fermentation technology development, phyto-technology/herbal medicines and micro propagation. Each business vertical has an individual technical head with respective teams. Screening and selection of incubatees by the Executive Committee is based on these 4 broad categories. There are currently 17 incubatee companies signed up and operating as start-ups from BioNest.

The finishing school and bio academy are training programs targeting students completing basic degree in life sciences. The aim of the program is to bridge the gap between basic academic learning and research, to help students conceptualize research ideas and to implement them. Under this scheme, 2 students completed training in bio academy and 3 students in industrial and bioprocess technology for 3 months. Besides, 3 faculty members were trained in high-end analytical techniques such as LCMS, GC and HPLC for 2 weeks. Additionally, mass spectrometry based techniques are available for in-born errors of metabolism. BioNest has the technology to conduct screening and this is achieved through close collaboration with private and government hospitals. BioNest has also developed a bioassay system for detecting antibacterial and antifungal activity to help incubatees in screening for antibiotic activity.

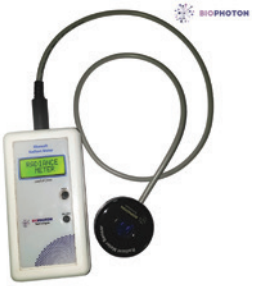
PRODUCTS LAUNCHED FROM **BIONEST**

AqueSense from Klonos Life Sciences Pvt Ltd: Klonos is a microbiology-based start-up focussing on food quality control products. AqueSense is a coliform detection kit developed and launched by M/s Klonos in the current year. This product is marketed at Rs. 200/- compared to the competitor's price of Rs. 2200/-

Control boards for Infant warmer with Touchscreen

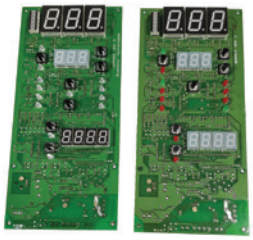
Luxurious type infant warmers are used in various developed countries and now we have Indian customers. Customized requirements with local language display are also supported.

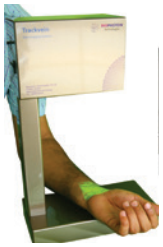
Blue Soft Irradiance Meter: This is battery operated device specially designed to measure exposure level of standard neonatal phototherapy systems directly in the patient plane and is designed for routine use in clinical settings. Ensuring adequate spectral light power has become increasingly important for effective neonatal jaundice treatment.



Infant Warmer Control Boards

Superior quality OEM control boards are being supplied to the continuous demand of various infant warmer manufacturers globally. Microprocessor based controlling with Thermistor temperature sensor for accurate temperature monitoring and controlling. Ready to integrate OEM modules with state of art design are available to support large production requirements.





Trackvein: Infrared Vein viewer

Peripheral venous access is an everyday procedure and is challenging for healthcare professionals. Trackvein is a battery-operated device uses Infrared imaging, in combination with augmented reality to visualize subsurface veins in real time and provide information about bifurcations.

Biophoton Technologies Pvt Ltd: Biophoton is a medical device company involved in indigenization of hospital setting equipment. Following are the list of the products developed by them from BioNest.

Blue Soft Phototherapy System: Next generation fiber optic based technology for treatment of indirect hyperbilirubinemia in new-borns. The flexible fiber optic blanket can be wrapped around the baby, allows phototherapy while breast feeding, portability to bedside/home increases comfort to both patient and care-taker.

LED phototherapy control Boards: LED Phototherapy is the common modality of treatment for neonatal jaundice in developing countries. There exists a demand for superior quality electronic hardware for durable, safe and optimum performance. The premium quality OEM control boards are occupied inside the LED Phototherapy systems of various domestic and international suppliers.

Kerala Nutraceuticals Pvt Ltd: RHUFPLUS is an instant pain reliever for all kinds of joint pains. It should be used only with recommendations from an expert, a medical practitioner, dietitian, or health adviser.

Kerala Nutraceuticals

A first time combination of purified standardized extracts of Turmeric Rhizome and Pomegranate Fruit (including rind) for the effective management of menopausal issues.

The second innovative product from Kerala Nutraceuticals is on a naturally bioavailability enhanced curcumin that contain piperine not by addition of piperine to turmeric extract as is usually done but by another innovative method. A patent for this process has been filed. This has genertaed higher percentage of piperine present in the final product.

WELCOME TO RGCB

Nirmalya Sen, PhD
DBT Ramalingaswami Fellow

2014-2017: Visiting Fellow, National Cancer Institute, NIH, Bethesda, USA

2013-2014: Post-Doctoral Scientist, George Washington University, USA

2008-2013: PhD, National Institute of Immunology, New Delhi

My laboratory studies the role of ETS transcription factors (ETV1, ERG) during progression of prostate cancer. The project tends to capture various aspects of hormone independent resistance to prostate cancer including metabolic reprogramming, clinical intervention, DNA damage and drug resistance.

Krishna Kurthkoti, PhD
DBT Ramalingaswami Fellow

2016-2017 : CSIR Pool Scientist, Indian Institute of Science, Bangalore

2012-2016 : Post Doctoral Fellow, New Jersey School of Medicine, Rutgers University, USA

2011-2012: Post Doctoral Fellow, Sanford Burnham Medical Research Institute, USA

2003-2010 : PhD, Indian Institute of Science, Bangalore.

The current research focus of the laboratory is to investigate the role of DnaE2, an error-prone DNA polymerase of mycobacteria towards stress induced mutagenesis. Another focus is to determine genetic factors necessary for mycobacterial survival in quiescent state.

Uma Subramanian Unni, PhD
Program Scientist

RGCB - BIONEST

2016-2017: Assistant Professor, Believers Church Medical College, Thiruvalla, Kerala, India

2013-2016: Biochemist, CPHL, WHO referral laboratory, Muscat, Sultanate of Oman

2006-2012: PhD, Medical Biochemistry, St John's Research Institute, Bangalore, India

The analytical laboratory at the RGCB - BIONEST focuses on industrial/ academic research and high-end diagnostic services. In addition to providing analytical services to the incubate companies, we do screening for inborn errors of metabolism in newborns and quantification of various molecules on the LC-MS/MS, GC-FID and HPLC platforms for a wide range of biological questions.

Pradipta Tokadar, MTech, PhD
Program Scientist

2015-2017: Scientist-II (Manager), Aurobindo Pharma Ltd, Hyderabad, India

2007-2014: Junior Research Scientist, Piramal Enterprises Ltd, Mumbai, India

2010-2017: PhD, VIT University, Vellore, India

2005-2007: M. Tech (Biotechnology), VIT University, Vellore, India

My work involves bioprocess development for the commercially important metabolites such as L-Methionine, Staurosporine, Echinocandin B, etc through strain improvement followed by process optimization and validation.

Ananda Mukherjee, PhD
DBT Ramalingaswami Fellow

2014-2017: Research Associate, Michigan State University, USA.

2012-2014: Post Doctoral Fellow, University of Rhode Island, USA.

2006-2012: PhD, Jadavpur University, Kolkata.

The goal of the laboratory is to understand the role of DNA repair defects in tumor initiation, progression and therapy. A well-known tumor suppressor, PTEN is often mutated and associated with genomic instability in cancers. I will be investigating the nuclear function of PTEN in the context of endometrial cancer. Further, we will explore how PTEN mediated DNA repair defect could contribute to support the tumor microenvironment.

RGCB YOUNG INVESTIGATOR **MENTORING PROGRAM**

RGCB provides a unique and nurturing ecosystem for young investigators to develop into professionals ready to move into faculty programs, nationally and internationally. Young investigators get close mentoring from senior faculty and are allowed to develop skills such as obtaining extra mural grants as well as develop research collaborations – all needed for becoming fully qualified for independent faculty positions. These are summaries of work done in the year by our young investigators.

Aravind Madhavan, PhD
SERB-National Post-Doctoral Fellow
Mycobacterium Research Laboratory

Identification and delineation of function of mycobacterial and host proteins that interact with HDAC1 in macrophages infected with *Mycobacterium tuberculosis*

Our laboratory has reported that MTB infection in macrophages induces recruitment of HDAC1, a ubiquitous suppressor of gene expression, to the promoters of *IL-12B* and *STAT4* and it hypo-acetylates histone H3 at the promoters leading to the suppression of their transcription (Chandran et al., 2015). Current studies employing ChIP PCR show that this HDAC1 is in its phosphorylated form when it is recruited to the *IL-12B* and *STAT4* promoters, a very interesting finding. Western blotting analysis revealed a significant increase in the level of phosphorylated form of HDAC1 in macrophages infected with *M. tuberculosis*. We have a keen interest in studying the role of interacting partners of HDAC1 during MTB infection. By IP, LC-MS/MS, ChIP and PCR analyses we have found that macrophage protein ZBTB25 and MTB protein Rv1899c, among others, associate with HDAC1 silencing complex and mediate the downregulation of *IL-12B* expression. Rv1899c protein seems to offer significant survival advantage to intracellular mycobacterium. Roles of ZBTB25 and Rv1899c in the recruitment to, and downregulation of, *IL-12B* promoter are under investigation.

Archana PR, PhD
DST SERB-National Postdoctoral Fellow
Cancer Research Program

Chemosensitization of cancer cells using phytochemical-loaded PLGA nanoparticles

Curcumin, a polyphenol phytochemical isolated from turmeric has been widely studied for its chemotherapeutic and chemosensitization properties. However, the clinical translation of curcumin is affected by poor bioavailability and aqueous solubility. Curcumin-loaded PLGA nanoparticles conjugated to tumor targeting ligand folic acid (PPF-curcumin) cause significant sensitization of cervical cancer cells towards paclitaxel both *in vitro* and *in vivo*. The chemosensitization potential of curcumin in PPF-curcumin was compared with that of curcumin-loaded PLGA nanoparticles, which showed that folic acid conjugation significantly improves cellular uptake of curcumin, which in turn enhances its chemosensitizing potential. The non-tumorigenic HaCaT cells, which did not significantly express folate receptors (FOLR1), did not uptake PPF-curcumin and were not sensitized by it. To further confirm the role of folic acid conjugation, cervical cancer HeLa cells which were FOLR1high, were pre-treated with folic acid prior to PPF-curcumin, showed that the uptake of PPF-curcumin was drastically reduced due to the quenching of FOLR1 by free folic acid. Moreover, the synergism between paclitaxel and PPF-curcumin was lost due to free folic acid pre-treatment. The study indicates the potential of PLGA nanoparticles in encapsulating poorly aqueous soluble drugs such as curcumin for successful chemosensitization.

K B Arun, PhD
DST SERB-National Post-Doctoral Fellow
Mycobacterium Research Laboratory

Possible role of Mycobacterium tuberculosis acetyltransferase Rv2170 in inactivating Isoniazid

Isoniazid (INH) is activated by KatG enzyme which further inhibits InhA affecting mycolic acids synthesis in Mycobacterium tuberculosis. INH-resistant strains have mutations in codon 315 of katG and position -15 in the inhA promoter. Interestingly, 10-25% of INH-resistant strains do not contain mutations in these genes. Hence INH-resistant strains may have other strategies to inactivate INH. We hypothesise that there may be MTB acetyltransferases which acetylate INH. We cloned and purified a putative MTB acetyltransferase Rv2170 in *E.coli*. We showed that Rv2170 is able to acetylate anti-TB first-line drug Isoniazid, *in vitro* and *in vivo*, as determined by HPLC and REMA. Rv2170 of MTB seems to be capable of inactivating INH by acetylation. Meanwhile the orthologus protein MSMEG_4238 in *M. smegmatis* is having less potential in acetylating INH and the recombinant Msm with Rv2170 is able to resist INH. Our preliminary results suggest that Rv2170-mediated acetylation of INH could be a novel mechanism employed by MTB to inactivate INH and consequently become resistant to this drug.

Asha P, PhD
DST SERB-National Post Doctoral Fellow
Cancer Research Program

Identification, characterization and validation of novel small molecule inhibitors targeting inflammation and colorectal cancer from marine sources

The polarity-graded single-solvent crude extracts "Searchin (E1 to E4)" prepared from brown *sea urchin, Arbacia punctulata,* showed significant reduction in cell viability of colorectal cancer cell lines; HCT15 and SW620 in a dose-dependent manner via cytotoxicity (MTT) assay. The most active fraction (IC50= 8µg/ml for HCT15 and IC50 =22 µg/ml for SW620) renamed as Searchin E2 (chloroform fraction) was chosen for further fractionation of small-molecule compounds. Next, we have developed a simple and reproducible methodology for scaffold-free generation of HCT116-3D free-floating spheroid models for anti-cancer drug screening with improved optimization for assay performance. By tracing the growth kinetics of 3D spheroids, we found that a plating density of 800–1,200 cells/well resulted in stable spheroid size and shape. Annexin V-FITC flow cytometry and cell-cycle distribution analysis indicated that Searchin E2 (5 and 10 µg/ml) could induce cell apoptosis in both 2D-monolayers and 3D-spheroid models, with a comparative percentage of live/apoptotic/necrotic cell population and cell-cycle arrest in G1, S and G2/M phases with significant reduction in the sub-G1 phase of *in vitro* tumoroid model. The rapid detection, pre-therapeutic prognostic marker E-cadherin was expressed only in spheroids and upregulated in treated spheroids, showed promising results for clinical drug screening. Our results warrant further investigations with *in vivo* experiments.

Aswathy PM, PhD
SERB-National Post-Doctoral Fellow
Neurobiology

Role of genetic risk factors associated with inflammation, autophagy and oxidative stress in Alzheimer's Disease and Fronto-temporal Dementia

The current project proposes novel NIR cage compounds and their nanomaterials those can be effectively used for the early detection, discovery of cancer biomarkers and for therapeutical applications of various cancers. For this purpose I have started the chemical synthesis of the following cancer drug by following the procedure as described:

Synthesis of 4-(8-Bromooctyloxy) benzaldehyde: A stirred suspension of 4-hydroxybenzaldehyde, 1,8-dibromooctane and K_2CO_3 in dry acetone was refluxed for 24 h. The reaction was monitored by TLC. The hot reaction mixture was filtered and evaporated to dryness. The residue was purified by chromatography.

Synthesis of 5,10,15,20-tetrakis-(4-(8-bromooctyloxyphenyl)-porphyrin: It involved the condensation of 4-(8-bromooctyloxy)benzaldehyde and distilled pyrrole in dry dichloromethane in a 1L RB flask and kept under argon atmosphere in presence of TFA. The reaction mixture was allowed to stir under argon atmosphere for 2 h at 30°C. 2, 3-Dichloro-5, 6-dicyanobenzoquinone was then added after 2 h, and the reaction mixture was allowed to stir at 30°C for 2 h. The progress of the reaction was monitored by TLC.

The reaction mixture was filtered through an alumina column using dichloromethane as eluent. The solvent was removed under reduced pressure to obtain a purple solid, which was chromatographed over silica gel using dichloromethane.

Betsy M, PhD
DST Woman Scientist
Cancer Research Program

Metal Cage compounds and Nano-materials for biological applications: A step forward to cancer treatment

The current project proposes novel NIR cage compounds and their nanomaterials those can be effectively used for the early detection, discovery of cancer biomarkers and for therapeutical applications of various cancers. For this purpose I have started the chemical synthesis of the following cancer drug by following the procedure as described:
Synthesis of 4-(8-Bromooctyloxy) benzaldehyde: A stirred suspension of 4-hydroxybenzaldehyde, 1,8-dibromooctane and K_2CO3 in dry acetone was refluxed for 24 h. The reaction was monitored by TLC. The hot reaction mixture was filtered and evaporated to dryness. The residue was purified by chromatography.
Synthesis of 5,10,15,20-tetrakis-(4-(8-bromooctyloxyphenyl)-porphyrin: It involved the condensation of 4-(8-bromooctyloxy)benzaldehyde and distilled pyrrole in dry dichloromethane in a 1L RB flask and kept under argon atmosphere in presence of TFA. The reaction mixture was allowed to stir under argon atmosphere for 2 h at 30°C. 2, 3-Dichloro-5, 6-dicyanobenzoquinone was then added after 2 h, and the reaction mixture was allowed to stir at 30°C for 2 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through an alumina column using dichloromethane as eluent. The solvent was removed under reduced pressure to obtain a purple solid, which was chromatographed over silica gel using dichloromethane.

Dhanya R, PhD
Kerala Biotechnology Commission - Post Doctoral Fellow
Cardiovascular Biology

Quercetin ameliorates pancreatic beta cell dysfunction under oxidative stress induced by tertiary butyl hydrogen peroxide

Pancreatic beta-cells are particularly vulnerable to apoptosis when compared to other tissues which might be due to oxidative stress, islet amyloid, or endoplasmic reticulum stress. Herein we evaluated the effect of bioflavonoid, quercetin on pancreatic cell line (TC6) under oxidative stress induced by tertiary butyl hydrogen peroxide (TBHP). Flow cytometry analysis revealed a reduction in apoptosis in cells treated with quercetin after induction of oxidative stress with TBHP. Insulin synthesis increased from 5± 0.6 to 8.6 ± 0.5 ng/ml in cells stimulated with 2 mM glucose on incubation with quercetin after induction of oxidative stress compared to cells treated only with TBHP. There was also a transient change in mitochondrial membrane potential associated with a change in AMP to ATP ratio pointing to the activation of mitochondrial target of rapamycin (mTOR) on quercetin treatment. Gene and protein expression analyses

confirmed activation of mTOR signaling pathway which could lead to mitochondrial biogenesis resulted in cell hypertrophy and increased insulin secretion. Our results indicate quercetin as a potential candidate to protect pancreatic beta cell from oxidative stress and that mTOR signaling pathway is a promising therapeutic target for diabetes and its complications.

Kalaivani V, PhD
DST-SERB- National
Post-Doctoral Fellow
Diabetes Research Laboratory

Effects of O-glycans of Apo(a) on angiogenesis and its implications in pre-eclampsia

Apolipoprotein(a) [apo(a)] is a unique protein subunit of lipoprotein(a) with extended O-glycan structure. Apo(a) deposits were found on the placenta that had undergone pre-eclampsia (PE). The pathogenesis of PE is caused by poor placentation with impaired angiogenesis of maternal spiral arteries. The emerging role of apo(a) as an anti-angiogenic agent suggests its involvement in PE pathogenesis. The extended O-glycan structure of apo(a) is a strong ligand for galectin-1, a pro-angiogenic, O-glycan specific lectin abundant in placenta. Galectin-1 binds to neuropilin-1 (NRP-1) and activates vascular endothelial growth factor receptor 2 (VEGFR2)-mediated mitogen activated protein kinases (MAPK) signalling pathway. In this scenario, we hypothesise that apo(a) modulates angiogenesis via binding of its O-glycan structure to galectin-1. HUVECs and de-O-glycosylated apo(a) were used for demonstrating the effect of apo(a) O-glycans on angiogenesis. A significant inhibition of the proliferation and migration of HUVECs along with a substantial reduction in protein level of galectin-1, NRP-1 and down-stream proteins in MAPK signaling pathway in HUVECs treated with native apo(a) suggest a modulatory effect of apo(a) O-glycans in angiogenesis.

Lekshmy Srinivas, PhD
DST- SERB - National Post Doctoral Fellow
Laboratory Medicine and Molecular Diagnostics

Pharmacogenetics of tacrolimus in renal transplant recipients

Tacrolimus (Tac), an immunosuppressant used in organ transplant recipients requires therapeutic drug monitoring of blood concentrations to prevent graft rejection or toxicity. Tac is metabolized by CYP3A5 and CYP3A4 and transported in the gut by P-glycoprotein, encoded by *ABCB1* gene. My research focuses on identifying the impact of *CYP3A4*, *CYP3A5* and *ABCB1* gene polymorphisms on dose-adjusted Tac trough concentration in blood and drug-induced adverse effects in renal transplant recipients. Renal transplant recipients receiving Tacrolimus as an immunosuppressant were recruited from Department of Nephrology, Government Medical College, Thiruvananthapuram. DNA was isolated from blood samples and SNP genotyping was performed. Statistical analyses were performed using UNPHASED software for genetic association analysis, *version* 3.1.7 and SPSS version 20.0 statistical software. We have identified specific genotypes in *CYP3A5 and CYP3A4* which are associated with higher dose-adjusted Tac trough concentration (C_0/D) in patients. We have also identified

genotypes associated with adverse effects like new onset diabetes mellitus after transplantation (NODAT). We found inter-ethnic differences in allele frequencies of these genes which underscores the need to consider population-specific genetic backgrounds when conducting pharmacogenetic analyses and clinical trials. The gene-gene interaction study will give a better predictive genetic marker of Tac level and drug induced side effects.

Liju V B, PhD
Kerala State Council for Science, Technology and Environment (KSCSTE)- Post Doctoral Fellowship
Cancer Research Program

Evaluation of the efficacy of curcumin to chemosensitize breast cancer stem-cell like population to 5-FU chemotherapy.

Cancer stem cells (CSCs) are promising targets to achieve a true cure for cancer. Breast cancer cells characterized by a high percentage of $CD44^{+}/CD24^{-/low}$ markers and ALDH1 activity are correlated with the development of distant metastasis and decreased survival. Studies from our laboratory have shown that curcumin can sensitize breast cancer cells to 5-FU treatment in a receptor-independent manner. The present study is intended to evaluate the effect of this synergistic combination against CSC like population in the triple negative breast cancer cell line, MDA-MB-231. Our results show that a combination of 10µM curcumin and 10µM 5-FU can significantly reduce the percentage of $CD44^{+}/CD24^{-/low}$ population as well as the ALDH1 activity in MDA-MB-231 monolayer and mammosphere as evidenced by FACS and confocal microscopy analysis. Curcumin pre-treatment has reduced the size and number of breast multicellular tumor spheroids *in vitro* and reduced the self-renewal ability of stem cell-like population of MDA-MB-231. Curcumin also down-regulates 5-FU-induced activation of major stem cell signaling molecules like β-catenin, c-Myc, Sox-2, VEGF, Oct3/4, Notch1 etc. Evaluation of the anti-tumor and anti metastatic effect of the combination against breast cancer stem cell like population is currently going on using orthotopic xenograft model in NOD-SCID gamma mice.

Mahesh S. Krishna, PhD
DST Young Scientist Program
Diabetes Biology Laboratory

Modulation of upstream/ downstream regulators of PPARγ using miRNA as molecular switches to reduce adipocyte hypertrophy and hyperplasia

Adipogenesis is a complicated process involving activation and interaction of various transcription factors and associated genes. This project was designed to make use of micro RNA that targets nuclear co-factors associated to PPAR γ to reduce adipocyte hypertrophy and hyperplasia. Gene and protein expression and immunoprecipitation studies has shown that the interaction of LXRα and SRC-1 with PPAR gamma play critical role in activating target gene expression. Based on prediction by TargetScan7.1 and previous reference, expression of eight micro RNAs viz. mmu-mir-17-3p, 23a-3p, 146a-3p, 206-3p, 31-5p, 33-3p, 126a-3p and 1a-3p were checked at different stages

of differentiation. Results showed that mmu-mir-206a-3p, 23a-3p, 1a-3p and 146a-5p varied corresponding to target mRNA level. Of these four micro RNAs, mmu-miR-146a-5p and mmu-miR-23a-3p were able to reduce luciferase activity by binding to the 3'UTR regions of NCoA1, NCoA2, NCoA3 and LXRα. Transient transfection of miR mimics and adipocyte differentiation later on proved that these two miRNAs were able to inhibit the differentiation and lipid droplet content in mature cells well effectively. So far from the results available, micro RNA mmu-miR-146a-5p and 23a-3p could effectively reduce the mRNA and protein levels of PPARγ interacting co-factors and reduce the lipid droplet content in mature adipocyte.

Neelima Singh, PhD
Department of Biotechnology-Post Doctoral Research Associate
Cardiovascular Biology

Insights into the regulation of lipid metabolites during lipotoxicity in cardiovascular diseases

Cardiac myocyte dysfunction is an important contributor to myocardial dysfunction, heart failure and serum fatty acid levels, including palmitate, have been observed at elevated levels in patients with acute myocardial infarction. Free fatty acids, when added to cells may lead to a significant increase of lipid droplet accumulation in the cytoplasm. Accumulation of a high concentration of lipid droplets in cells can be toxic, manifesting in apoptosis and necrosis if high levels are reached.
Evidences from animal model studies strongly implicate lipid metabolic derangements in the genesis of cardiac dysfunctions. However, the relationship between lipid metabolic abnormalities and cardiac lipotoxicity induced dysfunction remains to be established. In the present study, we evaluated the lipotoxic potency of PA on cardiomyocytes and role of RNA processing factors in modulation of various lipid metabolites under lipotoxic conditions. Microarray data analysis revealed that most of the genes involved in lipid metabolism are modulated by RNA processing factor and phosphoinositides signalling together. PA induced lipotoxicity was evaluated in H9c2 cells (Rat embryonic cardiomyoblast) and observed that 150 µM concentration of PA was sufficient to cause lipotoxicity in the cells. Under lipotoxic condition, expression of Star-PAP, a RNA processing factor was reduced in cardiomyocytes. These results suggested that RNA processing factors may play important role in lipid metabolism thereby controlling lipotoxicity in the cell.

Nisha Joy, PhD
DST Woman Scientist Program
Plant Disease Biology & Biotechnology

Elucidation of likely functions of tandem repeats in precursor sequences of miRNAs

The SSRs (Simple Sequence Repeats) are a fascinating part of genome. Although it's utility as genetic markers are well frame worked, debates still remain on the potential governing activities of SSRs, thus leaving open a fertile area of investigation. We presume that change in the number of repeat unit (n) may or may not become beneficial, depending on the position of SSRs in gene. The current study

focuses on two main points: first is to confirm the incidence of SSRs in pre-miRNAs (precursors of microRNAs) and second is to find out how exactly does the change in SSR units affect the miRNA function? Significant incidence of SSRs (29.844%) in pre-miRNAs were revealed and its possible functions were strengthened based on two observations (1) SSRs were consistently maintained even in the highly evolved phyla (2) Reduction in the detection of SREs (Splicing Regulatory Elements) when the corresponding SSRs in pre-miRNAs were computationally deleted. This is the first implication for the possible involvement of SSRs in shaping SREs to undergo Alternative Splicing events to produce different miRNAs in response to stress. Elucidation of crucial functions of SSRs in pre-miRNAs promise towards a better understanding about the interplay between SSRs and miRNAs.

Poulami Basu, PhD
DST- SERB-National Post Doctoral fellowship
Cardiovascular Diseases and Diabetes Biology

Role of LncRNAs and exosomes in the manifestation of Gestational Diabetes

The association between Gestational Diabetes (GDM) and Long noncoding RNAs (LncRNAs) is emerging as a novel causal factor behind the manifestation of GDM. Star-PAP is involved in the processing of LncRNAs involved in GDM, and exosomes are the carrier of the LncRNAs. An understanding on the role of LncRNAs and exosomes in GDM is still at infancy. The aim of the present study is to understand the role of LncRNAs and exosomes in GDM.

We performed a detailed *in silico* analysis of LncRNAs regulated by Star-PAP. A sizable portion of target LncRNAs showed association with GDM. We confirmed the LncRNA expressions with RT-PCR. Interestingly, selected LncRNAs regulated by Star-PAP and associated RNA processing proteins showed differential expression in GDM, suggesting role of distinct LncRNAs in GDM. The exosomal expression in blood was increased in GDM in comparison to control.
Our result showed that some LncRNAs are differentially expressed and processed in GDM in comparison to diabetes. Our result suggests a link between the expression and regulatory mechanism of LncRNA with GDM while confirming the association between the LncRNA and STAR-PAP and its carrier exosome.

Rajesh Raju, PhD
DST Fast Track Scientist
Computational Biology

Dynamic signaling networks in cancer

Cell signaling is a spatiotemporal dynamic process governed by both extracellular and intracellular cues. The patterns reflected in the spatiotemporal (intracellular and extracellular) expression of microRNAs, mRNAs, proteins and their PTMomes (along with the enzyme-substrate regulatory events) in response to specific signals are probably the most suitable read-outs for understanding the dynamicity of cell signaling. Towards this, I am integrating the temporal transcriptome (microRNA and mRNA) and proteome (protein and PTMomes) multiomics data in response to specific ligands in a

cell-type specific manner as a value-added tool for disease biology. These temporal snap shots will be used for analysis of co-regulatory networks and predict the hierarchy of signaling systems at both ligand/receptor and subcellular network levels that are dynamically regulated in biological systems.
One of the PTMs of relevance here is the phosphorylation of regulatory proteins. In this context, using p21-activated kinases (PAKs) as a working model, we are examining the nature of coordinated regulation of PAK signaling by the upstream regulatory sub-networks and by downstream effectors and substrates. Undertaking an integrated strategy to unearth a comprehensive matrix of kinases, regulatome, interactome, and genomic elements of PAK cancer biology, our team now unearths previously unknown contribution of PAK-network in human cancer (on-going studies).

Rajeswari Gopal, PhD
Kerala Biotechnology Commission-Post Doctoral Fellow
Plant Disease Biology

Evaluation of the functional role of osmotin, a plant derived stable protein from *Piper colubrinum* in cancer cells

Osmotin is a 24KDa multifunctional stress-responsive plant protein belonging to pathogenesis related (PR)-5 family. It is an adiponectin receptor agonist with structural and functional similarity to adiponectin, an insulin sensitizing hormone. We hypothesize that osmotin may affect the same signaling pathway as adiponectin and have a possible role in associated malignancies.
The objective is to express and purify osmotin protein from *Piper colubrinum* and to determine its potential role in malignancies. The full length osmotin gene from *P. colubrinum* was cloned and expressed in pET100/D-TOPO vector. The osmotin gene of 693bp was confirmed through sequence analysis. The recombinant plasmid pET100-PcOSM was expressed in BL-21 (DE3) competent *E.coli*. The recombinant histidine (His_6)- tagged PcOSM osmotin protein was purified by immobilized-metal (Ni2+) affinity column chromatography (NiNTA resin, Qiagen) under denaturing condition. The protein was confirmed by MALDI analysis. *In silico* protein-protein interaction studies were performed, which indicated a high possibility of *P.colubrinum* osmotin to adiponectin receptor (ADIPOR1). The biological activity of osmotin as an antifungal agent was also confirmed against *Phytophthora capsici*. The purified Osmotin protein from *Piper colubrinum* will be analysed further for its role in modulating key pathways regulated by adiponectin in suitable cancer cells.

Ratheesh Kumar T, PhD
DST-SERB-National Post Doctoral fellowship
Cancer Research Program

Risk evaluation of insulin administration and pancreatic carcinogenesis in BRCA1/ BRCA2 mutated patients with Type 2 Diabetes Mellitus: An *in vitro* approach

Pancreatic ductal adenocarcinoma (PDAC) is the most common disease among pancreatic cancers and is one of the greatest challenges in cancer research because of the late detection and lack of proper treatment strategies. Population

based studies indicate that insulin administration is a high risk factor in developing PDAC. In addition, PDAC is the third most common cancer seen in BRCA1/2 mutation carriers when both males and females are combined. Never the less the molecular mechanism behind this disease in BRCA1/2 mutated patients is largely unknown. Our preliminary objective is the *in vitro* evaluation of the molecular mechanism behind the occurrence of PDAC in BRCA1/BRCA2 mutated patients undertaking insulin administration. Towards this direction we have standardized the CRISPR/Cas9 protocol and BRCA1 knockout was generated in HPDE normal pancreatic cells and also in MCF-7 cell lines. In addition we have also generated HPDE pancreatic cells stably expressing shRNA against BRCA1 and BRCA2. Further evaluation of insulin mediated cancer progression in BRCA1/2 knockout/knockdown cells are in progress.

Rince John, PhD
DST-SERB-Post Doctoral Fellow
Cancer Research Program

Deciphering the nuclear functions of β-fodrin

Non erythroid spectrin also called fodrin is a tetrameric protein of two each of the subunit polypeptides called α-fodrin (240kDa) and β-fodrin (235kDa). These proteins are abundant in brain. Besides its role in maintaining the cellular architecture, it is also implicated in many biological processes such as cell cycle progression, differentiation, cell growth, DNA repair and signal transduction. The α-fodrin has been studied to some extent and recently it has been implicated in cell cycle regulation and DNA repair whereas functions of β-fodrin are unexplored and remain elusive. My study aims to understand the nuclear functions of β-fodrin. Using NucPred software, a potent nuclear localization signal was predicted within the β-fodrin protein sequence. In order to further explore the cellular abundance of β-fodrin, cellular fractionation was performed. Nuclear cytoplasmic fractionation revealed that β-fodrin is abundant in nucleus than cytoplasm. Further, we have also observed in nocodazole synchronized cells that β-fodrin level is low during M phase and it increases towards G1 phase. Finally, sub G1 population was increased in β-fodrin depleted cells than control suggesting that β-fodrin cells were more prone for apoptosis than control. These results therefore suggest the crucial role of β-fodrin in various nuclear functions such as cell cycle control, DNA repair, signal transduction etc.

Santanu Chattopadhyay, PhD
GN Ramachandran Fellow
Pathogen Biology

Microbial interplay in human gastric mucosa in the context of *Helicobacter pylori* infection and gastric diseases

Infection with *Helicobacter pylori* carrying *vac*As1i1m1*cagA* genotype is associated with peptic ulcer and gastric cancer. However, only 10-20% of the *H. pylori* infected individuals suffer from gastric diseases, while others remain asymptomatic. We hypothesize that *H. pylori* infection and its interaction with other gastric bacteria determines the clinical outcome. Our ongoing study indicates that the prevalence of *H. pylori* infection in Kerala (18%) is

low as compared to rest of India (80%). Genotype data based on 18 isolated strains suggest that 61.1% of the strains carry *vacA*s1i1m1*cagA*+ allele. RAPD-fingerprinting of 11 representative strains showed distinct pattern for each strain. Phylogenetic analysis showed that Kerala *vacA*m1 cluster with *vacA*m1 of Kolkata and Bangladesh and the Kerala *cagA* cluster with Western *cagA*. Antibiogram analysis revealed that 12 (66.66%) strains were resistant to metronidazole (8 microgram/ml), 2 (11.11%) were resistant to clarithromycin (0.5 microgram/ml), while no strain (0%) were resistant to amoxicillin (0.5 microgram/ml). Microbiome analysis indicated that *Streptococcus* and *Halomonas* are the dominant genera in stomach, while *Roseburia* and *Faecalibacterium* are the dominant genera in intestine. Interestingly, the microbiome composition of a *H. pylori* infected gastric cancer patient was significantly different than the microbiome composition of the other patients.

Sayuj KP, PhD
SERB- Post-Doctoral Fellow
Plant Disease Biology and Biotechnology

Comparative histopathology of *Zingiber* species infected by *Pythium myriotylum*

Pythium myriotylum, which causes soft rot disease in ginger, is a serious pest in ginger worldwide. No sources of resistance to this disease occur in the cultivated ginger germplasm. However, *Zingiber zerumbet*, a wild relative of cultivated ginger, is resistant to soft rot. Sections of the collar region of the healthy and the pathogen inoculated susceptible ginger and resistant *Z. zerumbet* plants were subjected to different staining methodologies using trypan blue, phloroglucinol-HCl, 3'-diaminobenzidine and Evan's blue to study pathogen life style in the host and the anatomical changes in the post inoculated plants. The pathogen showed an intra-cellular penetration pattern, typical of a necrotroph. In ginger, the pathogen colonized all the internal tissues of the plant including the vascular bundles in the pith. In resistant *Z. zerumbet*, the pathogen colonization was minimal, restricting the hyphae mostly at the peripheral leaf sheath layers of the pseudostem. The lignin deposition in cell wall differed markedly between the two hosts with heavy lignification in *Z. zerumbet*. The staining methodologies also revealed differences in cell death pattern and H_2O_2 accumulation between the two hosts. The results highlight a crucial role for the post inoculation anatomical changes in the host in controlling pathogen colonization.

Shyla G, PhD
Young Scientist: Kerala State Council for Science, Technology and Environment (KSCSTE)
Interdisciplinary Biology

Evaluation of the mechanism of induction of apoptosis by two Frog Skin Active Peptides, SSTP1 and SSTP3

Since Frog Skin Active Peptides (FSAPs) exhibit therapeutic potential, we characterized the bioactive peptides present in the skin secretion of *Indosylvirana aurantiaca,* an endemic frog of Western Ghats, India. Fourteen novel peptides identified by shotgun cloning were evaluated for their possible antitumor activities. Two peptides SSTP1 and SSTP3 that

induced cell death were compared to a non-cytotoxic sequence SSTP2 to uncover the mechanism of induction of cell death, which revealed the initiation of apoptosis mediated by mitochondrial pathway. SSTP1 is probably internalized by both pore formation and receptor mediated endosomal formation. RNA-Seq analysis revealed a cytokine-mediated apoptotic pathway, probably through IL6R-JAK/STAT and JNK/AP1 pathways, which was further confirmed by western blot analysis. Identification of the direct targets of SSTP1 is ongoing. The mechanism of induction of apoptosis by SSTP3 appears to be different from that of SSTP1 in several aspects. The mode of cellular entry of SSTP3 seems to be restricted to receptor mediated without co-localization with mitochondria, as observed for SSTP1. The RNA Seq analysis suggested that the regulation is primarily through lncRNAs. Detailed analysis of the mechanism of induction of apoptosis through the lnc RNA is undergoing.

Sourav Sen Gupta, PhD
GN Ramachandran Fellow

Colonic mucosal microbiota in colorectal cancer: a pilot study in south-Indian population

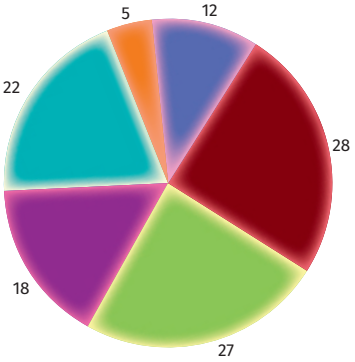
Initiation and promotion of colorectal cancer (CRC) may result from microbial action in the gut. Here we aim to establish an estimation of the gut microbiota in CRC patients in southern-India in a first pilot study. The study was jointly conceived and extensively supported by Dr S. Asha Nair's laboratory at RGCB. A total of six patients were enrolled and 10 colon biopsy samples collected including polyp, tumour and normal sections. High-throughput sequencing of the bacterial 16S rRNA gene was performed. QIIME was used for bioinformatic analysis. The observed species varied from 38 to 150 among the various samples. Phylogenetic diversity estimation showed global changes in the microbiome during carcinogenic transformation due to exposure to environmental factors and thus overall microbiome composition in normal sites did not significantly vary from that of polyp and tumour. However, we found seven OTUs that were significantly different among all the groups (data not shown). We are currently trying to understand what role these OTUs might play in the disease setting. The current pilot study provides us incentive to pursue large scale and better-designed studies to gain a better insight in the role of carcinogenic bacterial drivers that are pertinent in our population.

Vinitha Richard, PhD
DHR-ICMR Women Scientist
Cancer Research Program

Screening for a universal "invasive" molecular signature of metastatic tumorigenic stem cells in breast cancer

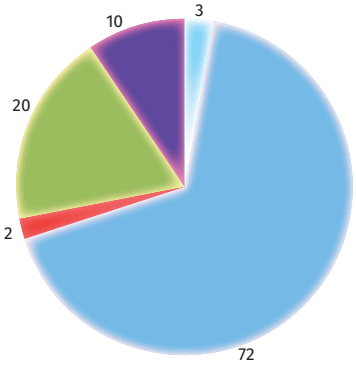
Statistical reports by WHO indicates an alarming rise in incidence and mortality rates of solid tumors affecting various sites in both genders of human beings. Reason behind this relapse is emergence of resistant clones or tumor cells that are resilient to current treatment practices and they mimic the survival strategies of normal adult stem cells. Our preceding research focused on detecting the presence and identity of such transformed stem-like cells in oral cancer and provided first-hand knowledge that eventhough hyperplastic cells resembled the normal stem cells in their cellular phenotype, they display varying potentials of tumorigenicity and drug-resistance and lead to micrometastases or minimal residual disease. Our current research goal is to elucidate the role of tumor stem cells in metastasis and relapse from early to later stages of breast cancer, thereby overlook the discrepancy of receptor protein expression based breast cancer subtyping and choice of treatment modality. Breast cancer cell lines in early passages have been utilized for flowcytometry based analysis for expression of stemness associated cell surface markers. RNA sequencing data of breast cancer clinical specimens from TCGA bioportal was analysed and developed into a database on breast epithelial transformation, progression, early metastases and recurrence leading to death.

VITAL STATISTICS 2017-2018



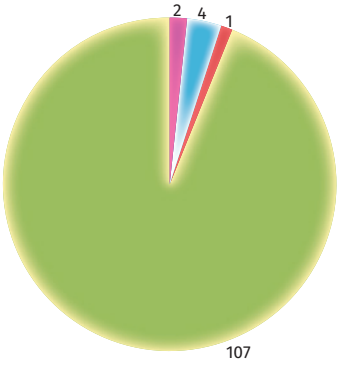
/Human Resource Development

- Doctoral degree conferred
- Doctoral students registered
- Post-doc registered
- Visiting faculty from Overseas
- Awards (National)
- Awards (International)



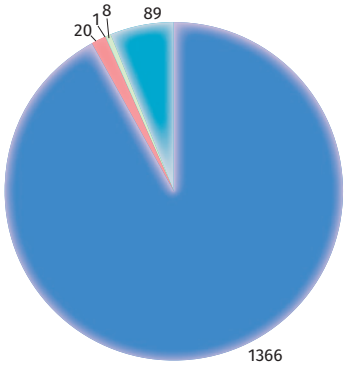
/Funding

- EMR Funding received
- International funding received
- Number of intra institutional collaborative programme
- Number of collaborations with national scientific organistations
- Number of collaborations with international scientific organisations and industries



/Science & Society Linkages and Outreach

- Trainings conducted for Schools/College Students
- Local level interventions for Societal Programmes
- Number of talks delivered by scientists at college and school level
- Open day for school and college students



/Publications and patents

- Number of citations
- Number of awards
- Number of patents filed Indian/International
- Number of patent granted Indian/International
- Number of publications

RGCB ROLL OF HONOR (2017-2018) FACULTY AWARDS

Debasree Dutta, PhD

National Women Bio-Scientist Award 2016 (Young Category) from Department of Biotechnology, Government of India.

Second Best Oral Presentation at World Congress on Cancer, Jaipur, 2018.

Devasena Anantharaman, PhD

Wellcome Trust (UK) India Alliance Intermediate Fellowship – 2018.

Hari Krishnan K, PhD

Nominated as member of the State Level Expert Appraisal Committee (SEAC), Kerala by the Ministry of Environment and Forest, Government of India.

Ruby John Anto, PhD

Elected as Fellow of the National Academy of Sciences, India.

EV Soniya, PhD

Elected as Fellow of the National Academy of Sciences, India.

Jackson James, PhD

National Bioscience Award for Career Development 2016, Department of Biotechnology, Government of India.

Priya Srinivas, PhD

Indian Council of Medical Research (ICMR) Prem Nath Wahi Award, 2013 for Clinical Cytology and Preventive Oncology.

Best Poster Presentation Award, World Congress on Cancer 2018. Mahatma Gandhi Medical College and Hospital, Jaipur, February 3-5, 2018.

Surya Ramachandran, PhD

ISHR-Torrent Young Investigator Award 2017 for presentation at Cardiovascular Research Convergence, Translational Health Science & Technology Institute, Faridabad, India 12 August, 2017.

Third prize for poster presentation at Women Scientists & Entrepreneurs Conclave, India International Science Festival-2017, Chennai, October 15-16, 2017.

STUDENT AWARDS

CM Shafeeque

Best Poster Award in 7th Pan Arab Genetics Meeting, January 2017, Dubai.

Best Poster Award in 2nd International conference on founder populations – The Landscape of Genetic Variants in Asian Founder Populations – from Near to Far East. 9-12 Nov. 2017, Kochi.

Aditi Majumder

International travel award from Department of Biotechnology for attending KAUST conference on Environmental Epigenetics, 2017, Saudi Arabia.

B Swathy

Early Career Investigator Program Travel Award: XXIV World Congress of Psychiatric Genetics (WCPG 2016), Jerusalem, Israel, October 2017.

Arathi Rajan

Shri Rambhau Kulkarni Award for Best Poster, 37th Annual Meet Indian Association for Cancer Research (IACR), Kolkata, November 2017.

Dhanesh SB

Dr MR Das Career award for the best outgoing PhD student.

Ann Mary Alex

Best poster award at National Seminar on Frontiers in Biotechnology – Molecular, Epigenetic and Genomic Research platforms in Healthcare and Food Security, University of Kerala, Trivandrum, March, 2017.

Haritha H Nair

Smt. Mangala Bamane Award for Best Oral Presentation at the 36th Annual Convention of IACR at Amala Cancer Research Centre, Thrissur, Kerala, February 2017.

Best Oral Presentation award, National seminar on "New horizons in Cancer Treatment and Prevention: From Bench to Bedside" on 16th & 17th March 2018, SN College, Kollam.

Best Oral Presentation award at 2nd International Conference On "Nutraceuticals and Chronic Diseases" INCD 2017 September 1 - 3, 2017.

Liju VB

Best Poster Presentation award, National seminar on "New horizons in Cancer Treatment and Prevention: From Bench to Bedside" on 16th & 17th March 2018, SN College, Kollam.

Sindura KP

Best Poster Award in 2nd International conference on founder populations – The Landscape of Genetic Variants in Asian Founder Populations – from Near to Far East, November 2017, Kochi EMBL Corporate Partnership Programme (CPP) Travel award Kollam.

Mohan Sankar

Best Poster Presentation award at 2nd International Conference On "Nutraceuticals and Chronic Diseases" INCD 2017 September 1- 3, 2017.

Sneha Singh

Best Oral Presentation Award. National Seminar on Frontiers of Biotechnology - Molecular, Epigenetic and Genomic Research Platforms in Healthcare and Food Security, March 2017, Trivandrum.

Shabna S

Best Poster Presentation award at 2nd International Conference On "Nutraceuticals and Chronic Diseases" INCD 2017 September 1-3, 2017.

Manendra Babu L

RGCB Merit Award 2017: Second Prize.

Mrunal V Wanjale

Newton-Bhabha Fellowship 2018 at University of Leeds, UK.

Sowmya Gunasekaran

Selected for the IBRO-APRC-Associate School of Neuroscience workshop held on March 26-31, 2018.

Mantosh Kumar

International Brain Research Organization - Asia Pacific International Travel Award 2017 RV at ISN-ESN Meeting in Paris. August 2017.

Satheesh Kumar S

Shri Rajanikant Shivprasad Baxi Award for Best Poster, 37th Annual Meet Indian Association for Cancer Research (IACR), Kolkata.

Nimmy Mohan

The 22nd Annual Meeting of the RNA Society (RNA 2017) Travel Award, RNA Society at Prague Congress Center, Prague, Czech Republic from May 2017.

Shabna A

Sri Rambhau Kulkarni Award for Best Poster Presentation at the 36th Annual Convention of Indian Association for Cancer Research (IACR) at Amala Cancer Research Centre, Thrissur, Kerala, February 2017.

Sethu Lakshmi

Selected for the B4 Workshop on Genomic Applications in Healthcare and Translational Research supported by LMSAI Harvard University, Institute of Bioinformatics and Applied Biotechnology and Department of Biotechnology. December 2017.

Aiswarya US

Best Poster Award at 30th Kerala Science Congress, Kannur, India, 2018.

Syed Khaja Moheiddin

Merit Award for Best Student Presentation, RGCB 2017.

Best Poster Award at Manipal Academy of Higher education among PhD students in their 3rd year of registration, 2018.

Travel award from IACR for attending IACR, Kolkata, 2018.

Soumya A

Best Poster Award. World Congress on Reproductive Health with Emphasis on Family Planning and Assisted Reproductive Technology & 28th Annual Meeting of the Indian Society for the Study of Reproduction and Fertility, February 2018, Maternal Health & Research Trust, Hyderabad.

Vikas Kumar

Dr Devendra K Agarwal Young Investigator Award at 10th Annual Conference of the IACS (India Section), Madurai Kamaraj University Madurai, India, February 2018.

Sudheesh AP

Young Scientist Research Award for the year 2018 in Biology by Dr K V Rao Scientific Society, March 2018, Hyderabad.

RGCB Meritorious Student Award, 2017.

Best Poster Award. 9th RNA Group Meet at Institute of Science from October 2017, Banaras Hindu University, Varanasi, India.

Vinitha A

Naranjan S Dhalla Best Poster Award in the 10th International Conference of International Academy of Cardiovascular Sciences-India Section at Madurai Kamaraj University, Madurai, Tamil Nadu, February 2018.

HUMAN RESOURCE DEVELOPMENT
PhDs AWARDED 2017-2018

Krishna Radhika N

Name of Mentor:
Asha V V, PhD

TITLE OF THESIS

Prospecting of Cheilanthes farinosa (Forsk.) Kaulf for its anti-angiogenic and anti-hepatocellular carcinoma activities.

Binil Raj SS

Name of Mentor:
Kartha C C, MD, FRCP

TITLE OF THESIS

Molecular basis of remodeling of pulmonary vascular endothelium in rats with left ventricular heart failure.

Ajith Kumar GS

Name of Mentor:
Kartha C C, MD, FRCP

TITLE OF THESIS

Remodeling of Cardiac Endothelium in Progressive Heart Failure- an Experimental Study in Rats.

Reshmy V

Name of Mentor:
Kumar K Santosh, PhD

TITLE OF THESIS

Isolation, Characterization and Structure-function studies of skin secreted peptides from frog Hylarana temporalis.

Anil Kumar TR

Name of Mentor:
Kumar Pradeep G, PhD

TITLE OF THESIS

Evaluation of Proto cadherin expression in relation to human male factor infertility.

Arun Kumar RC

Name of Mentor:
Omkumar RV, PhD

TITLE OF THESIS

A calcium sensing cell line to screen for modulators of calcium channels based on a simple end point assay.

Aiswarya G

Name of Mentor:
Soniya EV, PhD

TITLE OF THESIS

Isolation and Functional characterization of Type III Polyketide synthase (PKS) from Amla *(Emblica officinalis Gaertn.).*

Soumya V

Name of Mentor:
Laloraya Malini, PhD

TITLE OF THESIS

Molecular and functional analysis of autoimmune regulators in female reproduction.

Parvathy M

Name of Mentor:
Sreeja S, PhD

TITLE OF THESIS

Functional role of p21-activated kinases, pak1 and pak4, in oral cancer.

Wilson Peter Abraham

Name of Mentor:
Thomas Sabu, PhD

TITLE OF THESIS

Molecular studies on cold adaptation of *Pseudomonas psychrophila* MTCC12324 isolated from the Arctic at 79° N.

Akhilandeswaree D

Name of Mentor:
Thomas Sabu, PhD

TITLE OF THESIS

Identification of potential targets for inhibiting biofilm formation in *Vibrio parahaemolyticus* and *Vibrio cholera.*

RGCB EXTRA MURAL RESEARCH **GRANTS** (ONGOING 2017-2018)

Sl. No.	Principal Investigator	Name of grant	Funding agency	Duration
1	**Das Ani V**	Epigenetic regulation of multidrug resistance genes in embryonic carcinoma stem cells: implications in targeting cancer stem cells in germ cell tumors	Department of Biotechnology (DBT), Government of India	2018-2020
2	**Das Ani V**	Identification of and functional evaluation of Piwi-associated regulatory RNAs in the stem cell population of HPV-associated cervical cancer	Council of Scientific & Industrial Research (CSIR), Government of India	2017-2020
3	**Anantharaman Devasena**	Role of Human Papillomavirus Infection and other co-factors in the etiology of the Head and Neck Cancer in India.	Indian Council of Medical Research (ICMR), Government of India	2016-2019
4	**Anantharaman Devasena**	Biomarkers of oral cancer risk prediction.	Department of Biotechnology (DBT), Government of India	2018-2023
5	**Anto Ruby John**	Mechanistic evaluation and in vivo validation of the anticancer potential of Uttroside B against hepatocellular carcinoma	Department of Science and Technology (SERB), Government of India	2017-2020
6	**Anto Ruby John**	Mechanistic evaluation and in vivo validation of the anticancer principle isolated from Chromolaena odorata against cervical cancer	Kerala State Council for Science, Technology & Environment. (KSCSTE)	2016-2019
7	**Banerjee Moinak**	Evaluating pharmaco-epigenomic response of antipsychotic drugs	Department of Science and Technology (SERB), Government of India	2017-2020
8	**Banerjee Moinak**	Genomic and epigenomic characterization of 9p21 in Intracranial aneurysm patients from two distinct ethnic population of the world.	Department of Science and Technology –JSPS, Government of India	2017-2019

9	**Dutta Debasree**	Cellular transition-an epigenetic perspective in development and disease	Department of Biotechnology (DBT), Government of India	2017-2020
10	**Dutta Debasree**	Role of PKC signaling in dictating naïve vs. primed pluripotency	Department of Biotechnology (DBT), Government of India	2017-2019
11	**Dutta Debasree**	Histone chaperone HIRA as a novel modulator in dictating differentiation vs proliferation	Department of Science and Technology (DST)	2017-2020
12	**George Sanil**	Strategies for enhancing biological activity of novel peptides (brevinin-1and 2) identified from the skin secretion of an endemic frog.	Department of Science and Technology (DST), Science (SERB), Government of India	2018-2021
13	**Harikumar KB**	Sphingosine 1-phosphate signaling in pancreatic cancer	Department of Biotechnology (DBT) Government of India	2015-2017
14	**Harikumar KB**	An integrated network analysis to identify genomic alteration profiles of human pancreatic cancer	Department of Biotechnology (DBT), Government of India	2017-2020
15	**Harikumar KB**	Regulation of hepatic metastasis of colorectal cancer by exosomes.	Department of Science and Technology (SERB), Government of India	2018-2021
16	**Jaleel Abdul K A**	Identification of Metabolic Alterations in Sub-clinical Vitamin B12 Deficiency by Mass Spectrometry Based Metabolomics	Kerala State Council for Science, Technology & Environment. (KSCSTE)	2016-2019
17	**Jaleel Abdul K A**	Metabolomics Profiling of Normal Healthy People in Kerala: Impact of family History of Diabetes	Department of Biotechnology (DBT), Government of India	2017-2020
18	**James Jackson**	Guiding retinal ganglion cell axons to brain visual centers: Is Pax6 the key molecule?	Department of Science and Technology (SERB), Government of India	2017-2020
19	**James Jackson**	Expression of Notch independent Hes-1 (NIHes-1) specifically in ES cell derived Organoids representing developing neocortex: Understanding its functional significance	Department of Biotechnology (DBT), Government of India	2018-2020
20	**Joseph Iype**	Prevalence survey of rodent ectoparasites. Democratising Science through a Major Twinning Programme of the North East with other parts of India. DBT-India.	Department of Biotechnology (DBT) Government of India	2018-2019
21	**Kartha CC**	Screening lead molecules identified by structure-based rational drug design methods against cytochrome b5 reductase 3 and dopamine beta hydroxylase in spontaneously hypertensive rat models for antihypertensive effects.	Department of Biotechnology (DBT) Government of India	2017-2020
22	**Kartha CC**	Dr N Radhakrishnan Foundation for Research in Venous Diseases	Dr N Radhakrishnan Foundation Trust	2016-2020

23	**Kumar Ajay**	Dissecting the physiological role of Rv3423.1, a novel histone acetyltransferase in *Mycobacterium tuberculosis* H37Rv, in the bacterium as well as in infected guinea pig (RGCB-THSTI)	Department of Science and Technology (DST), Government of India.	2017-2020
24	**Kumar GS Vinod**	Development of a novel three dimensional self aggregating peptide fiber as an implant for brain tumors	Department of Science and Technology (SERB), Government of India.	2018-2021
25	**Kumar K Santhosh**	Bio-prospecting of Anti-Microbial Peptides from Hymenopteran (ants, bees and wasps) insects	Department of Biotechnology (DBT), Government of India	2016-2019
26	**Kumar K Santhosh**	Identification and immmunosensor based detection of peptide biomarkers in mastitic milk and development of synthetic anti-microbial peptide hydrogels as alternative therapy for bovine mastitis	National Agricultural Science Fund (NASF), Government of India	2016-2020
27	**Kumar Pradeep G**	Role of CLP-1 in cell cycle regulation in spermatogenic cells	Department of Science and Technology (SERB), Government of India	2013-2017
28	**Kumar Pradeep G**	Evaluation of cellular aging and genome stability in spermatogonial stem cells	Council for Scientific & Industrial Research (CSIR), Government of India	2014-2017
29	**Kumar Pradeep G**	Inter-relationship between polymorphisms in four obesity genes, their expression and its correlation with infertility and obesity in subjects from Kerala	Kerala State Council for Science, Technology & Environment. (KSCSTE)	2016-2019
30	**Kumar Pradeep G**	Transdifferentiation of sprematogonial stem cells (SSC) into somatic lineages via embryonic stem cell (ES) like intermediaries	Department of Biotechnology (DBT), Government of India	2017-2020
31	**Kumar Santhosh TR**	Understanding epigenetic changes and cell state transitions that contribute for recurrence in triple negative breast cancers	Department of Biotechnology (DBT), Government of India	2017-2020
32	**Kumar Santhosh TR**	The role of hypoxia induced mitophagy in cancer cell survival and resistance	Department of Science and Technology (SERB), Government of India	2018-2021
33	**Kumar Santhosh TR**	Design and characterization of peptide based cell targeting domains with live cell and animal imaging methods	Department of Biotechnology (DBT), Government of India	2018-2021
34	**Laishram Rakesh S**	Linking the two poly(A) tails - Prokaryotes vs Eukaryotes	Department of Biotechnology (DBT), Government of India	2017-2020
35	**Laishram Rakesh S**	Splicing independent function of RNA binding protein RBM10 in gene regulation and 3'-end processing	Department of Science and Technology (SERB), Government of India	2017-2020

36	**Laishram Rakesh S**	3'-UTR regulation of cardiac genes with roles in pressure overload cardiac hypertrophy	Department of Biotechnology (DBT), Government of India	2017-2020
37	**Lalorya Malini**	Mechanism of STAT5B in pancreatic beta cell proliferation/sustenance and its significance in diabetes	Board of Research in Nuclear Sciences, Government of India	2015-2018
38	**Lalorya Malini**	Deciphering the role of ER alpha in modulating the strength of STAT3 function.	Department of Science and Technology (SERB), Government of India	2015-2018
39	**Lalorya Malini**	Delineating the DNA-binding function of DOCK180	Department of Biotechnology (DBT), Government of India	2017-2019
40	**Mahendran KR**	Antibiotic translocation through porins in Gram-positive bacteria at the single-molecule level	Department of Biotechnology (DBT), Government of India	2016-2021
41	**Mahendran KR**	Controlled assembly of transmembrane α-helix-barrel pores for single-molecule sensing	Department of Biotechnology (DBT), Government of India	2017-2020
42	**Mahendran KR**	Single-molecule biosensing with hetero-oligomeric protein nanopores	Department of Science and Technology (SERB), Government of India	2018-2021
43	**Mahendran KR**	Functional membrane-spanning amyloid pores: from structure and assembly to medicine	Department of Science and Technology, Government of India	2018-2021
44	**Mishra Rashmi**	Mechano transduction through Caveolae: Lipid Rafts in homeostatic control of cell proliferation signaling and tumorigenesis.	Department of Biotechnology (DBT), Government of India	2012-2017
45	**Mishra Rashmi**	Mechano transduction through Caveolae in Neural Stem Cell Niches: Role in Cell Signaling and Proliferation Control.	Department of Biotechnology (DBT), Government of India	2012-2017
46	**Nair Asha**	Development of Novel NIR absorbing sensitizers and their nano-conjugates for the multimodal cancer imaging and therapy	Department of Biotechnology (DBT), Government of India	2017-2020
47	**Nair Radhika**	Deciphering the molecular circuitry of Cancer Stem Cells	Department of Science and Technology, Government of India	2016-2019
48	**Nair Radhika**	Deciphering Breast Cancer Metastasis	Department of Science and Technology, Government of India	2015-2020
49	**Nayar Saraswati**	Functional characterization of Chlorella hormone bio-synthesis and signaling genes for phytoremediation and bio-diesel production	Department of Science and Technology, Government of India	2015-2020
50	**Nayar Saraswati**	Characterization of a MADS box transcription factor in microalgae *Coccomyxa*	Science and Engineering Research Board, Department of Science and Technology, Government of India	2017-2020

51	**Nelson Shijulal**	Major gene influxes in microbial genome evolution	Department of Science and Technology, (DST) Government of India	2016-2021
52	**Nelson Shijulal**	Geospatial scale metagenomic profiling of mass transit systems in Kerala	Kerala State Council for Science, Technology & Environment (KSCSTE)	2017-2018
53	**Nelson Shijulal**	The structure and evolution of environmental resistomes	Department of Science and Technology (DST), Government of India	2017-2020
54	**Pillai M Radhakrishna**	Role of Human Papillomavirus Infection and other co-factors in the aetiology of the Head and Neck Cancer in India	Indian Council of Medical Research (ICMR) Government of India	2016-2019
55	**Pillai M Radhakrishna**	National Facility for Drug Discovery and Developmental Therapeutics (NFDDDT) at Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram	Department of Science & Technology (DST), Government of India	2016-2019
56	**Pillai M Radhakrishna**	Biomarkers of Oral Cancer Prediction	Glue Grant: Department of Biotechnology (DBT), Government of India	2018-2021
57	**Pillai M Radhakrishna**	Accurate and satisfactory analysis of all high risk HPV types and some of the low risks including HPV 6 and 11 antibody titers for the 2-versus 3 dose HPV vaccination clinical trial in India.	Bill & Melinda Gates Foundation and International Agency for Research on Cancer of the World Health Organization	2009-2021
58	**Pillai M Radhakrishna**	Program Support on Translational Research in Triple Negative Breast Cancer (Center of Excellence)	Department of Biotechnology (DBT), Government of India	2017-2020
59	**Pillai M Radhakrishna**	Understanding Measles Vaccine Failure (and success) in Southern India	National Institutes of Health (NIH), USA	2016-2020
60	**Rajakumari Sona**	Molecular regulation of Beige programming of adipocytes by Ebf2	Department of Biotechnology (DBT) Government of India	2015-2017
61	**Rajakumari Sona**	Early B Cell Factor 2 Orchestrate Chromatin Remodeling to Drive Brown Fat Gene Program	Department of Science and Technology, (DST) Government of India	2016-2019
62	**Rajakumari Sona**	Molecular reprograming of white adipose tissue to combat metabolic disease	Department of Biotechnology (DBT), Government of India	2016-2019
63	**Rajavelu Arumugam**	Functional role of tRNA modifications in *Plasmodium falciparum*	Department of Science and Technology (DST), Government of India	2014-2018
64	**Rajavelu Arumugam**	Role of epigenetic histone methylation marks in chromatin plasticity at various stages of malarial parasite	Department of Biotechnology (DBT), Government of India	2015-2018
65	**Rajavelu Arumugam**	Functional studies on the lncRNAs of Plasmodium falciparum and its role in antigenic variation process.	Department of Science and Technology (DST), Government of India	2016-2019

66	**Rajavelu Arumugam**	Molecular determinants of vascular differentiation in the pathogenesis of cerebral arteriovenous malformations.	Kerala State Council for Science, Technology & Environment. (KSCSTE)	2016-2019
67	**Ramachandran Surya**	How does cyclophilin A an oxidative stress induced secretory protein modulate vascular disease progression in type 2 diabetes?	Indian Council of Medical Research (ICMR), Government of India	2015-2018
68	**Ramachandran Surya**	Does Cyclophilin A, an Immunophilin under High Glucose Conditions Regulate Efferocytosis in Atherosclerotic Lesions?	Kerala State Council for Science, Environment & Technology (KCSCTE)	2018-2021
69	**Ramachandran Surya**	Cyclophilin A and Efferocytosis in Vascular Disease associated with Type 2 Diabetes	Madras Medical Mission, Chennai	2017-2020
70	**Sankutala Manjula**	Transcriptome analysis and characterization of key metabolic and hormone signaling pathway genes in Piper nigrum in response to defense elicitors (RGCB- NCBS)	Department of Biotechnology (DBT), Government of India	2018-2021
71	**Sankuntala Manjula**	Identification and functional characterization of Phytophthora capsici effectors specific to 'quick wilt' disease in black pepper (Piper nigrum)	Department of Biotechnology (DBT), Government of India	2018-2021
72	**Sengupta Suparna**	Analysis of Fodrin Association with Gamma-Tubulin Complex, the Microtubule Organizer	Dept. of Science and Technology (DST), Government of India	2017-2020
73	**Soniya EV**	Cataloguing of microRNAs and elucidation of its role in stress adaptation/response in black pepper	Department of Biotechnology (DBT), Government of India	2015-2018
74	**Soniya EV**	Characterization of key structural genes involved in flavonoid synthesis in Indian Gooseberry, (*Emblica officinalis* Gaertn.)	Kerala State Council for Science, Technology & Environment. (KSCSTE)	2015-2019
75	**Sreeja S**	Screening and Pre-Clinical evaluation of compounds of Pomegranate in Antagonizing Endogenous SERM-27 Hydroxycholesterol in Breast cancer	Department of Science and Technology (DST), Government of India	2016-2019
76	**Sreekumar E**	Elucidation of the role of endothelial cell signaling pathways in vascular permeability modulation in Dengue virus infection	Indian Council of Medical Research (ICMR), Government of India	2017-2020
77	**Sreekumar E**	Identification of cellular pathways differentially modulated in Human microvascular endothelial cells upon Dengue virus infection	Kerala State Council for Science, Technology & Environment. (KSCSTE)	2016-2019
78	**Sreekumar E**	Characterization of the role of Nucleophosmin and other selected host proteins identified from differential proteomics in Chikungunya virus infection	Department of Biotechnology (DBT), Government of India	2016-2019

79	**Sreekumar E**	Antivirals from medicinal plants of Western Ghats selected based on traditional knowledge (TK) / Ethnomedical information	Department of Biotechnology (DBT)	2015-2018
80	**Srinivas Priya**	Assessment of cell growth and microbial contamination in mammalian cell culture using foldscope in the laminar flow hood	Department of Biotechnology (DBT), Government of India	2017-2018
81	**Srinivas Priya**	Targeting Cancer associated fibroblasts for Metastasis Inhibition in BRCA1 defective cancer	Department of Science and Technology, (DST) Government of India	2018-2021
82	**Sumi S**	Genetic and epigenetic mediated regulation of gene expression in pancreatic β cells by metabolites of gut microbiota	Dept. of Science and Technology (DST), Government of India	2014-2018
83	**Sumi S**	Role of hemodynamic shear stress in the pathogenesis of varicose veins	Kerala State Council for Science, Technology & Environment (KSCSTE)	2018-2021
84	**Thomas George**	Development of rice varieties for Kerala with pyramided genes for resistance to BLB by marker assisted selection	Department of Biotechnology (DBT), Government of India	2013-2018
85	**Thomas George**	*De novo* transcriptome sequencing microarray development and elucidation of *Pythium* responsive defense pathways in *Zingiber zerumbet* Smith	Council of Scientific & Industrial Research (CSIR), Government of India	2015-2017
86	**Thomas Sabu**	Analysis of polymicrobial biofilms in chronic wound infections and development of anti-biofilm therapeutic to promote wound healing.	Department of Biotechnology (DBT), Government of India	2017-2020
87	**Thomas Sabu**	A study on the antimicrobial resistance pattern in Kerala	Dept. of Health and Family Welfare, Govt. of Kerala	2018
88	**Thomas Sabu**	Health promoting properties of potential probiotic strains isolated from infant gut microflora	Indian Council of Medical Research (ICMR).	2018-2020
89	**Thomas Sabu**	Development of probiotic therapy for enhancing urolithin production by using bacterial flora of human origin	Department of Science and Technology (DST), Government of India	2018-2021
90	**Thomas Tessy**	Evaluation of the role of TIF1γ in the regulation of self-renewal ability of OSCC stem cells	Department of Science and Technology (DST), Government of India	2016-2019
91	**Umasankar PK**	Endocytic modulation of BMP signaling: deciphering mechanistic insights into health and disease	Department of Biotechnology, Government of India	2016-2021
92	**Umasankar PK**	Uncovering mechanisms to remodel cholesterol landscape in cancer cells (SERB-DST- Extramural Research grant)	Department of Science and Technology, Government of India	2018-2021

RGCB LIST OF PUBLICATIONS 2017-18

Anantharaman Devasena

PUBLICATIONS

AM Tanner, A Mazul, D Farquhar, J Taylor, P Brennan, **Anantharaman D,** B Abedi-Ardekani, NN Hayes, M Weissler, S Patel, BS Chera, A Olshan, JP Zevallos (2018). Comparative Analysis of New Staging Systems for HPV-associated Oropharyngeal Squamous Cell Carcinoma in a Population-Based Cohort. ***International Journal of Radiation Oncology Biology Physics* 100 *(5), 1350***

Perdomo S, **Anantharaman D**, Foll M, Abedi-Ardekani B, Durand G, Reis Rosa LA, Holmila R, Le Calvez-Kelm F, Tajara EH, Wünsch-Filho V, Levi JE, Vilensky M, Polesel J, Holcatova I, Simonato L, Canova C, Lagiou P, McKay JD, Brennan P (2018) Genomic analysis of head and neck cancer cases from two high incidence regions. ***PLoS One. Jan 29;13(1)***

Perdomo S, Avogbe PH, Foll M, Abedi-Ardekani B, Facciolla VL, **Anantharaman D**, Chopard P, Calvez-Kelm FL, Vilensky M, Polesel J, Holcatova I, Simonato L, Canova C, Lagiou P, McKay JD, Brennan P (2017) Circulating tumor DNA detection in head and neck cancer: evaluation of two different detection approaches. ***Oncotarget. Aug 7;8(42):72621-72632.***

Mena M, Lloveras B, Tous S, Bogers J, Maffini F, Gangane N, Kumar RV, Somanathan T, Lucas E, **Anantharaman D**, Gheit T, Castellsagué X, Pawlita M, de Sanjosé S, Alemany L, Tommasino M (2017) Development and validation of a protocol for optimizing the use of paraffin blocks in molecular epidemiological studies: The example from the HPV-AHEAD study.; HPV-AHEAD study group. ***PLoS One. Oct 16;12(10):e0184520.***

Gheit T, **Anantharaman D**, Holzinger D, Alemany L, Tous S, Lucas E, Prabhu PR, Pawlita M, Ridder R, Rehm S, Bogers J, Maffini F, Chiocca S, Lloveras B, Kumar RV, Somanathan T, de Sanjosé S, Castellsagué X, Arbyn M, Brennan P, Sankaranarayanan R, Pillai MR, Gangane N, Tommasino M (2017). Role of mucosal high-risk human papillomavirus types in head and neck cancers in central India.; HPV-AHEAD study group. ***Int. J of Cancer. Jul 1;141(1):143-151.***

Anantharaman D, Abedi-Ardekani B, Beachler DC, Gheit T, Olshan AF, Wisniewski K, Wunsch-Filho V, Toporcov TN, Tajara EH, Levi JE, Moyses RA, Boccia S, Cadoni G, Rindi G, Ahrens W, Merletti F, Conway DI, Wright S, Carreira C, Renard H, Chopard P, McKay-Chopin S, Scelo G, Tommasino M, Brennan P*, D'Souza G (2017) Geographic heterogeneity in the prevalence of human papillomavirus in head and neck cancer. ***Int. J of Cancer. doi: 10.1002/ijc.30608.***

Anto Ruby John

PUBLICATIONS

Saikia M, Retnakumari AP, Anwar S, Anto NP, Mittal R, Shah S, Pillai KS, Balachandran VS, Peter V, Thomas R, **Anto RJ** (2018). Heteronemin, a marine natural product, sensitizes acute myeloid leukemia cells towards cytarabine chemotherapy by regulating farnesylation of Ras. ***Oncotarget. 9:18115-18127.***

Thulasidasan AKT, Retnakumari AP, Shankar M, Vijayakurup V, Anwar S, Thankachan S, Pillai KS, Pillai JJ, Nandan CD, Alex VV, Jacob CT, Chirayil TJ, Sundaram S, Kumar GSV, **Anto RJ** (2017). Folic acid Conjugation improves the Bioavailability and Chemosensitizing efficacy of Curcumin-encapsulated PLGA-PEG Nanoparticles towards Paclitaxel Chemotherapy. ***Oncotarget 8:107374-107389.***

Asha V.V

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Sreejith PS, **Asha VV** (2017). In vitro pharmacological, in vivo toxicological and in silico molecular docking analysis of glycopentalone, a novel compound from Glycosmispentaphylla(Retz.)Correa. ***Medicinal Chem Res 26:1697-1707.***

Radhika NK, Indira K, Wills PJ, **Asha VV** (2018). Inhibition of Angiogenesis and metastasis by Cheilanthes farinosae (Forsk.) water extract. ***Int J Appl Res Nat Prod*. 11: 1-14**

Tom G, Philip S, Isaac R, Praseetha PK, Jiji SG, **Asha VV** (2018) Preparation of an efficient and safe polymeric-magnetic nanoparticle delivery system for sorafenib in hepatocellular carcinoma. ***Life Sci. 206:10-21.***

Banerjee Moinak

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Swathy B, **Banerjee M** (2017). Understanding epigenetics of Schizophrenia in the backdrop of its antipsychotic drug therapy. ***Epigenomics*. 9:721-736.**

Swathy B, Saradalekshmi KR, Nair IV, Nair C, **Banerjee M** (2017). Pharmacoepigenomic response of antipsychotic drugs on pharmacogenes is mediated by microRNAs. ***Epigenomics. 9:811-821.***

Swathy B, **Banerjee M** (2017). Haloperidol induces pharmacoepigenetic response by modulating miRNA expression, global DNA methylation and expression profiles of methylation maintenance genes and genes involved in neurotransmission in neuronal cells. ***Plos One. 12: e0184209.***

Swathy B, Saradalekshmi KR, Nair IV, Nair C, **Banerjee M** (2018). Understanding the influence of antipsychotic drugs on global methylation events and its relevance in treatment response. ***Epigenomics. 10: 233-247.***

Das Ani V

PUBLICATIONS

Shankar S, Prasad D, Sanawar R, **Das AV**, Pillai MR (2017). TALEN-based HPV-E7 editing triggers necrotic cell death in cervical cancer cells. ***Sci Rep. 7: 5500.***

Sreekanth S, Rasheed VA, Soundararajan L, Antony J, Saikia M, Sivakumar KC, **Das AV** (2017). miR Cluster 143/145 Directly Targets Nrl and Regulates Rod Photoreceptor Development. ***Mol Neurobiol. 54:8033-8049.***

Dutta Debasree

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Majumder A, Syed KM, Mukherjee A, Lankadasari MB, Azeez JM, Sreeja S, Harikumar KB, Pillai MR, **Dutta D** (2018) Enhanced expression of histone chaperone APLF associate with breast cancer. ***Mol Cancer. 17:76.***

Dutta D (2017). Histone chaperone in regulation of cellular metabolism dictating stem cell fate? ***Stem Cell Investig 4:50.***

Dutta D, Syed KM, Mukherjee A (2018). Histone Chaperones Regulate Mammalian Gene Expression. ***In "Gene Expression and Regulation in Mammalian Cells". Ed. Fumiaki Uchiumi, Intech Open.***

George Sanil

PUBLICATIONS

Vineethkumar TV, Gopal S, **George S** (2018). Smallest lectin-like peptide identified from the skin secretion of an endemic frog Hydrophylax bahuvistara. ***Acta Biol Hung. 69: 110-113.***

Suryaletha K, John J, Radhakrishnan MP, **George S**, Thomas S (2018). Metataxonomic approach to decipher the polymicrobial burden in diabetic foot ulcer and its biofilm mode of infection. ***Int Wound J. 15:473–481.***

Vineethkumar TV, Asha R, Gopal S, **George S** (2018). Studies on the mode of membrane interaction of C-terminally amidated Brevinin1 HYba1& 2 peptides against bacteria. ***Int J Pept Res Ther. 24:117–129.***

Vineethkumar TV, **George S** (2017). A Review of the Mechanism of Action of Amphibian Antimicrobial Peptides Focusing on Peptide-Membrane Interaction and Membrane Curvature. ***Curr Protein Pept Sci.18: 1263-1272.***

Harikrishnan K

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Arjun J K, Aneesh B, Kavitha , T and **Harikrishnan K**. (2018). Characterization of a novel asparaginase from soil metagenomic libraries generated from forest soil. ***Biotechnol Lett. 40:343-348.***

Balakrishna Pillai A, Jaya Kumar A, Thulasi K, Reghunathan D, Prasannakumar M and **Harikrishnan K**. (2017). Draft genome sequence of *Bacillus aryabhattai* strain PHB10, a poly(3-hydroxybutyrate)-accumulating bacterium isolated from domestic sewerage. ***Genome Announc 5:e01072-17.***

Harikumar KB

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Lankadasari MB, Aparna JS, Mohammed S, James S, Aoki K, Binu VS, Nair S, **Harikumar KB** (2018). Targeting S1PR1/STAT3 loop abrogates desmoplasia and chemosensitizes pancreatic cancer to gemcitabine. ***Theranostics.8: 3824-3840.***

Majumder A, Syed KM, Mukherjee A, Lankadasari MB, Azeez JM, Sreeja S, **Harikumar KB**, Pillai MR, Dutta D (2018). Enhanced expression of histone chaperone APLF associate with breast cancer. Mol Cancer. 17:76.

Rajagopal C, **Harikumar KB** (2018). The Origin and Functions of Exosomes in Cancer. ***Front Oncol. 8:66.***

Rajagopal C, Lankadasari MB, Aranjani JM, **Harikumar KB** (2018). Targeting oncogenic transcription factors by polyphenols: A novel approach for cancer therapy. ***Pharmacol Res.130:273-291.***

James S, Aparna JS, Paul AM, Lankadasari MB, Mohammed S, Binu VS, Santhoshkumar TR, Reshmi G, **Harikumar KB** (2017). Cardamonin inhibits colonic neoplasia through modulation of MicroRNA expression. ***Sci Rep. 7:13945***.

Jaleel Abdul K A

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Krishna MS, Aneesh Kumar A, Abdul **Jaleel KA** (2018). Time-dependent alterations in mRNA, protein and microRNA during in vitro adipogenesis. ***Mol Cell Biochem.***

Vijayakumar G, Sreehari GK, Vijayakumar A, **Jaleel KA** (2017). Distinct Predictors and Co-morbidities in Early Onset Type 2 Diabetes Mellitus Among Asian Indians. ***Metab Syndr Relat Disord. 15:458-464***

Sharan AA, Nikam AN, **Jaleel A**, Tamhane VA, Rao SP (2018). Method for Label-Free Quantitative Proteomics for Sorghum bicolour L. Moench. ***Tropical Plant Biol. 11: 78–91.***

Azeez JM, Vini R, Remadevi V, Surendran A, **Jaleel A**, Santhosh Kumar TR, Sreeja S. (2018). VDAC1 and SERCA3 Mediate Progesterone-Triggered $Ca2^{+}$ Signaling in Breast Cancer Cells. ***J Proteome Res. 17: 698-709.***

Sengodan S K, Rajan A, Hemalatha S K, Nadhan R, **Jaleel A**, Srinivas P (2017). Proteomic Profiling of β-hCG Induced Spheres in BRCA1 Defective Triple Negative Breast Cancer Cells. ***J Proteome Res 17:276-289.***

Abraham R, Singh S, Nair SR, Hulyalkar NV, Surendran A, **Jaleel A**, Srikanth J, Sreekumar E (2017). Nucleophosmin (NPM1)/B23 in the Proteome of Human Astrocytic Cells Restricts Chikungunya Virus Replication. ***J Proteome Res. 16:4144-4155.***

Kumar V, Aneesh KA, Kshemada K, Ajith KGS, Binil RSS, Deora N, Sanjay G, **Jaleel A**, Muraleedharan TS, Anandan EM, Mony RS, Valiathan MS, Santhosh KTR, Kartha CC (2017). Amalakirasayana, a traditional Indian drug enhances cardiac mitochondrial and contractile functions and improves cardiac function in rats with hypertrophy. ***Sci Rep.7:8588.***

James Jackson

PUBLICATIONS

Divya MS, Rasheed VA, Schmidt T, Lalitha S, Hattar S, and **James J** *(2017).* Intraocular injection of ES cell-derived neural progenitors improve visual function in retinal ganglion cell-depleted mouse models. ***Front Cell Neurosci. 11:295.***

Subashini C, Dhanesh SB, Chen CM, Riya PA, Meera V, Divya TS, Kuruvilla R, Buttler K, **James J** *(2017).* Wnt5a is a crucial regulator of neurogenesis during cerebellum development. ***Sci Rep. 7:42523.***

Dhanesh SB, Subashini C, Riya PA, Rasheed VA, **James J** *(2017).* Pleiotropic Hes-1 Concomitant with its Differential Activation Mediates Neural Stem Cell Maintenance and Radial Glial Propensity in Developing Neocortex. ***Cerebral Cortex. 27: 3943-3961.***

Joseph Iype

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Narendrakumar L, **Joseph I**, Ramamurthy T, Thomas S (2018). Changing facades of *Vibrio cholerae:* An enigma in the epidemiology of cholera. ***Indian J Med Res. 147:133-141.***

Kartha CC

PUBLICATIONS

Ramachandran S, Anandan V, Kutty VR, Mullasari A, Pillai MR, **Kartha CC** (2018). Metformin attenuates effects of cyclophilin A on macrophages, reduces lipid uptake and secretion of cytokines by repressing decreased AMPK activity. ***Clinical Sci. 132:719-38.***

Radhakrishnan N, George D, Jayakrishnan R, Sumi S, **Kartha CC** (2018). Vein size and disease severity in chronic venous diseases. ***Int J Angiology. doi: 10.1055/s-0038-1639355.***

Sumi S, Ramachandran S, RamanKutty V, Patel MM, Anand TN, Mullasari AS, **Kartha CC** (2017). ENPP1 121Q functional variant enhances susceptibility to coronary artery disease in South Indian patients with type 2 diabetes mellitus. ***Mol Cell Biochem. 435:67-72***

Kumar V, Aneesh KA, Kshemada K, Ajith KGS, Binil RSS, Deora N, Sanjay G, Jaleel A, Muraleedharan TS, Anandan EM, Mony RS, Valiathan MS, Santhosh KTR, **Kartha CC**.(2017). *Amalaki rasayana*, a traditional Indian drug enhances cardiac mitochondrial and contractile functions and improves cardiac function in rats with hypertrophy. ***Sci Rep. 7:8588.***

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Sumi S, **Kartha CC** (2017). Role of Non-coding RNAs in Vascular Complications of Diabetes Mellitus. ***In Mechanisms of Vascular Defects in Diabetes Mellitus, Advances in Biochemistry in Health and Disease 17. Eds. Kartha CC, Ramachandran S, Pillai MR. Springer International Publishing. 341- 357.***

Kumar Rakesh

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Marzook H, Deivendran S, Kumar TRS, **Kumar R**, and Pillai MR (2017). Cytoplasmic translocation of MTA1 coregulator promotes de-repression of SGK1 transcription in hypoxic cancer cells ***Oncogene. 36(37):5263-5273.***

Deivendran S, Marzook H, Santhosh Kumar TR, **Kumar R**, Pillai M R. MTA1, a novel regulator of DNMT3a, stimulates insulin-growth factor binding protein-3 in human cancer (2017). ***Sci Rep. 7, 44225***.

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Kumar R, Deivendran S, Santhosh Kumar, TR, Pillai, MR. Signaling Coupled Epigenomic Regulation of Gene Expression (2017). ***Oncogene 36(43):5917-5926,***

Ganju A, Chauhan SC, Hafeez BB, Doxtater K, Tripathi MK, Zafar N, Yallapu MM, **Kumar R**, Jaggi M (2018). Protein kinase D1 regulates subcellular localisation and metastatic function of metastasis-associated protein. ***Br J Cancer. 118(4):587-599.***

Kumar Ajay R

PUBLICATIONS

Muralikrishnan B, Dan VP, Vinodh JS, Jamsheena V, Ranjit Ramachandran, Thomas S, Dastager SG, Kumar KS, Lankalapalli RS, **Kumar RA** (2017). Anti-microbial activity of Chrysomycin A produced by Streptomyces sp. against Mycobacterium tuberculosis. ***RSC Advances.7: 36335-36339.***

Kumar GSV

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Kumar Pradeep G

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Anilkumar TR, Devi AN, Pillai SM, Jayakrishnan K, Oommen OV and **Kumar PG** (2017). Expression levels of Protocadherin 11Yb (PCDH11Y) in the germ cells in the semen correlate with fertility status in men. ***Reprod Fertil Dev. 29:2100-2111***

Mohan JJ, Narayan P, Padmanabhan RA, Joseph S, **Kumar PG** and Laloraya M (2018). Silencing of dedicator of cytokinesis (DOCK180) obliterates pregnancy by interfering with decidualization due to blockage of nuclear entry of autoimmune regulator (AIRE). ***Am J Reprod Immunol. 80:e12844***

Laishram Rakesh Singh

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Li W, Li W, **Laishram RS**, Hoque M, Ji Z, Tian B, Anderson RA. (2017). Distinct regulation of alternative polyadenylation and gene expression by nuclear poly(A) polymerases. ***Nucleic Acids Res.45: 8930-8942.***

Lalorya Malini

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Maliekal Tessy T

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Mishra Rashmi

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Nair Asha

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Nair Radhakrishnan R

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Dayakar S, Pillai HR, Thulasi VP, Jayalekshmi D, **Nair RR** (2018). Comparative study of Molecular Approaches for the Detection of Influenza Virus from Patient Samples Using Real-time PCR - Prospective Disease Burden Study in Kerala (India) from 2010 to 2016. ***Curr Infect Dis Rep. 20:24.***

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Nair Radhika

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Nayar Saraswati

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Nelson Shijulal

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RGCB ANIMAL RESEARCH FACILITY

The vivarium at RGCB supports biomedical research experiments of all its scientists and students. The facility accommodates exquisitely controlled environments for the care and maintenance of small animal models such as transgenic mice, rats and rabbits. The procedure room is equipped with class II level Biosafety cabinet, Isoflurane inhalant anesthesia machine, small animal ventilator, non-invasive blood pressure monitoring apparatus and ECG machine. The facility is registered with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). At RGCB, all research involving animals is subject to rigorous review by the Institutional Animal Ethics Committee. The facility strives to provide animals used in research to the investigators with the best care available.

In 2017-18, the animal research facility supported research involving transgenic mice models and Wistar rats. The studies described the Interferon regulated gene (IRG) expression-signature in a mouse model of chikungunya virus neurovirulence. Amalaki rasayana, a traditional Indian drug was studied in rats with hypertrophy and shown to enhance cardiac function. BRCA1 status and hCG overexpression was seen in BRCA1 conditional knockout mouse suggesting that hCG promotes breast cancer progression. The expression pattern and functional significance of Wnt5a in cerebellar development was described using Wnt5a-/- and Nestin-Cre mediated conditional knockout mouse models. Possible improvement of visual function was evaluated by transplantation of embryonic stem cell derived neural progenitors in Retinal ganglion cell depleted glaucoma mice models.

All these achievements have been possible through efficient maintenance and handling of the facility by experienced veterinary surgeons supported by well trained technicians.

RGCB LIBRARY AND INFORMATION SERVICES

The primary objective of the library and information services is to organize, preserve and deliver information and resources required for scholarly pursuits of the RGCB academic community. Activities of the library such as acquisition, cataloguing, classification, circulation, reservation, membership management and easy retrieval of information have been supported by LIBSOFT user friendly library management software. Global accession of bibliographic records of books, journals, CDs and PhD theses were facilitated by Online Public Access Catalogue (OPAC/Web OPAC). The library provides campus wide IP and Wifi enabled access to e- resources. In the financial year 2017-18, new books were acquired in diverse subject areas. Books for general reading selected by the users themselves, recorded substantial increase in the year. About 25 print journals, both national and international were added. Total collection of documents in the RGCB library is now 8500, which includes CD ROMs, PhD theses, conference proceedings and reports. The institute library subscribed to the anti-plagiarism software, Turnitin, for the convenience of its users for proper citation and check on potential plagiarism. The library also acquired Grammarly – Writing Support Tool for supporting error free and correct grammar for writing manuscripts. Membership in the Department of Biotechnology's e- Library Consortium (DeLCON) continues to provide access to more than one thousand e-journals of nineteen international publishers. RGCB continued to be a member of Bio MedCentral and this enabled the publication of five articles during the period. The Journal of Visualized Experiments (JoVE) Biology which publishes peer-reviewed scientific online video protocols to accelerate biological, medical, chemical and physical research was added to the collection.

RGCB RESEARCH ENGINEERING SERVICES

The Research Engineering Group is responsible for the installation, maintenance and repair of sophisticated research instruments as well as the maintenance of Central Instrumentation Facility in both the campuses of RGCB. The group also maintains a well-equipped engineering workshop with facilities required for the repair and calibration of the sophisticated instruments as its part. By attending to essential repair works of instruments, dependence on expensive maintenance contracts with dealers has been reduced. The Research Engineering group also carries out design, modification, and fabrication of research instruments according to the specific research needs. During the financial year 2017-18, technical issues with Confocal Laser Scanning Microscope, Spectrophotometers, Ultra Centrifuges, High speed Centrifuges, Table Top Centrifuges, Gel Documentation systems, Transmission Electron Microscope, Upright and Inverted Microscopes, PCR machines, Electronic balances, Speed Vac Concentrator, CO2 Incubators, HPLC, Freeze Dryers, Micro plate Washer, DNA sequencer, Liquid Nitrogen Plant, FACS ARIA Flow Cytometer and Animal Imager have been repaired successfully.
The Research Engineering Group had started a Calibration facility for pipettes, electronic balances, centrifuges and temperature controlled instruments like freezers, incubators, PCRs etc. The facility is equipped with standards and measuring instruments with proper certification from FCRI, Govt. of India, Palakkad. This facility has calibrated various instruments of different labs for NABL accreditation.
More than 180 instruments were installed and about 2000 complaints related with various instruments using in-house facilities during this period were corrected. Spares and consumables required for these repairs were procured from local market or imported from direct manufactures (like solid state Lasers, various transducers, optical filters etc,) and thus reducing the total expense. Most of our instruments are maintained without AMC which retained approximately Rs 2 Cr/annum for the institution. Major electrical works completed during this period were the electrification of RGCB labs and diagnostic facilities located in Medical College and Government hospitals, replacement of APFC relay – RT8 in capacitor panel, Installation of temperature indicator in 1600 KVA Transformer, testing of insulation resistance of transformer, VCB and cables etc., replacement of PCC2 ETU in ACB, maintenance and servicing of exhaust line of 1010 KVA D.G set and reconditioning of 750 KVA D.G engine.

INFORMATION TECHNOLOGY DIVISION

The IT infrastructure of RGCB main campus includes 9 Servers, more than 400 Desktops and Laptops, Network printers etc and houses one of the best computing network with constant up-gradation in a bid to provide the students and staff with state-of-art facilities. The institute has been connected to National Knowledge Network, which provides 1 GBPS leased line with multiple redundant backups. The highly distributed computing environment at RGCB uses sophisticated computer simulation to solve problems for staff and research scholars. It is managed and actively supported by experienced engineers in the IT department. IT department is also responsible for maintaining and administrating RGCB Website, intranet applications and Mail Servers. IT department provides technical support to staff and students within the institute on LINUX, WINDOWS platforms. IT department maintains and host online exam portal and leave management system for PhD students. Internet facilities are provided throughout the campus through 1 GBPS and 10 MBPS leased lines from NKN and BSNL respectively. RGCB has installed a high speed Fibre Optic Backbone with high-end security for networking across the campus. Wireless connectivity is also provided for connectivity. The Information Technology Division of Bio Innovation Centre at Kazhakkuttam uses cutting-edge technology to provide high quality services and capabilities to different research groups. It includes two servers with active directory domain infrastructure, secured network with state-of-art firewall system, 10 MBPS leased line and 100MBPS broadband lines with failover backup connection, secured wifi connectivity, meeting room with video conferencing and wireless projection facilities etc. State-of-the-art IP security cameras for surveillance have been installed in both RGCB and BIC campuses.

RGCB TECHNICAL SUPPORT TEAM: THE PEOPLE WHO MAKE **TECHNOLOGY WORK**

RGCB Technical Support Team includes highly skilled and dedicated personnel providing essential support for biological, chemical, physical, computational and life science research. They do sampling, testing, measuring, recording, data mining and analysis of results as part of the scientific team. These personnel manage core research facilities and equipment

ensuring effective functioning, adhering to correct procedures and safety guidelines. Major facilities supported by the technical team include Mass Spectrometry & Proteomic Core, Animal Imagers, Confocal Laser Scanning Microscopes, High Speed Flow Cytometer Sorter Systems, Super Resolution Microscope, Next Generation Genetic Sequencing Systems and Animal Research Facility.

RGCB GENERAL ADMINISTRATION

The main responsibility of general administration is to ensure the efficient performance of all departments at RGCB serving as the connecting link between the senior management and the employees. The major mandates of general administration include good coordination among all the departments ensuring attainment of organizational goals, optimum utilization of resources, minimization of cost, human resources and payroll, vigilance and security, transportation, fulfillment of social and economic needs of the employees and organization as well as development and growth of the institute.

RGCB FINANCE & ACCOUNTING GROUP

The RGCB Finance & Accounts appropriately ensured Budget Planning and Reporting work, right from the stage of preparation of budget to accounting of expenditure. Resource generation by the Institute has also been accurately accounted for. Preparation of various MIS, liaison with the Department of Biotechnology, matters related to Finance Committee, processing of all payments in time, coordination in internal and statutory Audit, matters related to statutory payments and rendition of utilization certificates & statements of expenditure have also been done by the Finance & Accounts Division of RGCB. The Project Management group RGCB supports the Finance & Accounts Division in all work related to extra-mural funded projects, PhD and Post doctoral Fellowships and revenue generation accounts of the institute, rendition of utilization certificates & statements of expenditure in respect of various extra mural projects.

RGCB LEGAL & ESTATE AFFAIRS GROUP

The Legal & Estate Affairs Division (L&EA) looks after all legal matters under various Acts, including RTI. This Division is also entrusted with works related to Estate Affairs, House Keeping & Welfare, Building Engineering & Construction, Security & Surveillance and Vigilance & Disciplinary. The performance of L&EA Division of RGCB during 2017-18 is summarized as:

1. Forty one applications seeking information under RTI Act were received during 2017-18, and information sought was provided to all the applicants within the prescribed time limit. The replies were all self-contained and only 3 appeals were received, which were also disposed within the authorized time-frame.
2. Meetings of TOLIC (Town Official Language Implementation Committee) were held twice at RGCB. In addition, the Quarterly Reports prescribed under the Official Languages Act, were submitted promptly to the Department of Biotechnology and the TOLIC, Thiruvananthapuram.
3. Vigilance Awareness Week was observed in the Institute. Seminars and Competitions were conducted among the staff and students of the Institute.
4. Various work requirements at RGCB Main Campus, Transit Campus as well as BioNest were promptly attended to and the upkeep of premises were ensured at all times.
5. Swatch Bharat Abhiyan was conducted in the Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram in line with the Government Guidelines and Swachhta Shapath was administered as part of national cleanliness campaign.
6. Other programs in line with the Government of India's directions namely Anti-Terrorism Day, Martyrs' Day was observed in the Institute.
7. The Division also coordinated and made all arrangements for various meetings, seminars and conferences organized by the Institute.
8. Numerous Industrial visits and visits to various Laboratories of RGCB by students from various parts of the country were properly coordinated by the Division.

RGCB STORES AND **PURCHASE**

The purchasing department occupies a vital and unique position in RGCB. This department ensures procurement of the right material in right quantities and of correct quality. The section ensures procurement from right and reliable source or vendor as well as procurement of the material economically, i.e., at right or reasonable price.

The RGCB Central Stores serves all three campuses of the institutute. The most common yet major responsibilities that are carried by stores include receipt of incoming goods, inspection of all receipts, storage and preservation, identification of all materials stored, materials handling, packaging, maintenance of stock records, inventory control and stock-taking.

RGCB OFFICE OF ACADEMIC AFFAIRS

The academic activities of RGCB are managed by the Office of Academic Affairs (OAA). The OAA facilitates the PhD program, short term and long term training Programs, Post-doctoral training, Specialized Training Programs and Biotechnology Skill Development Programs. The mission of the Office of Academic Affairs (OAA) is to provide leadership in development of a strong academic program, policy formulation, program planning and student research progress evaluation.

RGCB is credited with the first exclusive PhD program in Translational Science & Medicine (TSM) designed to train candidates with degrees in medicine, dentistry, veterinary sciences and pharmaceuticals. This program is in addition to the main stream PhD program in Biotechnology. RGCB today has over 140 students pursuing their PhD and affiliated to many universities. Office of Academic Affairs coordinates with different universities for smooth running of PhD program.

Students of each batch are guided by a comprehensive course work for four months after the PhD admission. As per the guidelines of UGC the students have to take courses for 16 credits and they have to secure a minimum Cumulative Grade Points Average (CGPA). OAA facilitates the course work with the help of both internal and external faculties. At the end of the course work the OAA helps the students to choose the laboratory/research area by lab rotation. The Office of Academic Affairs is responsible for supporting all academic programs of the institute, supports RGCB faculties and guest faculties with planning and implementation of PhD student's admissions, PhD course work, examinations, transcripts, allocation of students in labs, etc.

Office of Academic Affairs is also involved in the selection of research fellows and research associates in the various research projects handled by RGCB faculties.

In the Year 2017-18, OAA implemented online leave application forms for PhD students in coordination with IT department. OAA also plays a key role in organizing all RGCB training programs, academic meetings, and Scientific Advisory Council meetings.

RGCB OFFICE OF TECHNOLOGY VENTURES (OTV)

Office of Technology Ventures (OTV) at RGCB has entered its fourth year. During this period, OTV successfully implemented its primary portfolio in effective administration and execution of the Intellectual Property and know-how (IP) developed out of RGCB research activities. To date, RGCB has filed 25 patent applications and has been granted 14 patents, with the rest of the applications presently under process. The jurisdictions of grant of these patents include India, USA, Europe, Japan and China.

For the year 2017-18, two new Preliminary Invention Disclosure forms (PIDF) were submitted to OTV by scientists of RGCB. A prior-art search for patentability was conducted and the future course of action was decided. OTV managed the correspondences with patent attorneys and patent offices for nine patents which have been filed in India and USA during this period. RGCB was granted one Indian Patent during this period. Commercialization efforts for these patents are in progress. OTV has put in substantial effort in coordinating RGCB scientist's applications with National Biodiversity authority for attaining approval for research involving materials from biodiversity origins. Six applications for transfer of research information to foreign collaborators and for Indian IPR filing were filed with NBA, out of which one application for IPR filing has been granted and others are under active consideration and deliberations. OTV also assisted in accomplishing twelve material transfer agreements and four MoUs for research collaboration.

RGCB OFFICE OF THE DIRECTOR

The Office of Director is responsible for successful leadership and management of the organization according to the strategic directions set by the institute management. This office develops the vision and strategic plan to guide the organization, develop an operational plan which incorporates goals and objectives that work towards the strategic direction of the organization, ensures that the operation of the organization meets expectations of its stakeholders and funding agencies. The Office of the Director also oversees efficient and effective day-to-day operation of the organization, draft policies for approval of the Governing Council; prepare procedures to implement organizational policies; review existing policies and recommend changes as appropriate; ensure that programs and services offered by the institute contribute to its mission; monitor day-to-day delivery of programs and services to maintain or improve quality, determine staffing requirements for organizational management and program delivery, recruit, interview and select staff that have the right technical and personal abilities to help further the organization's mission. The Office also is responsible to supervise prepartion of a comprehensive budget and work with the Governing Council to secure adequate funding for the operation of the organization.

RGCB INVITED SPEAKERS 2017-18

Professor Jerry Coyne
Department of Ecology and Education, University of Chicago, USA

Dr Sharon Prince
Professor in Cell Biology, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Dr Rohan Kamat
CCAMP Bangalore

Dr Barbara Pauly
Director of Fellowships, Human Frontiers Science Program

Professor Didier Picard
Département de Biologie Cellulaire, Université de Genèv, Switzerland

Dr Sharmila Nair
Postdoctoral Fellow, Diamond Laboratory, Washington University, St. Louis, MO, USA

Dr Soman Ninan Abraham
Professor in Pathology, Dept. of Immunology, Duke University School of Medicine, Singapore

Professor Asgi T Fazleabas
Professor and Associate Chair for Research, Department of Obstetrics, Gynecology & Reproductive Biology and Director, Center for Women's Health & Co-Director, Reproductive and Developmental Sciences Program Michigan State University, Michigan, USA

Dr Surendra Sharma
Professor of Pediatrics, Director, Center of Biomedical Research Excellence for Perinatal Biology, Women and Infants Hospital-Brown University, Providence, RI, USA

Dr Ramkumar Sambasivan
Research Investigator & DBT-Ramalingaswami Fellow
Institute for Stem Cell Biology and Regenerative Medicine
GKVK Campus Bellary Road Bengaluru 560065 India

Dr Manjunatha Sankaranarayanan
Post Doctoral Fellow, Mayo Clinic, Rochester, Minnesota, USA

Dr B Anand
Associate Professor
Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Assam, India

RGCB OUTREACH TO SOCIETY

FIRST INTERNATIONAL AYUSH CONFERENCE AND EXHIBITION **NOV 2017, DUBAI**

RGCB @ INDIA INTERNATIONAL SCIENCE FESTIVAL
IIT MADRAS

RGCB @ INDIA INTERNATIONAL SCIENCE FESTIVAL
IIT DELHI

RGCB SKY GREEN: GETTING READY FOR **ONAM FEAST**

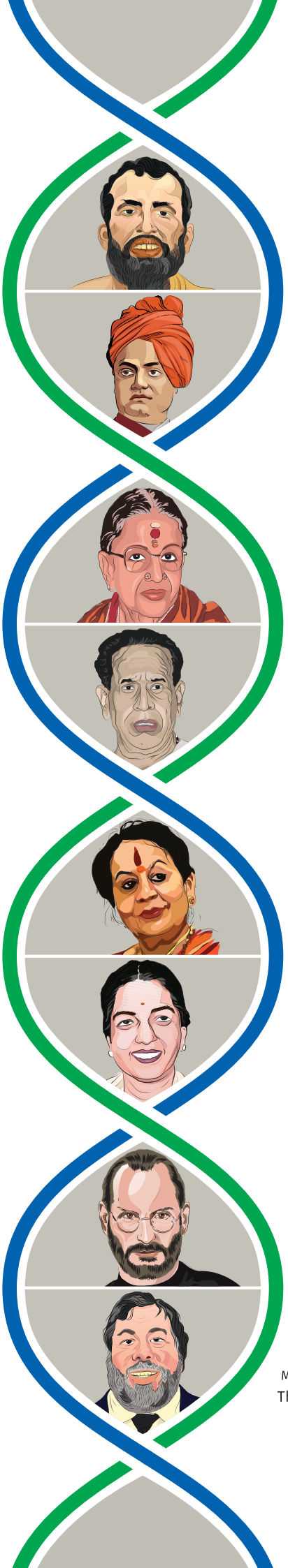
THE RGCB **ONAM FEAST 2017**

EDUCATING SCHOOL CHILDREN ON **NUTRITION, DIABETES AND HEART DISEASE**

[Courtesy: International Academy of Cardiovascular Sciences - India Section, Professor Sivasankaran, Sree Chitra Thirunal Institute for Medical Sciences & Technology and Professor Dr Zulfikar Ahmed, Medical College Hospital, Thiruvananthapuram at SMV School, Kendriya Vidyalaya and Manacaud Girls High School]

TAKING BIOTECH TO **SCHOOL CHILDREN**

Scientific Advisory Council Members with a traditional "Theyyatom" performer during the RGCB Scientific Retreat at Munnar



SRI RAMAKRISHNA PARAMAHAMSA
SPIRITUALITY
SWAMI VIVEKANANDA

M S SUBBULAKSHMI
MUSIC
BHIMSEN JOSHI

SONAL MANSINGH
DANCE
RUKMINI DEVI ARUNDALE

STEVE JOBS
COMPUTING
STEVE WOZNIAK

RGCB
DISCOVERIES FOR A BETTER TOMORROW

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