Abstracts of papers presented

Design: Madhushree Kamak, TIFR

PROGRAMME

30/01/2016, Saturday

	Arrive at Lonavala from Mumbai and check into room. Pick up name tags and meeting schedule, put up posters. Arrivals between 9:30am and 11am will be provided breakfast.
12:30-2:00	Lunch
2:00-2:10	Mahabaleshwar seminar series: Spirit of discussion, promote scientific interactions between students/post-doctoral fellows and faculty

Session I: *elegans* cell biology

Session chairs: Virupakshi Soppina, IIT-Gandhinagar and **Anoopkumar Thekkuveetil,** Sree Chitra Institute for Medical Sciences and Technology

2:10-3:00	Ronen Zaidel-Bar, National University of Singapore: Regulation of actomyosin contractility (45 min talk)
3:00-3:20	Anup Padmanabhan, National University of Singapore: Non-junctional adhesion-independent E-cadherin clusters regulate the actomyosin cortex and slow cytokinesis (12min talk)
3:20-3:40	Parul Sood, TIFR: Crowded locations along the neuronal process regulate cargo flux (12min talk)
3:40-4:10	Tea break
4:10-4:45	Sachin Kotak, IISc: Aurora A kinases dictates proper spindle positioning from worms to humans (30 min talk)
4:45-5:05	Swati Pal, The hospital for sick children Toronto: *C. elegans* CCM-3 promotes biological tube development by regulating vesicle trafficking and polarity (12min talk)
5:05-5:25	Sharika Rajashekaran, Alagappa University: Analysis of differentially regulated proteins during Gram positive and Gram negative bacterial infection in *Caenorhabditis elegans* (12min)
5:30-7:30	**Posters and Tea**
7:30-9:00	Dinner
8:30	"Getting the most out of graduate school". Panel members: Kavita Babu (IISER-Mohali), K. Subramaniam (IIT-Madras), Antony Jose (Univerity of Maryland), Arjumand Ghazi (University of Pittsburgh), Sudip Mondal (University of Texas) and Abhishek Bhattacharya (Columbia University)

31/01/2016, Sunday

7:30-9:00	Breakfast

Session II: Molecules to circuitry

Session chairs: **Jaya Bandyopadhyay,** Maulana Abdul Kalam University of Technology and **Ashwini Godbole**, Institute of Trans-disciplinary Sciences and Technology

9:00-9:50	Michael Nonet, WUSM: Cellular mechanisms controlling mechanosensory neuron synapse development (45 min talk)
9:50-10:25	Sandhya Koushika, DBS-TIFR: Regulation of cargo transport in neurons (30 min talk)
10:25-10:45	Abhishek Bhattacharya, Columbia University: Stress induced plasticity of the *C. elegans* electrical synapse network (12 min talk)
10:45-11:15	Tea Break
11:15-11:50	Kavita Babu, IISER-Mohali: Understanding the molecular mechanism of RIG-3 functioning at the synapse (30 min talk)
11:50-12:25	Varsha Singh, IISc: An odorsensory circuit for aversion response of *C. elegans* to bacterial pathogens (30 min talk)
12:25-12:45	Madhushree Kamak, TIFR: UNC-16/JIP-3 regulates early steps of synaptic vesicle protein trafficking via LRK-1/LRRK-2 and the AP1 complex (12min talk)
12:45-1:05	Pratima Pandey, IISER-Mohali: Understanding the role of RIG-3 at the *C. elegans* neuromuscular junction (12min)
1:05-2:15	Lunch

Session III: Circumventing ageing

Session chair: **Rakesh Pandey**, CSIR-CIMAP

2:15-3:05	Arnab Mukhopadhyay, NII: A panoply of post-transcriptional regulatory events determine dietary restriction-induced longevity (45 min talk)
3:05-3:40	Arjumand Ghazi, University of Pittsburgh: Fat, Fertility and Aging Worms (30 min talk)
3:40-4:00	Jamuna Subramaniam, Sri Ramachandra Medical University: Reserpine utilizes novel neuronal pathways for lifespan extension and alleviation of Amyloid beta toxicity in *Caenorhabditis elegans* (12min talk)
4:00-4:20	Akanksha Pant, CSIR-CIMAP: b-caryophellene ameliorates age-related decline in mitochondrial turnover and b-amyloid induced toxicity in *Caenorhabditis elegans* (12min)
4:20-6:30	**Posters and Tea**
6:00-7:30	**Murder in the *ELEGANS* mansion (team game)**
7:30-9:00	Dinner and bonfire
8:30	"Academic careers in different settings in India: rewards and challenges" Panel members: Virupakshi Soppina (IIT-Gandhinagar), Kavita Babu (IISER-Mohali), Varsha Singh (IISc), Rakesh Pandey (CSIR-CIMAP), Jamuna Subramaniam (Sri Ramachandra Medical University), Medha Rajadhyaksha (Sophia College)

01/02/2016, Monday

7:30-9:00	Breakfast

Session IV: Genome editing and inheritance

Session chair: **Arnab Mukhopadhyay**, NII

9:00-9:50	Geraldine Seydoux, JHMI: High efficiency genome editing using Cas9 ribonucleoprotein complexes (45 min talk)
9:50-10:25	Antony Jose, University of Maryland: Inheritance of RNA from somatic cells to progeny in *C. elegans* (30 min talk)
10:25-11:10	Bhagwati Gupta, McMaster University: Genetic control of reproductive system development in nematodes (30 min talk)
11:10-11:30	Tea Break

Session V: Signalling and gene regulation

Session chair: **P. Rajini**, CFTRI

11:30-12:10	Gautam Kao, University of Gothenburg: ASNA-1 and insulin secretion: Lessons from worms for mammalian cell biology (30 min talk)
12:10-12:30	G. P. Manjunath, IISER-Mohali: *C. elegans* Homeodomain Protein DVE-1 regulates transcription in response to Insulin/Insulin like Growth Factor (IGF) Signaling (12min talk)
12:30-12:50	Syed Tabrez, NII: Non-sense helps, sometimes! Role of post-transcriptional gene regulation during dietary restriction (12min)
12:50-1:10	Medha Rajadhyaksha, Sophia College: Lithium alters behavior of *Caenorhabditis elegans* under hypoxia by modulating HIF-1 (12min)
1:10-1:30	Latika Matai, CSIR-IGIB: Oxidative quality control regulates response to ER stress through translation control (12min)
01:30-2:30	Lunch

Session VI: Newer technologies

Session chair: **Kisan Babu**, University of Agricultural Sciences

2:30-2:50	Crispers for gene knockout and targeted integration, Sigma Aldrich (12 min talk)
2:50-3:10	Siddharth Khare, IISc: Techniques to measure and exert forces in micro Newton range, applied to C. elegans (12min talk)
3:10-3:30	Sudip Mondal, University of Texas: A Large-scale high-throughput microfluidic screening platform for drug discovery using C. elegans disease models (12min talk)
3:30-5:30	**Posters and Tea**
5:30-7:30	**Attendees can choose to walk to the dam or see other local attractions at Lonavala**
7:30-9:00	Pool-side Dinner
9:00	Post Dinner party

02/02/2016, Tuesday

7:30-9:00	Breakfast and Check out

Session VII: Rewiring the nervous system after injury

Session Chair: **Apurba Koner,** IISER-Bhopal

9:00-9:35	Anindya Ghosh-Roy, NBRC: Functional restoration after neuronal injury (30 min talk)
9:35-10:10	Strahil Pastuhov, Nagoya University: Regulation of axon regeneration by axotomy-induced serotonin signaling (30 min talk)
10:10-10:30	Sucheta Kulkarni, NCBS: UNC-16/JIP3 inhibits the function of the regeneration promoting isoform of DLK-1 (12min talk)
10:30-11:00	Tea Break

Session VIII: Germline

Session chair: **Sachin Kotak**, IISc

11:00-11:50	K. Subramaniam, IIT-Madras: A decade-long obsession with puf-8 and germ cell decisions (45 min talk)
11:50-12:20	Anilkumar Ganga, IIT-Kanpur: PUF-8 facilitates synaptonemal complex formation by promoting the perinuclear localization of dynein (12min)
12:30-2:00	Lunch
2:00	Departure to Mumbai
	Visit to Bhaja caves (for those leaving late or leaving on 03/02/2016)

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Oral Presentations

Poster Presentations

The actin-bundling protein PLST-1 is required for long-range cortical force transmission in the *C. elegans* embryo and is essential for polarization and cytokinesis

Ronen Zaidel-Bar[1,2] and Wei Yung Ding[1],

1) Mechanobiology Institute, National University of Singapore, Singapore; 2) Department of Biomedical Engineering, National University of Singapore, Singapore

The cell cortex, an actomyosin network underlying the plasma membrane, is responsible for the control of cell shape and the generation of contractile forces that drive polarization and cell division. It depends on myosin activity as well as the organization of filamentous actin (F-actin) by actin regulatory proteins.

In *C. elegans*, PLST-1 is the sole ortholog of plastin (a.k.a. fimbrin), an evolutionarily conserved actin-bundling protein containing two EF-hand motifs followed by two tandem repeats of calponin homology (CH) domains. Endogenous PLST-1, labeled by GFP via CRISPR/Cas9 knock-in, forms both filamentous and punctate structures at the cell cortex, co-localizing with both CYK-1- and ARX-2/3-dependent F-actin structures, respectively. In *plst-1*(tm4255), a deletion mutant that abrogates the third and fourth CH domains, the myosin foci in the cortex of the newly fertilized zygote are distinctly smaller than wildtype (1.47μm2 in *plst-1*(tm4255) vs 1.98 μm2 in wildtype). This results in weaker force generation as evidenced by slower cortical flow (1.7μm/s in *plst-1*(tm4255) vs. 7.8μm/s in the control), and leads to defects in the establishment of polarity. In addition, the interconnectedness of the meshwork, as measured by directional flow correlation, decays much faster in *plst-1*(tm4255) compared to the control.

PLST-1 is also required for cell division. In the control, PLST-1 forms a thick parallel filamentous furrowing band with a concurrent rotational flow and ingression to form the cytokinetic ring. Loss of PLST-1 function leads to substantially slower division (420 s in *plst-1*(tm4255) vs. 243 s in the control) in 85% of embryos and failure to complete the first cell division in 15% of the embryos. Following a delay in furrowing initiation, the subsequent furrowing speed was similar in mutant and control (0.25μm/s in *plst-1*(tm4255) vs. 0.28μm/s in the control), suggesting that PLST-1 is only required for furrowing band formation, but not in the subsequent ingression itself.

In conclusion, our results support a model whereby PLST-1 organizes F-actin into a bundled, interlinked meshwork. This interlinked network allows force to be transmitted at a much longer length scale, permitting an additive effect of individual contractile forces generated by myosin foci scattered throughout the meshwork. Such effective force transduction in turn allows the dynamic reorganization of cortical actomyosin into higher order structures that is critical for polarity establishment and cell division.

Non-junctional adhesion-independent E-cadherin clusters regulate the actomyosin cortex and slow cytokinesis

Anup Padmanabhan and Ronen Zaidel-Bar

Mechanobiology Institute, National University of Singapore, Singapore

During cytokinesis in metazoan cells, the furrow ingression is resisted by intercellular adhesion mediated by cell-cell junctions. Although E-cadherins are best known for their essential role in mediating adhesion at cell junctions, a significant amount of E-cadherin on the cell surface is found outside of cell-cell junctions. The cellular function of these non-junctional cadherin clusters has not been addressed before. Here using live imaging and genetics we show that during in early *C. elegans* embryos E-cadherin/HMR-1 formed non-junctional puncta at the cell surface associated with cortical F-actin. Depletion of E-cadherin/HMR-1 puncta in 1-cell stage embryo lacking cell-cell junctions accelerated furrow ingression during the first cell division. At the molecular level we observed E-cadherin/HMR-1 and myosin II/NMY-2 to negatively regulate each other and localize to distinct regions both at the cortex and along the ingression furrow. This antagonistic interaction and spatial segregation of E-cadherin/HMR-1 and NMY-2 was dependent on the formin/CYK-1 polymerized F-actin. Finally, we discovered that the non-junctional E-cadherin/HMR-1 puncta localized at the cell surface helps in holding the cortex and membrane together, a hitherto unknown cellular function of non-junctional E-cadherin/HMR-1.

Our results thus show that surface localized non-junctional E-cadherin/HMR-1 could regulate cytokinesis beyond its canonical role in inter-cellular adhesion by (1) regulating cortical myosin activity and (2) holding the membrane and cortex together thus resisting cortical deformations such as during furrow ingression.

Crowded locations along the neuronal process regulate cargo flux

Parul Sood[1], Kausalya Murthy[2], Aparna Ashok[2], T. Vinod Kumar[3], Gautam Menon[3, 4], Sandhya P. Koushika[1]

1) Department of Biological Sciences- Tata Institute for Fundamental Research, Mumbai, India; 2) Neurobiology, National Centre for Biological Sciences-Tata Institute for Fundamental Research, Bangalore, India; 3) Institute of Mathematical Sciences, Chennai, India; 4) Mechanobiology Institute and Department of Biological Sciences, NUS, Singapore

In the narrow geometry of a neuron, a complex cytoskeletal network (Hirokawa 1982, Cueva et al 2007), multiple proteins bound at the end of microtubules (Leduc et al 2012, Conway and Ross 2014) and immobile cargo (Kaasik et al 2007, Daphne et al 2015), all contribute to create a complex and potentially crowded environment. We investigate the behavior of multiple types of cargo at such crowded locations, in vivo, using both *C. elegans* and Drosophila as model systems. We find that at the ends of microtubules and actin-rich regions, more than one type of cargo marked with synaptic vesicle or endosomal protein markers, and organelles like mitochondria, are predominantly stationary. Interestingly, moving cargo show behaviors like stopping, change in direction of motion, that are largely restricted to such crammed locations. Cargo also move shorter distances in relatively more crowded regions of neuronal process. These observations suggest that congested locations along the neuronal process can regulate motion of the cargo.

We further investigate the functional implications of such regulation. Using a simulation model benchmarked to our experimental data, we predict that change in direction of motion specifically at crowded locations is essential to avoid permanent traffic jams along the neuronal process. Furthermore, we observe a reduction in the density of stalled vesicles in touch receptor neurons of *C. elegans* when they are repeatedly stimulated using an eyelash or an artificial dirt PDMS chip. This reduction in density is dependent on the ability of the animal to sense touch. We therefore propose the role of vesicles stalled at crowded locations as dynamic reservoirs of cargo that are mobilized in conditions of high vesicle demand at the synapse. Alternatively, mobilization of stalled vesicles can allow the cargo to move longer distances without stopping, thus increasing the net number of vesicles that reach the synapse. We are currently characterizing these details of the phenomenon. We are also investigating if this reduction in density of stalled vesicles after stimulation, in TRNs of *C. elegans*, is a consequence of general changes in the cytoskeletal architecture of the neuron or, a specific motor-dependent mechanism.

Aurora A kinases dictate proper spindle positioning from worms to humans

Sachin Kotak

Department of Microbiology and Cell Biology, Indian Institute of Science, Bangalore, India

Accurate spindle positioning is essential for error-free mitosis. The one-cell *C. elegans* embryo has proven instrumental for dissecting mechanisms governing spindle positioning. Despite important progress, how the cortical forces that act on astral microtubules to properly align mitotic spindle are modulated in space and time remains elusive. We reveal that the PP6 phosphatase PPH-6 and its regulatory subunit SAPS-1, which negatively regulate pulling forces, associate with the Aurora A kinase AIR-1 in *C. elegans* embryos. We show that acute inactivation of AIR-1 during mitosis results in excess pulling forces on astral microtubules. Furthermore, our findings indicate that AIR-1 acts downstream of PPH-6/SAPS-1 in modulating spindle positioning. Intriguingly, we discovered that PPH-6/SAPS-1 depletion causes AIR-1 to localize to the cell cortex, in a manner that requires AIR-1 kinase activity. Moreover, we uncovered that Aurora A is required for spindle positioning in human cells, where it is needed for the cortical localization of NuMA/dynein during mitosis. Overall, our work indicates that Aurora A kinases have an ancient function in modulating spindle positioning, thus contributing to faithful cell division.

C. elegans CCM-3 promotes biological tube development by regulating vesicle trafficking and polarity

Swati Pal and Brent. W. Derry

The Hospital for Sick Children, Toronto, Canada

Cerebral Cavernous Malformations (CCMs) are vascular disorders of central nervous system that arise from loss of integrity of blood capillaries causing blood leakage. This leads to a variety of symptoms, including headaches, seizures and hemorrhagic stroke. Three genes causing familial CCM in humans have been identified: CCM1, CCM2 and CCM3. CCM3 mutations cause the most aggressive form of this disease, characterized by early onset and higher lesion burden. However, the in vivo function of this gene is poorly understood at present. *Caenorhabditis elegans* contains orthologues of CCM1 (*kri-1*) and CCM3 (*ccm-3*). CCM-3 protein is localized along the apical membrane of biological tubes (i.e., excretory canal, intestine and germline) and promotes endocytic recycling to maintain membrane integrity (Lant et al., 2015). To investigate the function of CCM-3 in multicellular tube development we used the *C. elegans* germline as a model system.

C. elegans germ cells undergo incomplete cytokinesis during development that creates openings into a common lumen called the rachis. *ccm-3* mutants have a collapsed rachis and underdeveloped oocytes that result in sterility. Our data reveal that CCM-3 and its binding partner, germinal centre kinase III (GCK-1), mediates endocytic recycling of cell surface receptors that regulates multiple signaling pathways, such as Notch and Ras/MAPK. *ccm-3* mutants also fail to present vitellogenin receptor RME-2 on the surface of oocytes, which prevents uptake of yolk proteins required for oocyte growth. CCM-3 is also localized to the contractile ring of dividing cells and in its absence the cleavage furrow breaks creating multinucleated cells. We hypothesize this is due to defective membrane transport at the nascent partition. This is corroborated by improper distribution of RAB11/ RAB-11, which is a marker of the recycling endosomes. We also observed that CCM-3 promotes cortical localization of the anillin scaffold protein ANI-1, as well as non-muscle myosin (NMY-2) in germ cells. Similar to what we observed in the excretory canal, ablation of *ccm-3* causes defective CDC42/ CDC-42 localization in oocytes, which in turn perturbs polarity establishment in the otherwise highly polarized *C. elegans* zygote. Collectively, our work indicates that CCM-3 lies at the hub of a key intracellular signalling network that couples vesicle trafficking with proper acto-myosin organization required for establishment of polarity. This leads to defective lumenization of biological tubes, which may explain how the vasculature of CCM patients becomes dilated and leaky. Currently, the only treatment for CCM patients is invasive brain surgery. Understanding the mechanism by which CCM-3 functions in vivo may help identify non-surgical therapies for treating CCM patients.

Analysis of differentially regulated proteins during Gram positive and Gram negative bacterial infection in *Caenorhabditis elegans*

Sharika Rajasekharan and Balamurugan Krishnaswamy

Alagappa University, Karaikudi, India

Every multicellular organism is having their own set of microbes that they carry in their skin and gut. The association with these microbes will have an overall impact on the host either in a beneficial or in a harmful way depending upon the mode of action of the microbe. According to WHO reports, infectious diseases are one of the top ten leading causes for death world-wide. Every year there is an increase in the incidence of infectious diseases, which is even made worse by the occurrence of antibiotic resistant bacterial infections. In order to understand the pathogenesis and host response to the virulence of the pathogenic bacteria, we require the aid of model organisms. *Caenorhabditis elegans* is simple and tractable model organism that have been used to understand various mechanisms such as cellular differentiation and development, neuronal regulation, host-pathogen interaction, functional genomics, proteomics and so on for past five decades. Our lab focuses to analyze the key pathways involved during interaction between bacterial pathogens and the host through both genomic and proteomic approaches.

Each pathogen has a different tactics in invading and evading the host response. The cell wall of Gram positive bacteria is composed of Lipoteichoic acid (LTA) and Gram negative bacteria is composed of Lipopolysaccharides (LPS). The induction of infection by the pathogen and the response of host system to the pathogenesis are different between the Gram positive and Gram negative bacterial infections. To understand the various regulatory players that are involved during infection that alter the host homeostasis, *C. elegans* have been infected with a Gram positive and Gram negative pathogen. The total proteins were isolated and fractionated based on the size-exclusion column chromatography method. The fractions were collected separately and run on 12% SDS-PAGE to differentiate the differentially regulated proteins. Further the differentially regulated proteins with respect to control (OP50) were identified by using MALDI-TOF-TOF and characterized further for their role and contribution during bacterial pathogenesis.

Cellular mechanisms controlling mechanosensory neuron synapse development

Michael Nonet

Washington University School of Medicine, St. Louis, USA

My laboratory focuses on understanding the molecular mechanisms that orchestrate the development, structural organization, and secretory signaling functions of the presynaptic nerve terminal. Signaling via chemical synapses is the major mode of cell-cell signaling in the nervous system. Presynaptic nerve terminals contain discrete morphological features including synaptic vesicles (SVs), active zones (AZs), and mitochondria. They communicate with their post-synaptic partners under the direction of electrical signals by releasing neurotransmitter stored in synaptic vesicles through fusion of these vesicles with the plasma membrane at release sites juxtaposed to the post-synaptic partner. We use the PLM mechanosensory as a simple system with a large presynaptic nerve terminal on a collateral branch that develops in the late L1 larvae. The PLM branch forms via an actin filopodial mediated process, which requires the action of CDC-42, TOCA-1 and WSP-1. This branch formation mechanism is distinct from HSN collateral branching, which was recently shown to be WAVE dependent, rather than WASP dependent.

Interestingly, only a single branch forms. How the decision to form only one branch is not well understood. However, we have evidence of a feedback mechanism linking synapse formation and branch formation. Specifically, in several distinct mutants when branches form but synapses are either unstable of fail to form, ectopic supernumerary branches are formed. For example, in *zyx-1* mutants, branches break and ectopic branches are formed.

After the branch has extended and stabilized in the ventral nerve cord, active zone components, synaptic vesicle components and finally mitochondria are transported sequentially into the developing varicosity. Mutants in *sam-4* fail selectively to transport synaptic components to the nerve terminal, but still transport active zone and mitochondria normally to synapses. *sam-4* encodes a myristoylated protein that is associated with transporting vesicles. Vesicle cargo in the mutant moves at normal speeds, but the movement is less processive. Because dominant gain-of-function mutations in the Kif1A *unc-104* kinesin motor are capable of suppressing *sam-4* vesicle trafficking defects, we postulate that SAM-4 regulates the activity of cargo bound motors.

Biochemically, *sam-4* encodes a component of the **B**LOC **O**ne **R**elated **C**omplex (BORC), which in vertebrate fibroblasts has been demonstrated to regulate transport of lysosomes. BORC consists of 8 subunits, and mutants in genes encoding at least 6 of the 8 complex subunits we have created in *C. elegans* using CRIPSR/cas9 methods have defects in SV transport. Three of the components of the BORC complex are also subunits of the **B**iogenesis of **L**ysosomal-related **O**rganelle **C**omplex one (BLOC-1). For example, *blos-2* and *snpn-1* mutants in this complex have severe defects in lysosome related organelle biogenesis. However, the BORC subunits that are not also BLOC-1 subunits, have no substantive lysosomal formation or trafficking defects in the embryo or the intestine. Analysis of lysosomal transport in neurons in ongoing. Thus, the BORC complex appears to mediate the transport of distinct organelle types in different cell types. Whether these differences are species specific, or conserved throughout the animal kingdom, remains ill-explored.

Regulation of cargo transport in neurons

Sandhya Padmanabhan Koushika

Department of Biological Sciences, Tata Institute of Fundamental Research, Mumbai, India

Neurons communicate with each other through synapses. Nearly all components necessary for this process travel to the synapse from the cell body. The axon provides a highway for necessary cargo movement between the cell body and the synapse. I will present highlights of our investigation of axonal transport of synaptic vesicles, a prominent and essential organelle for neuronal function. Molecular motors pick up synaptic vesicles in the cell body, move them along the axon and deliver them at synapses. This multi-step process involves several different interesting phenomena with corresponding regulatory mechanisms. I will discuss the regulatory mechanisms we have identified involved in (1) cargo formation and motor exit from the cell body (2) cargo motion along the axon and (3) motor degradation at synapses.

Stress induced plasticity of the *C. elegans* electrical synapse network.

Abhishek Bhattacharya[1] *and Oliver Hobert*[1,2]

1) Columbia University, New York, USA; 2) Howard Hughes Medical Institute, Columbia University, New York, USA USA

Stress induced plasticity of the nervous system allows animals to adapt to changing environments by modulating their behavior. We are studying the nervous system rewiring in response to environmental cues by investigating the hibernation-like alternative diapause state of *C. elegans*, the dauer state. In adverse environmental conditions, mainly starvation, population density and high temperature, *C. elegans* larvae molt into dauer, which not only show altered morphology, but also show a remarkably altered responsiveness to various environmental cues and strikingly different locomotory behavior. However, the neuronal circuit responsible for these altered behaviors and the molecular mechanism responsible for the circuit plasticity is poorly understood.

We focused our study on innexin (inx) genes, which encode the functional units of invertebrate electrical synapses. In a screen, using fosmid-based fluorescent reporter transgenes, for neuronally expressed inx genes that show altered expression in dauer state, we have identified the cellular specificity of *inx-6* expression is altered in dauer. In favorable condition, *inx-6* is only expressed in pharyngeal muscle cells throughout the life of the animal. In dauer, inx-6 expression is additionally turned on in the glutametergic interneuron pair AIB, which regulates locomotion during chemotaxis and odortaxis, by promoting reversals and turns. Furthermore, the *inx-6* expression in AIB is reversible. As animals recover from dauer stage, *inx-6* expression disappears from AIB. Another diapause stage, the starvation-induced L1-diapause, also shows similar plasticity of *inx-6* expression in AIB. In dauer, INX-6 expressed in AIB interacts with CHE-7, another innexin that is not expressed in AIB, to form electrical synapses. Using a temperature sensitive *inx-6*(rr5) allele and an AIB-specific inx-6 mutant allele, generated using CRISPR/Cas9 based genome editing, we identified that the loss of INX-6 activity in AIB affects locomotion speed and locomotory quiescence, specifically in dauer stage. Loss of *che-7* and genetic-ablation of AIB neurons also have similar effects on dauer locomotion. I will present our data en route to identifying the dauer-AIB neuronal circuit involving INX-6-mediated electrical synapses. I will also present data on the transcriptional control of the *inx-6* expression plasticity in the dauer nervous system that provides cellular specificity and also integrates environmental information. Our studies provide insights into the process of stress induced nervous system plasticity at different levels of gene regulation, circuits and behaviors.

Understanding the molecular mechanism of RIG-3 functioning at the synapse

Kavita Babu

Indian Institute of Science Education and Research, Mohali, India

Cell surface Immunoglobulin superfamily proteins (IgSFs) have been shown to play important functions in the development and functioning of the nervous system. One such IgSF protein, RIG-3, has been previously shown by us to be required for maintaining normal Acetylcholine Receptor (AChR) levels at the Neuromuscular junction (NMJ) (Babu K., et al., Neuron; 2011). I will describe the molecular mechanism of RIG-3 functioning in motor neurons, a single sensory neuron and a single interneuron.

Our work suggests that RIG-3 functions through the WNT ligand, LIN-44 and the non-canonical WNT receptor, CAM-1 to maintain normal AChR levels at the NMJ. We also find that WNT/LIN-44 functions through RIG-3 and CAM-1 to maintain normal polarity of the sensory neuron in the *C. elegans* tail.

I will also present evidence that implicates RIG-3 in circuit function at the level of a single interneuron. Our work indicates that mutants in *rig-3* function through interneurons for normal behaviour in *C. elegans*.

Survival of *Caenorhabditis elegans* in the wild: Role of sensory neurons in avoidance behavior and innate immunity

Varsha Singh

Indian Institute of Science, Bangalore, India

How does a bacterivore defend itself from pathogenic microbes? *C. elegans* lives in soil, close to dead or decaying matter which provides source of nutrition. A decaying piece of fruit may have both pathogenic bacteria and food bacteria making it essential for worms to pick and choose. One might imagine the use of specific pattern recognition receptor or novel sensors of microbial factors in *C. elegans* to prevent coming in contact with pathogenic bacteria. *C. elegans* is indeed capable of avoiding some bacteria such as *Pseudomonas aeruginosa*. At the same time *C. elegans* is unable to avoid another pathogenic bacterium *Salmonella enterica*. This may point to evolution of *C. elegans* with *P. aeruginosa* in the wild. Olfactory neurons appear to play a big part in attraction to non - pathogenic bacteria as well as avoidance of pathogenic bacteria.

UNC-16/JIP-3 regulates early steps of synaptic vesicle protein trafficking via LRK-1/LRRK-2 and the AP1 complex.

Bikash Choudhary[1],Madhushree Kamak[2],Neena Ratnakaran[2], Jitendra Kumar[1], Anjali Awasthi[3], Takashi Fukuzono[5], Li Chun[5], Ken Nguyen[4], Kunihiro Matsumoto[5], Naoki Hisamoto[5], and Sandhya Koushika[2].

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Synaptic vesicle protein trafficking occurs via vesicular cargo compartments formed at the cell body of the neuron. The identity of the cargo compartment as a precursor of a synaptic vesicle is determined by multiple factors. It carries a defined set of synaptic vesicle proteins such as RAB-3 and SNB-1 and is transported by molecular motors such as kinesin-3 and dynein in the axon. Our study has identified UNC-16/JIP-3 as a regulator of early steps in synaptic vesicle protein trafficking. In the absence of UNC-16, we observe that vesicular cargo exit the cell body into the neuronal process, carrying both synaptic vesicle proteins and Golgi resident enzymes. These synaptic vesicle proteins also atypically enter the dendritic process. We propose that the altered nature of the cargo compartment-both composition and size- could lead to the mis-trafficking phenotypes previously observed. (Byrd et al, 2001; Brown et al 2009).

Our study demonstrates that the formation of aberrant vesicular cargo compartments in *unc-16* is dependent on the function of LRK-1, a homolog of the familial Parkinsonism gene LRRK2 (Sakaguchi-Nakashima et al, 2007). *lrk-1* mutants exhibit similar atypical cargo compartments exiting the neuronal cell body. The over-expression of LRK-1 in *unc-16* is able to rescue a subset of the trafficking defects observed in *unc-16*. The AP1 complex is known to have roles in formation of cargo compartments at the trans-Golgi and its μ chain UNC-101 is a known interactor of LRK-1 (Guo et al, 2012; Sakaguchi-Nakashima et al, 2007). We therefore examined the localization of UNC-101 on the Golgi and found it to be altered in both *unc-16* and *lrk-1*animals. This mis-localization can be rescued in *unc-16* animals by the over-expression of LRK-1. This suggests that the formation of an appropriate synaptic vesicle protein cargo compartment depends on the Golgi localization of UNC-101 regulated by UNC-16 at least partially through LRK-1. Interpreting a set of genetic interactions and biochemical evidence, we propose a model in which UNC-16 and LRK-1 present at the Golgi regulate synaptic vesicle protein trafficking.

Understanding the role of RIG-3 at the *C. elegans* neuromuscular junction

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The neuronal synapses of *C. elegans* neuromuscular junction (NMJ) shows conserved features, such as multiple classes of neurotransmitters and receptors for both excitatory (cholinergic) and inhibitory (GABAergic) synaptic inputs. The regulation of potentiation at NMJ can play important role in the stabilization of circuits and further in worm movement. Previous studies have reported that RIG-3, a member of Ig superfamily (IgSF), shows increased paralysis in the presence of the Acetylcholine (ACh) Esterase inhibitor, aldicarb. It was shown that RIG-3 functions in a CAM-1 (ROR receptor tyrosine kinase) dependent manner and controls the localization of ACh (acetylcholine) receptor, ACR-16 at the NMJ (Babu et al., 2011). CAM-1 also acts as a receptor for Wnt ligands (Green et al., 2008), indicating that the effects of RIG-3 on synaptic function could be a result of changes in Wnt signaling at the NMJ. In this study we have provided genetic evidence to show that CAM-1 functions as a receptor for a LIN-44/Wnt ligand and additional evidence that RIG-3 is present in close proximity to CAM-1 at the NMJ and thus more likely to regulate Wnt signaling through CAM-1. Further we have characterized the downstream signaling components and have identified the possible target gene functioning in this pathway. We have also elucidated the role of RIG-3 in Wnt mediated developmental processes. Therefore, our studies provide interesting information that RIG-3 functions as an anti-potentiation molecule for *C. elegans* NMJ signaling and also regulates developmental processes of Wnt signaling pathways.

A panoply of post-transcriptional regulatory events determine dietary restriction-induced longevity

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Dietary restriction (DR) is known to increase life span and health span across species. In higher mammals, including non-human primates and human beings, DR has positive effects on debilitating age-related diseases like type II diabetes, atherosclerosis and neurodegenerative disorders. How DR achieves such robust effects is an area of intense research. Model systems like *Caenorhabditis elegans* have provided valuable insights into the process of DR-mediated life span extension. In *C. elegans*, DR can be initiated by multiple ways including using genetic mimics (the *eat-2* mutants that have slow pumping or knocking down *drl-1*, a MEKK3-like kinase), diluting the bacterial food or by supplementing the media with non-hydrolysable sugar. Interestingly, the different DR regimes evoke diverse gene expression profiles and require distinct transcription factors. Our lab is interested in understanding the intricate gene regulation events associated with nutrient sensing and DR. Using a combination of genetics and genomics, we are trying to reveal the signaling events that lead to the complex transcriptional as well as post-transcriptional regulation of gene expression downstream of DR. In this presentation, I will present examples from our recent studies to show how nature has installed checks and balances to regulate gene expression during times of energy crisis.

Fat, Fertility and Aging Worms

Arjumand Ghazi

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The coordination of lipid production and degradation is essential for animals' health - lipid imbalances are characteristic of obesity and a feature of many reproductive pathologies and age-related diseases. But how these processes are balanced in multicellular organisms is poorly understood. In *C. elegans*, removing the germline, using mutations in genes such as *glp-1*, extends lifespan. Germline loss is a major metabolic challenge that compels the animal to stop fat deposition into eggs and remodel its lipid reserves. This phenomenon provides a unique platform to understand how complex metazoans retain metabolic homeostasis when challenged with alterations in fertility and age. Recent studies, including ours, have shown that germline loss activates conserved transcription factors such as DAF-16/FOXO, TCER-1/TCERG1 and NHR-49/PPARα, in the intestine, the worms' main fat depot. In this presentation, I will discuss some of our recent data that indicate that these transcription regulators enhance both lipid synthesis and degradation widely and concurrently in response to germline loss, and the coordination of lipogenic and lipolytic pathways facilitates the adaptation to germline loss by ensuring lipid homeostasis.

Reserpine utilizes novel neuronal pathways for lifespan extension and alleviation of Amyloid beta toxicity in *Caenorhabditis elegans*

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Despite, lifespan extension being an all systems encompassing event, the neural contribution to lifespan extension is not well understood due to the refractory nature of neurons to small RNA interference. Recently, we reported that an antihypertensive drug, Reserpine, extends lifespan and alleviates amyloid beta toxicity (AAT) through modulation of neurotransmitter, especially, acetylcholine release in *C. elegans*. Intriguingly, neither the lifespan extension nor the alleviation of Abeta-toxicity (AAT) brought about by reserpine happens through the known pathways. Here, we report two novel modes of reserpine action. While loss of the neurotransmitter, dopamine, does not affect RMLE, dop-3, a D2-type dopamine receptor absence shortens the RMLE. DOP-3 acts through the G0i pathways. Absence of Goi, *goa-1* and the downstream transcription factor, *jun-1* decreases RMLE. Another novel modulator is *eri-1*, a 5'-3' exoribonuclease, a negative regulator of sRNAi, whose loss of function makes neurons amenable to sRNAi. Both *dop-3*, and *eri-1* are essential and sufficient as their absence eliminates RMLE. More importantly, reserpine alleviates Amyloid beta toxicity. , is a candidate identified by the microarray. Intriguingly, the promoter fusion reporter of FMRFamide family neuropeptide, FLP-11, PFLp-11::GFP, background reduced Abeta toxicity in *C. elegans* and almost abolished Abeta toxicity in combination with reserpine. Thus, novel neuronal genes play a major role in reserpine action.

β-caryophellene ameliorates age-related decline in mitochondrial turnover and β-amyloid induced toxicity in *Caenorhabditis elegans*

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Aging has been associated with the accumulation of damages in cellular organelles and molecules. The cellular damage rate is closely tied to age related neurodegenerative disorders like Alzheimer's disease (AD). The decline in mitochondrial health is closely linked to increment in oxidative stress and damaged cellular components. The deterioration of mitochondrial function is known to alter lifespan in various model organisms. Previously, we have reported the longevity promoting and stress modulatory potential of a FDA approved phytomolecule β-caryophellene (BCP) in *Caenorhabditis elegans*. Therefore, present study intended to explore in vivo protective effects of BCP against β-amyloid (Aβ) induced Alzheimer's phenotype and age related mitochondrial dysfunction. We found that BCP treatment enhanced the lifespan and health span of Aβ expressing transgenic strain of *C. elegans*. The progression in age and environmental exposures may result in decline in mitochondrial genome and function. The mitochondrial dysfunction is early features of AD. Therefore, we assessed effect of BCP treatment on mitochondrial copy number as status of mitochondrial function can be deciphered by assessing amount of mtDNA. The mtDNA copy number per cell varies from hundreds to thousands among different animal species and different tissues. The increment in health span on BCP treatment was accompanied by improved mitochondrial DNA copy number with significant change in the mortality rate and oxidative damages to proteins. BCP treatment reduced protein carbonyl levels and mitochondrial DNA (mtDNA) oxidative damage. Altogether, the present findings suggest BCP supplementation could lead to better mitochondrial functionality with age and can also ameliorates Aβ-induced paralysis in *C. elegans* transgenic model of Aβ-induced toxicity. The protective role of BCP against Aβ-induced toxicity and mitochondrial damage can be subjected to future investigation to unravel possible mechanistic insights. These findings recommend BCP as an attractive molecule for the development of new drugs with therapeutic potential for the treatment of AD.

Genome editing using CRISPR in *C. elegans*

Geraldine Seydoux

Johns Hopkins University, Baltimore, USA

I will present approaches to mutate, delete or replace any gene in the *C. elegans* genome using homology-dependent repair (HDR) of double strand breaks induced by Cas9. We have found that HDR in the *C. elegans* germline proceeds by a highly local gene conversion process that requires only ~30 bases of homology between the repair template and the target locus. I will describe how to choose guide RNAs, design repair templates, and develop efficient screening strategies to obtain your desired edit in less than a week.

Inheritance of RNA from somatic cells to progeny in *C. elegans*

Antony Jose

University of Maryland, College Park, USA

An animal that can transfer gene-regulatory information from somatic cells to germ cells may be able to communicate changes in the soma from one generation to the next. In *C. elegans*, expression of double-stranded RNA (dsRNA) in neurons can result in the export of dsRNA-derived mobile RNAs to other distant cells. We recently showed that neuronal mobile RNAs can cause transgenerational silencing of a gene of matching sequence in germ cells. Consistent with neuronal mobile RNAs being forms of dsRNA, silencing of target genes that are expressed either in somatic cells or in the germline requires the dsRNA-selective importer SID-1. In contrast to silencing in somatic cells, which requires dsRNA expression in each generation, silencing in the germline is heritable after a single generation of exposure to neuronal mobile RNAs. Inherited silencing can persist for more than 25 generations in the absence of the ancestral source of neuronal dsRNA. Progress in dissecting the mechanism of silencing within germ cells by neuronal mobile RNAs and studies examining how extracellular RNA causes silencing in progeny will be presented at the meeting.

Genetic control of reproductive system development in nematodes

Bhagwati Gupta, Devika Sharanya, Sujatha Marri, B. Nagagireesh, Ashwin Seetharaman, and Philip Cumbo

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The nematode vulva serves as a powerful system to investigate mechanisms of cell proliferation, cell differentiation and tissue morphogenesis. In both *C. elegans* and *C. briggsae* hermaphrodites, vulva develops from the division of three of six multipotential vulval precursor cells (VPCs). The induced VPCs divide three rounds to generate 22 progeny that differentiate and undergo morphogenetic changes to form the vulval tissue. The vulva connects to the uterus, muscles and neurons to form a functional reproductive system in an adult animal.

The morphology of the vulva and the underlying cellular events during development appear almost identical in *C. elegans* and *C. briggsae*. This suggests that the underlying genes and genetic networks are likely to be conserved in both species. We have investigated this hypothesis by isolating mutants in *C. briggsae* using forward genetic screens that affect the number and fates of vulval progeny. Three broad categories of mutants that were recovered in our screens are termed as Vulvaless (Vul, fewer than three VPC inductions), Multivulva (Muv, more than three VPC inductions) and Protruding vulva (Pvl, abnormal vulval morphology).

The study of Vul and Pvl mutants resulted in the identification of a total of10 genes, including orthologs of *lin-39* (Hox) and *lin-11* (LIM-Hox) (Sharanya et al., G3, 2012). The Muv category defines seven genes all of which negatively regulate vulval cell proliferation (Sheetharaman et al., DevBiol, 2010; Sharanya et al., EvolDev, 2015). Three of the Muv genes are cloned and encode orthologs of *pry-1* (Axin), *lin-1* (ETS) and *lin-31* (Winged-helix).Some of the uncloned Vul, Pvl and Muv genes map to chromosomal regions that lack obvious candidates when compared to corresponding regions in *C. elegans*, suggesting that these might represent novel genes.

The progress and latest findings that reveal evolutionary changes in signaling pathway function in the two nematode species will be summarized.

ASNA-1 and insulin secretion: Lessons from worms for mammalian cell biology

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The insulin/IGF signaling (IIS) pathway in *C. elegans* controls a variety of functions including aging, diapause regulation, metabolic homeostasis, stem cell behavior, germline development, memory and response to cellular stresses. This wide range of functions is perhaps reflected in the large number of insulin/IGF type ligands encoded in the worm genome but paradoxically limited by the likely requirement of all ligands having to act via a single insulin receptor DAF-2. A full understanding of the functions mediated by the IIS requires the identification of proteins that directly modulate its activity. In our group we have identified ASNA-1 as a regulator of IIS activity based its role in the 1st larval stage diapause. It is a positive regulator of the IIS pathway activity and acts at the level of insulin/DAF-28 secretion. Analysis of DAF-28 function reveals that it has the properties of an insulin molecule rather than an IGF. However, as is the case with IIS function, the effects of ASNA-1 are multiple with impacts on ER homeostasis, response to metals and membrane protein targeting. Work from the group shows that at least two of its functions are separable from its role in the modulation of IIS activity and provides support for the idea that ASNA-1's role(s) in insulin secretion is direct in nature. Insight into ASNA-1 function also comes from the analysis of its homologs across the phylogenetic spectrum and the totality of the findings suggests that it is a versatile protein capable of adopting different physical configurations and functions depending on the cellular milieu. Recent work in mice shows that targeted knockout of ASNA1 in the pancreatic Langerhans beta cells causes a diabetic phenotype. In an attempt to sort through the diversity of functions promoted by ASNA-1, we identified *enpl-1*/endoplasmin/HSP90B1 based on the L1 diapause phenotype. ENPL-1 physically binds to ASNA-1, promotes insulin/DAF-28 secretion and mutants in the gene have overlapping phenotypes with those of *asna-1* for some but not all of its functions. We will present our work in worms and mammalian cells that provide new information on how ASNA-1 and ENPL-1 cooperate to regulate insulin secretion.

C. elegans Homeodomain Protein DVE-1 regulates transcription in response to Insulin/Insulin like Growth Factor (IGF) Signaling

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We have identified a role for Special AT-rich Binding protein (SATB1) in regulating IGF signaling. SATB1 has been shown to have prognostic correlation with aggressive forms of breast ($P < 0.0001$), prostrate and colorectal cancer incidence. Furthermore, expression of SATB1, CBP and p300 can be used as a marker for age, are reduced with aging and diabetes and can be induced by CR and ablation of IGFR activity.

We therefore, hypothesized that SATB1 and its interacting partners may participate in IIS mediated regulation of lifespan. Consistent with this hypothesis, we discovered that both SATB1 and SATB2 act as robust repressors of transcription from Insulin Responsive Sequences (IRS) in human cell lines and that DNA binding domains of SATB1 are essential for this transcriptional repression activity. SATB1 interacts physically with human IRS sequences in vitro as well as DAF-16 homologs FoxO1, FoxO3a and FoxO4 in vivo. We observed that down regulation of DVE-1, a SATB homolog in *C. elegans*, leads to an increase in median lifespan. DVE-1 is subject to post translational modification by AKT-1 in response to IGF signaling. We found DVE-1 expression in all stages of worm development with the exception of the fourth larval stage. This expression was seen in worm gonads, early embryonic stages of worm development and neurons in the adults. When considered with the role of DVE-1 in IIS, these results indicate that DVE-1 may play a role in both germline as well as neuron regulated longevity in *C. elegans*.

Non-sense helps, sometimes! Role of post-transcriptional gene regulation during dietary restriction

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Dietary restriction (DR) is known to extend life span and delay the onset of age-related chronic diseases across species, from nematodes to higher mammals. In mammals, DR has positive impact on debilitating diseases like type II diabetes, cancer, atherosclerosis and neurodegenerative diseases. The molecular mechanisms involved in DR-mediated longevity and health span extension is an intense area of research where studies using the nematode *Caenorhabditis elegans* have contributed immensely. In *C. elegans*, DR is attained either by diluting the amount of bacteria in the culture media or by using the eat-2 mutants that have lower pharyngeal pumping leading to reduced food intake. In order to shed light on the mechanisms of DR, we studied the changes in the transcriptome in *eat-2*(ad1116) at different stages of adulthood. We observed an upregulation of more than 3000 genes in *eat-2*(ad1116) compared to wild type, in an age-dependent manner consistent with the dramatic metabolic reprogramming during DR. Among these, several genes involved in mRNA splicing were significantly upregulated. Further bioinformatic analysis revealed a significant increase in splicing and alternative splicing events in the DR condition. In support of the increased requirement of splicing machinery during DR, knocking down several of the splicing factors or components of the spliceosome machinery in *eat-2*(ad1116) led to complete suppression of the increased lifespan. Using transcriptome analysis, we identified the role of a putative splicing factor *psm-1* in regulating majority of the alternative splicing events during DR. Elevated levels of splicing as well as alternative splicing of mRNA during DR may lead to more unproductively spliced mRNA that need to be degraded by the mRNA surveillance pathway. Interestingly, we found that all genes involved in Nonsense-Mediated mRNA Decay (NMD) pathway were unregulated in *eat-2*(ad1116) and knocking them down reduced longevity of the mutant worms. Using transcriptomics, we showed an increased retention of pre-mature termination codon-containing introns during DR. Our study shows how the transcriptome is dynamically modulated during DR to support increased transcription and generation of larger number of alternate protein forms on one hand, while ensuring protection against misincorporated introns that may lead to truncated or improperly folded proteins.

Lithium alters behavior of *Caenorhabditis elegans* under hypoxia by modulating HIF-1

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Neuroprotective effects of lithium, a drug in use for bipolar disorder, have been well documented in the last couple of decades and it is likely to be used for treatment of neurodegenerative diseases. Interestingly, despite extensive reports of lithium protection after insults to cells by variety of environmental conditions, very few have demonstrated and analyzed effect of lithium on behavior under hypoxia. Low levels of oxygen in the environment is a challenge faced by most organisms, albeit sometimes transiently. The compensatory mechanism that helps organism tide over such adversaries range from physiological adaptation to altered gene expression. One major molecular pathway sensitive to oxygen content in micro environment involves Hypoxia Inducible Factor (HIF-1) which dimerizes with constitutively expressed Aryl Hydrocarbon receptor Associated protein (AHA-1) to form a stable complex. Highly conserved through evolution, the HIF molecule is a transcription factor that triggers gene expression which helps organisms survive the oxygen deprivation. Role of lithium, a GSK-3β inhibitor, as a potential modulator of HIF pathway has not been investigated and deserves attention.

The molecular events of HIF induction and its effect have been substantially deciphered in *Caenorhabditis elegans.* However, it has not been established whether HIF plays a role in behavioral adaptation that is exhibited by the worms under hypoxic condition. We, therefore, have investigated whether hypoxia alters behaviour and whether HIF has a role to play in rescuing the worms from behaviour alteration. Behavioral assays were standardized for motor activity and associative memory formation. The worms were subjected to hypoxia which is known to cause heightened HIF-1 expression in cells. Further, to assess the effects of lithium, the worms were pre-treated with lithium under normoxia and chemically induced hypoxia. Alteration in behaviour in response to hypoxia was measured in wild type N2 worms and *hif-1* deletion mutants (Worm Base id: WB Gene 000001851).

The motor activity of worms was assessed by quantitating the distance travelled, the numbers of turns during movement of the worm and the total displacement. To measure associative memory, sodium chloride was paired with starvation and the change in response to sodium chloride was quantitated as response index. Hypoxia altered both motor behaviour and associative memory. Lithium treatment restored associative memory in wild type but not in *hif-1* mutants suggesting that HIF-1 regulation by lithium was one of the major pathways of lithium action under hypoxia. Transgenic worms carrying pHJ06 reporter gene containing 2.7kb of *hif-1* 5'regulatory sequence and the entire *hif-1* coding region fused to GFP were used to confirm that lithium upregulated HIF-1 expression.

Oxidative quality control regulates response to ER stress through translation control

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The Unfolded protein response is a signalling network that is triggered by the accumulation of misfolded proteins within the ER lumen, a condition termed as ER stress. Importantly, with progressing age, the ability of an organism to mount an effective response to ER stress declines significantly (Taylor and Dillin, 2013), the reason if resolved completely could have tremendous implications in aging research. In a comprehensive genetic screen to identify modulators of reductive stress-induced UPRER in *S. cerevisiae,* we found that oxidative quality control (OQC) genes modulate the cellular response to chronic reductive stress. Further studies in *Caenorhabditis elegans* revealed that ROS accumulation through pharmacological or genetic interventions results in non-canonical translation attenuation, blocking UPRER. Interestingly we find ROS accrual to be a potent reason for age related decline in UPRER. We also show evidence that, ironically, the evolution of Perk-dependent translation attenuation system allows higher eukaryotes to bypass ROS-dependent non-canonical mode of translation attenuation by decreasing protein load in the ER.

Techniques to measure and exert forces in micro Newton range, applied to *C. elegans*

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Measurement of locomotive forces applied by *Caenorhabditis elegans (C. elegans)* and application of external mechanical forces to *C. elegans* can provide insight into the effect of mechanosensory and muscle mutations on the organism behavior as well as biomechanics of undulatory crawling motion.

To measure the forces we developed an innovative technique that eliminates the common drawbacks of micro-machined force sensing tools like highly complicated, fragile construction and low throughput. We fabricated colored Polydimethyl Siloxane (PDMS) micropillar array. The color of the micropillars enhances the contrast facilitating the detection of pillar tip deflection as the organism crawls between the pillars. We also developed a semi-automated graphical user interface to analyze images for pillar deflections that reduced the data processing time per animal to minutes. The forces were measured while the animals were moving on an agarose pad. The wild type *C. elegans* exerts an average force of ~1 μN on individual pillar and a total average force of ~7.68 μN. The middle of *C. elegans* exerts more forces than its extremities. We also observed that the *C. elegans* mutants with defective body wall muscles apply significantly lower forces while those defective in sensing external mechanical forces apply the same average force per pillar compared to the wild type animals. The conventional mechanosensory assay for *C. elegans* is accomplished using an eyelash hair to exert force on the animal body. We observed that the manual application of such forces using an eyelash can produce forces ranging from below 5 μN up to 200 μN. Thus we introduce a new approach to exert localized mechanical forces on *C. elegans* body in a reproducible and non-contact manner. We designed a system to generate an air microjet with diameter restricted to ~800 μm. The microjet can exert total force up to ~ 84 μN on a flat surface from distances as long as 6 mm. The long working distance simplifies the operation and non-contact approach eliminates mechanical damage to the animal body and reduces contamination risks. We observed that the response of wild type *C. elegans* to the air jet was similar to that observed when the animal is touched manually by an eyelash. This demonstrated the applicability of the technique for the *C. elegans* mechanosensory assay.

A Large-scale high-throughput microfluidic screening platform for drug discovery using *C. elegans* disease models

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High-throughput studies such as drug screening using *C. elegans* would require technological advancements for high-resolution imaging at high enough speed. To enable both high-speed and high-resolution imaging of *C. elegans* nervous systems, we developed an automated microfluidic imaging platform. The platform includes a large-scale microfluidic chip with 96 wells designed in standard microtiter plate format and densely packed trapping channels in each well. The channels are uniquely designed to immobilize approximately 4,000 animals simultaneously in 3 minutes. The automated imaging platform takes 15 z-stack images of all trapped animals, capturing their whole volume in less than 16 minutes with a resolution of a micron. A fully-automated image analysis algorithm can analyze a whole 96-well chip with a polyglutamine (polyQ) induced protein aggregation model within 15 minutes. Using this platform, we achieved a large screening window with Z'-factor of 0.8 for this model. In assay validation experiments, we tested the protective nature of small molecule regulators in polyQ induced degeneration model in *C. elegans*. Geldanamycin, a benzoquinone specifically binds and inhibits molecular chaperon Hsp90, showed strong dose dependence and high efficacy against the aggregate formation in this animal model. The platform provides a leap forward for high-throughput screening of *C. elegans* disease models with subtle phenotypes at the cellular or sub-cellular levels.

Functional restoration after neuronal injury

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Neuronal injury often leads to devastating consequences such as loss of senses or locomotion. Restoration of function after injury relies on the fact whether the injured axon can find their target cells. Fusion between the injured proximal axon and the distal fragment has been observed in many organisms. It is proposed that axon fusion would likely to result in functional repair. However a quantitative behavioral data is not available to conclude whether the fusion indeed restores the lost function back or not. Here using *C. elegans* mechanosensory neurons and two-photon lasers we address this question. Using two femtosecond lasers simultaneously we show that axotomy of posterior touch neurons on both sides of a worm leads to a dramatic loss of posterior touch sensation. During the regenerative phase, only the axons those get fused to their distal counterparts contribute to the functional recovery. Our data reveal a functional property of regenerating neuron following injury.

Regulation of axon regeneration by axotomy-induced serotonin signaling

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The study of the molecular mechanisms of axon regeneration is driven not only by the scientific thirst for knowledge but also by the hope of developing therapies for currently untreatable axon injuries such as spinal cord injury. Numerous recent studies have demonstrated that the central role of MAPK signaling cascades in regulation of axon regeneration has been conserved from *C. elegans* to mammals. Here we briefly summarize several recently discovered pathways regulating MAPK signaling, and then focus on the role of serotonin in axon regeneration. We found that serotonin is ectopically synthesized in severed neurons and signals through the SER-7 receptor to upregulate diacylglycerol and cAMP, which ultimately converge to activate the MAPK pathway and promote axon regeneration.

UNC-16/JIP3 inhibits the function of regenerating promoting isoform of DLK-1

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Neurons in the adult nervous system have a limited ability to regenerate after injury. The extent of neuronal regeneration after injury depends on the intrinsic growth potential of neurons and their extracellular environment, both influenced by several genes. We show that UNC-16/JIP3 plays an inhibitory role during the early stages of neuronal regeneration after axotomy in *Caenorhabditis elegans*. UNC-16, a *C. elegans* JIP3 (JNK Interacting Protein 3) homologue, is a scaffolding protein for MAP kinases and binds to the Kinesin-1 and Dynein motors. JIPs are a family of classical scaffolding molecules and they are known to be able to switch their roles from growth promoting to inhibitory based on their levels and times of activation or deactivation. We also show UNC-16's inhibitory role is independent of JNK-1, Kinesin-1 and Dynein but is dependent on Dual Leucine Zipper Kinase-1 (DLK-1). DLK-1 is an essential MAPKKK for neuronal regeneration and has been reported to interact with JIP3. DLK-1 has two isomers, long and short, of these, DLK-1 long promotes regeneration while DLK-1 short inhibits regeneration. We show that UNC-16 inhibits the regeneration promoting activity of DLK-1 long but does not influence the activity of DLK-1 short. We suggest a model where UNC-16 may hold DLK-1 long in a complex and restrict the availability of active DLK-1 long and thereby inhibit regeneration. The dual inhibitory control by both UNC-16 and DLK-1 short can calibrate the intrinsic growth promoting function of DLK-1 long in vivo. We thus show that JIP3 could play its inhibitory role to allow tight temporal and spatial control of DLK-1 function.

A decade-long obsession with *puf-8* and germ cell decisions

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RNA-binding proteins of the PUF family are conserved regulators of stem cell proliferation in diverse species. PUF proteins primarily function as translational regulators that control translation through direct 3' UTR binding. Thousands of potential targets have been identified in multiple species, but the actual regulation by PUF proteins have been demonstrated only for a small fraction of the potential targets.

The *C. elegans* protein PUF-8 – the most conserved among the *C. elegans* PUF proteins – regulates a number of decision points in the germline including the mitosis-meiosis and sperm-oocyte decisions. We exploited the temperature-sensitive nature of the *puf-8* null alleles and performed a genetic screen for synthetic-sterile mutations. In this screen, we isolated mutant alleles for a number of genes whose functional importance have not been known earlier. Phenotypic characterization of these synthetic mutations reveals that *puf-8* controls at least three different known signaling cascades to regulate the mitosis- meiosis decision-making. First, we find that PUF-8 promotes the GLP-1 Notch signaling, which is crucial for the maintenance of germline stem cells, via the ER protein FARL-11. In the absence of PUF-8, FARL-11 expression is reduced, which in turn disrupts the membrane localization of GLP-1 due to ER dysfunction. Like in *glp-1(-)* germlines, cells in *farl-11(-)* germlines prematurely enter meiosis and, as a consequence, the germline stem cells are eventually lost. Second, PUF-8 controls the expression of proteins involved in the mitochondrial fusion-fission cycle; misexpression of these mitochondrial proteins activate germline apoptosis and impairs oocyte development. Furthermore, in the absence of PUF-8, the somatic transcription factor PAL-1 is upregulated, which in turn activates the expression of the pro-apoptotic protein CED-3 in the germline. Third, PUF-8 negatively regulates RAS / MAPK signaling by suppressing the expression of LET-60 RAS in the transitioning germ cells. Higher levels of activated MPK-1 ERK are found through the germlines missing PUF-8 and the GTPase-activating protein GAP-3, a known negative regulator of RAS. As a consequence, germ cells in these germlines fail to undergo the mitotic-to-meiotic switch. Due to the uncontrolled mitotic proliferation, these germlines develop germ cell tumors.

In summary, PUF-8 activates the translation of *farl-11* mRNA and inhibits the translation of *pal-1* and a few other mRNAs that encode proteins involved in mitochondrial dynamics to promote mitosis. On the other hand, it inhibits the *let-60* mRNA to promote the mitosis-to-meiosis fate switch. How do the meiosis-promoting signals overcome the mitosis-promoting signals in the transitioning cells? We think the spatial regulation of PUF-8 levels in the germline and its coordination with the other known players in this process, especially the GLP-1 / Notch signaling from the GSC niche, hold the key to answer this question.

PUF-8 facilitates synaptonemal complex formation by promoting the perinuclear localization of dynein

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Haploid gametes are formed from diploid cells through a special type of cell division called meiosis. Unlike mitosis, meiosis first separates the homologous chromosomes into two daughters. This is achieved by the pairing of homologous chromosomes, stabilization of the pairing by synaptonemal complex proteins and crossovers. Here, we present evidence that the conserved RNA-binding protein PUF-8 promotes dynein localization to the nuclear periphery, which is essential for the processive chromosome motions that enable homologous chromosomes to and pair.

In a genetic screen for enhancers of the *puf-8* mutant phenotypes, we have isolated a new mutant allele called *kp23*. Staining of *puf-8*; *kp23* germlines with the DNA-binding dye DAPI revealed morphological abnormalities of meiotic chromosomes. The localization patterns of ZIM proteins – zinc-finger proteins that concentrate at special regions of specific chromosomes called pairing centers – showed that the homologous chromosomes failed to pair in these germlines. Additionally, SYP-1, a component of the central element of the synaptonemal complex, did not spread along the length of the chromosomes; instead it formed aggregates at specific foci. Furthermore, the dynein heavy chain DHC-1, which concentrates around the nucleus prior to the pairing event in the wild-type, did not do so in the *puf-8*; *kp23* worms. Consistently, chromosome movements mediated by the dynein at the nuclear periphery were decreased in these worms. In summary, results presented here show that PUF-8 enables the homologous chromosomes to pair by promoting the perinuclear concentration of dynein.

The Role of the CREB-1 homolog, CRH-1, in associative learning in *Caenorhabditis elegans*

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Memory formation is crucial for the survival of animals. The process of memory formation is largely conserved across animal species at the cellular and molecular level. One such conserved molecule is CREB-1, a transcription factor that can be activated in the neurons in an activity-dependent manner (Silva et al., 1998).

In order to study aspects of learning and memory formation, we have developed three new olfaction based assays to test LTM formation in *C. elegans*. Using these assays we have gone on to find LTM defects in the *crh-1* mutant gene, which codes for the *C. elegans* homolog of the mammalian creb-1 gene. Our experiments show that of the six CRH-1 isoforms in *C. elegans*, one specific isoform of CRH-1, CRH-1e, can largely rescue all the associated learning and memory defects in the mutant animals. Further, by temporally regulating the expression of the CRH-1 transcription factor using a heat shock promoter we demonstrate that CRH-1 is required for memory formation/consolidation and not the retrieval of memory in our learning and memory paradigms.

Transcriptome profiling of *Caenorhabditis elegans* and *Drosophila melanogaster* exposed to Methyl parathion: insights to organismal susceptibility/tolerance

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The environment provides critical support for life, offering optimal ecological niches, to more than 1.7 million of the world's species. The global trend of industrialization, urbanization and tremendous anthropogenic activities resulted in the contamination of habitats with various synthetic chemicals to alarming levels that can potentially threaten the organismal survival across ecological taxa. In this context, it is essential to assess the ecotoxicity potential of synthetic chemicals. Such an assessment in one particular species, however, fails to reflect the adversities on other organisms in the ecosystem because organisms vary in their responses to environmental chemicals because of variability in their genes and their genes' epigenetic modification. To address this complex issue, USEPA has recommended toxicity evaluation in variety of model organisms representing different ecological strata. Accordingly, in the present study, we exposed two model organisms, *Caenorhabditis elegans* and *Drosophila melanogaster*, to a synthetic chemical and evaluated their response at the transcriptome level, to gain insights to molecular players/pathways underlying organismal tolerance/susceptibility to xenobiotics.

Initially, determination of LC50 (concentration at which 50% of population is dead), in both model organisms for 48hrs of exposure to Methyl Parathion (MP) revealed higher (~90 fold) tolerance of *C. elegans* (275µM) in comparison to *D. melanogaster* (3.12µM). Subsequently, global gene expression changes were evaluated through microarray after 24 and 48h exposure to 1/10th and 1/100th of the respective LC50 concentrations. Overall, 2358 genes (of 22,625 genes screened) were significantly mis-regulated in *C. elegans* with a cut-off of 1.5 fold change in comparison to solvent control and at a FDR(False Discovery Rate) corrected P value <0.05. The extent of mis-regulation of genes was dose as well as time-dependent. Further, the ontology clustering (through DAVID's functional annotation tool) of mis-regulated genes revealed that 60% of them are associated with cellular components while the remaining 40% represented biological processes, suggesting the adverse effects of MP on cellular integrity and basic biological processes of exposed worms.

Further, to understand the role of genetic makeup in organismal tolerance/susceptibility we compared the *C. elegans* transcriptome profiles with those of D. melanogaster. Interestingly, predicted biological processes (such as stress, metabolism, respiratory process, reproductive process and development) were similar between *C. elegans* and *D. melanogaster* exposed to MP. Bioinformatic analysis suggested 20-25% homology among genes mis-regulated in *C. elegans* and *D. melanogaster* exposed to MP. These findings provide base-line data with which the complexity underlying the organismal response to chemical exposure can be deciphered. In addition, these findings reflect the potential of *C. elegans* and *D. melanogaster* as models to address complex issues of toxicology.

Ayurvedic nootropics for enhanced cognition and protection from neurodegenerative diseases

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Optimal development and function of nervous system is vital for quality of life. Enhanced cognition and memory, adequate sensory-motor activities and absence of disease are the indications of healthy nervous system.

Advancements in the scientific research have led to a very good understanding of nervous system structure, function and physiology at cellular and molecular level. However, scientifically studied, effective healthcare solutions for cognition enhancement and management of neurodegenerative disease like Alzheimer's and Parkinson's are largely lacking. Thus, we need to look at novel prevention and treatment strategies. Unlike conventional bio-medicine, Ayurveda has a holistic understanding of the function of the nervous system including cognition. It offers various nootropic herbs called "Medhyarasayana" as a part of therapy specially focused on nervous system function. Some of the Medhyarasayana herbs are *Bacopamonnieri* (Brahmi), *Convolvulus pleuricaulis* (Shankhapushpi) and *Centellaasiatica* (Mandookaparni). These herbs are prescribed not only as neurotonics for enhanced cognition and memory, but also as a part of treatment of neurological disorders including Alzheimer's and Parkinson's disease. However, scientific evidence justifying the efficacy of the herbs and the underlying mechanism of action is largely lacking.

We have used *Caenorhabditis elegans* model system for studying effect and mode of action of Ayurvedic nootropics on learning-memory and neurodegeneration. Our data suggests that multiple dosage forms of Brahmi namely juice, lipid extract and alcoholic extract can protect the worms from developing the disease phenotypes like Abeta induced paralysis and MPP+ iodide induced degeneration of dopaminergic neurons. Brahmi juice also enhanced short term memory in wild type worms.

The results from such research will provide scientific evidence for use of Medhyarasayana in managing various clinical conditions as well as for promotion of nervous system health. Further, it would also offer leads to novel nootropic products to fulfill contemporary health needs.

Experimental tryst with *C. elegans*: a triumphant model in pesticide toxicology and toxicity amelioration

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Pesticides are chemicals, which are inevitable and ubiquitous. They exert adverse effects on both target and non-target organisms. Since long, understanding their modes of action as well as quantifying exposure concentration and duration, has been intriguing toxicologists and environmental health scientists. Exposure to most of them results in adverse effects, especially on the nervous system. The nematode *Caenorhabditis elegans* is a model organism, which is gaining popularity for studying various aspects of toxicity, since the organism facilitates measurements of various physiological, biochemical and molecular endpoints with ease. Studies from our laboratory over the past decade have established its robustness as a model to elucidate the mechanism of toxicity of various classes of pesticides. Comprehensive studies have been conducted to understand the toxicity of organophosphorus, synthetic pyrethroid insecticides and the fumigant, phosphine. Besides, the worm has facilitated studies on toxicity amelioration employing bioactive compounds. Wild-type worms, as well as various transgenic and mutant strains of *C. elegans*, were used to obtain insights employing various physiological/ behavioural, biochemical and morphological endpoints to assess the impact of the pesticides under various exposure conditions. Our studies have clearly demonstrated that *C. elegans* can serve as a functional model in appraising the effects of pesticides at sublethal level, thereby promoting our understanding of the mechanisms underlying toxicity induced by these chemicals, which will also immensely aid in developing strategies to combat pesticide-induced illnesses.

Elucidating the organismal level end points of neurotoxicity of dichlorvos on nontarget model nematode *Caenorhabditis elegans* and validation of 2-PAM and Atropine therapy

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The nematode *Caenorhabditis elegans* has been a valuable model system to investigate specific functions and regulations in vivo of compounds of interest. Due to its short life span, ease of rearing in the laboratory on agar medium and facilitates detection of organism -level endpoints (feeding, reproduction, life span, and locomotion), multiple targets (Enzymes, heat shock proteins, ageing marker and detoxification mechanisms etc.) and changes at behavioral level. Organophosphorous insecticides (OPI) are one of the most widely used classes of insecticides in the world, are irreversible inhibitors of acetylcholinesterase (AChE), an enzyme that is characteristic of the neuromuscular junctions responsible for the hydrolysis of the neurotransmitter acetylcholine and biomarker of exposure, suggesting increase in the cholinergic transmission and consequent accumulation of acetylcholine in the synapses and neuromuscular junctions leads to over stimulation of cholinergic receptors that result in a general pattern of nerve poisoning, hyper excitability, tremors, paralysis and causes neurotoxic effects. In mammals, death is caused by asphyxiation, but the action in aquatic organisms including fishes and invertebrates is less clear. Hence study was designed to understand the organismal effect on exposure to OPI at sub lethal doses and doses where residual effects are undetected on lifelong exposure conditions. The assays performed on exposure were Lethality (LC50), Feeding, Pharyngeal Pumping, Acetylcholinesterase activity, Acetylcholine accumulation, Nose contraction, paralysis, egg laying response, Heat Shock Protein, dopamine levels and changes at fatty acids and Ageing marker Lipofuscein as endpoints and compared the kinetics of Acetylecholinesterase of rat brain and *C. elegans* homogenate system. At sub-lethal concentration exposure resulted in cessation in feeding (72%), shutting of pharyngeal pumping, inhibition of egg laying (34-55%), contraction of nose (45%) and significant paralysis (50%) after 4h of exposure and induced a concentration and time dependent AChE inhibition, accumulation of acetylcholine, expression of heat shock proteins, decreased brood size. Comparison of inhibition pattern of acetylcholinesterase in-vitro kinetic parameters revealed *C. elegans* homogenate system IC-50 is more sensitive to inhibitor dichlorvos and was irreversible in nature. Decrease in body length ranged from 50 - 67%, significant differences in fatty acid composition, the dopamine content measured after 72 h of exposure (from egg stage) showed a 97% increase in dichlorvos treated worms. Remarkable concentration and age dependent increase in lipofuscin accumulation was observed on exposure to dichlorvos and control worms was restricted to intestine only. The therapy for the poisoning by dichlorvos is administration of 2-PAM and Atropine AS antidotal therapy hence we tested these drugs on exposure to dichlorovs and our results clearly demonstrated that the atropine alone did not induce any paralysis. Atropine at 10 and 15mM completely relieved the paralysis induced by dichlorvos and worms exposed to 2-PAM at 1 and 10 mM after exposure to dichlorvos alone revealed concentration dependent marked reversal in feeding. Similarly, maximum reversal in feeding was also evident in worms exposed to 10mM PAM and 5 and 10mM atropine.

Investigating the Role of Amphid neurons of *Caenorhabditis elegans* in regulating the immune response against Gram positive and Gram negative bacteria

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The survival of an organism depends on its ability to sense potential threats and develop defense mechanisms to fight against infections. Both anecdotal evidence and published studies indicate that the immune response is influenced by alterations in the state and function of the nervous system. However, the mechanism of regulation of immunity by direct sensing of environmental cues by the nervous system is not known. Using a simple host-pathogen system, *Caenorhabditis elegans-Enterococcus faecalis/Pseudomonas aeruginosa*, we want to understand how sensory perception of environmental cues by the nervous system regulates the susceptibility to an infection. *Enterococcus faecalis* is a Gram-positive bacterium commonly found in the gastrointestinal tracts of humans. It is known to cause life-threatening infections, especially it is the major cause of hospital acquired infections. *Pseudomonas aeruginosa* is a Gram-negative, rod-shaped bacterium commonly found in the environment. It is a potent human opportunist pathogen infecting those with compromised immunity. To understand if the amphid sensory organ of *C. elegans* plays a role in sensing of *E. faecalis* or *P. aeruginosa*, we have created amphid neurons ablation lines and testing them for survival on these bacteria. Preliminary experiments suggest that the sensing and survival on these microbes is regulated by distinct amphid sensory neurons.

Effect of Fipronil on Physiology of *Caenorhabditis elegans*

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Fipronil is a highly effective, broad-spectrum insecticide, belonging to the phenyl pyrazole or fiprole group of chemicals. It is a potent disrupter of the insect central nervous system. Fipronil is widely used for the control of various crops and veterinary insects. Uses of fipronil in many insect control products may also affect the non-target organisms either by a direct contact or through runoff and leaching. Thus, there is a need to understand theecotoxic potential of fipronil.

In the present study, we employed *Caenorhabditis elegans* as a model organism to understand the ecotoxic potential of fipronil. The ecotoxic endpoints such as growth, reproduction, behavior and feeding potential of worms were analyzed. The concentration of fipronil, for the above study was decided, based on reactive oxygen species generated (ROS) in exposed worms, to a range of fipronil concentration (0.5µM - 50µM). Our results indicate dose dependent significant adverse effect on all the parameters tested. This indicates that fipronil show eco-toxic potentials and needs appropriate regulation.

The Immunoglobulin Superfamily protein RIG-3 is required for normal exploratory behavior in *Caenorhabditis elegans*

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Cell surface Immunoglobulin superfamily proteins (IgSF) play important roles in the development & function of nervous systems. Here, we describe the role of RIG-3 (an IgSF protein) in interneurons of *Caenorhabditis elegans*. Mutants in *rig-3* show an increase in their spontaneous reversal frequency when compared with wild type control animals. We go on to show that this increase in reversal frequency is caused by increase in glutamatergic signalling. As reversal frequency is dependent on the extent of glutamatergic signalling. The mutants with decreased signalling, such as *glr-1*, have decreased reversal frequency and those have increased glutamatergic signalling show increased reversal frequency. These results suggest that RIG-3 is a key regulator of glutamatergic signalling in interneurons. We propose that RIG-3 may control this signalling by maintaining normal GLR-1 receptor levels.

In search for novel regulators of synaptic vesicles

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Neurons are polarised cells and need transport of cargo from the cell body where cargos are made to synapses. Synaptic vesicles (SV) are a major cargo that is transported. SV can be formed at the synapse but, little is known about how the precursors of these vesicles (pre-SVs) are formed in the cell body. Several proteins present on these precursors are trafficked through the Golgi complex. One critical step that enables these vesicles to leave the cell body is their ability to recruit a specific microtubule dependent anterograde motor, UNC-104/Kinesin-3. Mutations in *unc-104* lead to accumulation of SV proteins in the cell body (Hall and Hedgecock, 1991), demonstrating that this step is a critical bottleneck in how this cargo reaches the synapse. Thus genetic modifiers of *unc-104* provide us with means to identify multiple steps that allow SV proteins to exit the cell body in a motor-dependent manner. Genetic modifiers of *unc-104* were isolated from two independent genetic screens performed on two different alleles of *unc-104*. Genetic suppression utilised *unc-104*(e1265) which is a strong hypomorphic allele with severe cargo binding defects (Hall and Hedgecock, 1991; Kumar et al., 2010). Using an intragenic suppressor *unc-104*(e1265tb120) with less severe cargo binding defects, we isolated several enhancers that could identify motor dependent steps in SV protein trafficking in the cell body. From this screen, five enhancers were isolated. Each enhancer has defects in distribution of pre-SVs either in the cell body, process and/or at the synapse. Here, we are presenting preliminary characterization and genetic interaction of enhancer with other molecules known to affect transport of pre-SVs.

AWC-mediated behavioral studies of *crt-1* and *cnx-1* in *Caenorhabditis elegans*

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C. elegans is a free-living soil nematode which is able to sense different chemical cues using their chemosensory olfactory neurons. Calreticulin and calnexin are Ca^{2+} binding and molecular chaperones residing in endoplasmic reticulum (ER). These proteins play a role in Ca2+ homeostasis and e the proper folding of newly synthesized proteins in the lumen of ER. Calreticulin (*crt-1*) and calnexin (*cnx-1*) are expressed in several tissues including head neurons. To study chemosensory behavior of *C. elegans*, we used null mutants of *crt-1* and *cnx-1*. *crt-1*(JH101) and *cnx-1*(NR2009) do strong chemotaxis as wild type for AWC sensed odorants, isoamyl alcohol, benzaldehyde and butanone. Prolonged odorant exposure diminished the sensitivity of attraction towards the adapting odorant, the process known as adaptation. In our investigation, 90 mins of odorant specific adaptation in wild type diminished their attraction towards the adapting odorant; *crt-1*(JH101) animals hyper-adapt whereas *cnx-1*(NR2009) failed to adapt. These results indicate that CRT-1 and CNX-1 may be involved in adaptation of AWC-mediated chemosensation. We investigated the dual role of calcium and the underlying mechanism by drug treatment and genetic epistasis.

***Lactobacillus salivarius*: health benefit evaluation in *Caenorhabditis elegans* model system**

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Probiotics are defined as bacteria with physiological benefits for humans. They provide functions that are of importance to health and well-being and contribute in a number of ways toward the functional improvement of food. Lactic acid bacteria (LAB) are renowned for its probiotics potentials has been clinically accepted and recommended for consumption as dietary supplements for its antioxidants efficacy, antimicrobial and influence on longevity. *Lactobacillus salivarius* is one of the many strains of probiotic bacteria that play an important role in human health. *Lactobacillus salivarius* has been often isolated from the mammalian digestive tract and has been studied as a candidate probiotic. Several studies have described the immunomodulatory properties of *Lactobacillus salivarius* in cell-lines, animal models and humans for the alleviation of intestinal disease and the promotion of host well-being. In the present study, we employed the nematode *Caenorhabditis elegans* (N2-wild type) as a eukaryotic model to establish the health benefits of *Lactobacillus salivarius. Lactobacillus salivarius* (CH71e) were spread on NGM agar plate at various concentrations (5, 10 and 15mg). OP50 (E. coli, 15mg) was used as control feed bacteria. The synchronized larva of the worms at L3/L4 were exposed to OP50 and *L. salivarius* at various concentrations and incubated for 24h. Later the worms were observed for various physiological parameters, lifespan and lipid staining. Lifespan of worms fed *L. salivarius* (5, 10 and 15mg/25µl) was enhanced (30, 31 and 32d) while OP50 fed worms survived till 26d. Pharyngeal pumping rate determined in worms by counting of the movement of pharynx terminal bulb showed slight decrease in intake of *L. salivarius*: 57±062; 54±0.7 and 51±1.2 v/s 64±0.9 of OP50. Feeding or food clearance assay performed by measuring bacterial OD at 550nm suggested that *L. salivarius* was taken up by the worm similar to that as OP50. A marginal decrease in body size was evident in worms exposed for 24h to *L. salivarius* at 15mg (0.72±0.01mm) compared to OP50 fed worms (0.8±0.01mm). The lipid deposit in worm was also monitored by staining method and it was observed that the worms fed *L. salivarius* did not have enhanced fat levels. In conclusion, our data suggests that a proper dietary intake of probiotic bacteria (LAB) has no adverse effects but provides various health benefits to host organism by enhancing lifespan and *C. elegans* appears to be a suitable model for screening useful probiotic strains.

Plant extracts: Modulators of *C. elegans* memory?

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Memory lays an important role in the survival of complex organisms. It enables learning from experiences of the past. Failure of memory as age advances is a matter of record in a number of situations which has consequences for the survival of the organisms. The Indian traditional medicines since years employed many plants as cognitive enhancers such as *Bacopamonnier, Centellaasiatica, Evolvulusalsinoides* etc. These plants are known to promote healthy ageing by decreasing the rate of decline in cognitive activity of brains. The effect of one of these plant extracts on the short and long term memory of the *C. elegans* is tested and the results are discussed.

Role of olfactory neurons in *Pseudomonas aeruginosa* (pathogen) avoidance in *C. elegans*

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Caenorhabditis elegans in its ecological niche survives by the ability to differentiate food from pathogenic bacteria, thus feeding on food sources and avoiding pathogens. This sense of segregation is probably brought about by various sensory neurons of the worm which are mostly confined to the head region (amphid neurons). The amphid sensory neurons (12 pairs) include chemosensory, olfactory and thermosensory neurons. These neurons might detect and identify bacterial cues leading to attraction towards food and avoidance towards pathogen. Using *C. elegans* as the host and a Gram negative bacteria *Pseudomonas aeruginosa* as the pathogen, host pathogen interaction can be studied. Worms although initially, attracted to *P. aeruginosa* learn to avoid it on second exposure when given a choice between food vs the pathogen. When grown monoaxenically on the pathogen, after an initial phase of attraction, the worms begin to move out of the pathogen lawn. This lawn leaving behaviour is likely a result of integration of multiple sensory cues. Very little is known about the role of olfactory neurons leading to lawn leaving behaviour. We are interested in understanding the role of three pairs of olfactory neurons (AWA, AWB and AWC) in detection of the pathogen leading to avoidance behaviour. We have found that both AWB and AWC neurons regulate avoidance response. Screening of *P.aeruginosa* mutant library is underway to identify the pathogen molecules which are recognized by *C. elegans* olfactory neurons.

Dynamic mode chemotactic assays for *C. elegans*

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Chemotactic assays of *C. elegans* have always been measured in a static mode where the spatial location of the attractant or repellent is static and the worms move towards the source over time. One of the drawbacks of such measurements is the relatively long measurement time of the order of several hours. Further, in most cases chemotactic assays are quantified by a chemotactic index which only provides information about the final state in terms of fractional occupancy of the source relative to control location. Information about temporal response and the search behaviour is not accessible with such a mode of measurement. We are working towards a "dynamic mode" measurement of chemotactic behaviour by measuring the response of individual worms to a moving attractant or repellent source. The path taken by the worm in response relative to the path provided as input should help us quantify parameters such as degree of attraction/repulsion, temporal response characteristics and most importantly a significantly higher throughput compared to the static mode measurements because measurement over a single worm could be carried over a few minutes instead of hours as is done currently. Combining such measurements over multiple individuals can give as robust statistics of the population response. For instance, it can provide us information on the amount of time it takes to sense the change in position of the attractant, the sampling time of the worms with which they sense their environment, the distance from the attractant at which it effectively senses the presence of the attractant and so on. Preliminary experiments involving 1:100 diacetyl :water has been done where the diacetyl concentration at the source is maintained constant through capillary effect from a reservoir. Using an unsynchronised population of worms, we observed tracking of the moving target by the worms. It has also been observed that some worms sense the spatial changes better than the rest. The reason for this is yet to be investigated using single worm resolved measurements. Current efforts are directed towards optimizing the experimental setup to allow measurements from multiple worms, one at a time, and to reduce the spatial dimensions of the probe area using microfabricated, computer controlled, movable reservoirs of attractants or repellents.

Role of soluble guanylyl cyclases against oxidative stress in *Caenorhabditis elegans*

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Oxidative stress reflects a disturbed redox state of an organism. This disturbance can result from production of high amount of reactive oxygen species or defective detoxification system. It can be caused by biotic or abiotic stresses. High levels of ROS inside cells can damage proteins, lipids and DNA. Oxidative stress is suspected to be important in aging, pathogenesis as well as manifestation of many neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and Huntington's disease. Therefore, it is important to understand mechanisms which protect cells from oxidative stress. Guanylyl cyclases (GCY) are the proteins which catalyzes conversion of GTP to cGMP. cGMP is an important secondary messenger in the cell. GCY family is diverse in *C. elegans* consisting of 34 GCYs, 27 receptor and 7 soluble receptors. Majority of these GCYs are expressed in nervous system of the worm. In *C. elegans* some of the GCYs havebeen shown to play an important role in salt sensing, thermal regulation and lifespan. Since lifespan is intricately linked to ability to deal with oxidative stress, we set out to understand if soluble guanylyl cyclases are required for redox homeostasis in *C. elegans* and its ability to deal with oxidative stress. Preliminary data from our screen for gcy mutants against oxidative stress shows involvement of soluble GCYs in oxidative stress response.

Study of microtubule dynamics during neuronal regeneration in *C. elegans*

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Neurons are highly polarized cells with two distinct compartments, axons and dendrites. Formation of the polarized structure in neurons is governed by the stabilization of microtubule (MT) cytoskeleton. Stability of MT cytoskeleton is also a limiting factor in the initiation of axon regrowth after injury. Previous work from our lab suggested that MT dynamics is locally regulated near the site of injury in *C. elegans* mechanosonsory neurons. However, detailed understanding of the mechanism involved in remodeling of MT cytoskeleton in mature neuron during regeneration is lacking. How new MTs form after injury and how their polarity is established in regenerating axon are questions of high interest.

The questions stated above remain only partially solved till date due to the technical challenges of imaging neuronal MTs in whole animal model. Recently, microfluidic technology has been applied to the whole-organism study. We have also developed a microfluidic device in which worms can be immobilized using regulated pressure in order to visualize neurons in vivo. By using either femtosecond laser in a 2-photon microscope or a nanosecond pulsed UV laser, we are severing the axonal projections and then looking at the regulation of MT cytoskeleton. We are using the reporters of plus and minus ends of microtubules in order to visualize the changes in the microtubule dynamics after axotomy. We observe a differential response in microtubule dynamics when axotomy is performed near the cell body as opposed to when it is done far away from the cell body. By combining the genetics and live imaging, we are in the process of deciphering the basis for this phenomenon. We will present a comprehensive analysis of the development of the microfluidic device and the study of microtubule dynamics using these devices.

Investigating mechanisms of transport of synaptic vesicle precursors in the PLM neuron of *C. elegans*

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In neurons, transport of synaptic vesicles precursors (pre-SVs) to the synapse is critical for synapse maturation and neuronal function (Yonekawa et. al., 1998). Across vertebrate and invertebrate systems, it is observed that neurons exhibit complex cellular morphologies by extending processes that form branches. Since pre-SVs need to traverse such complex morphologies to reach the synapse to function, a question that arises is whether the transport is regulated or random. In order to study the distribution and motion dynamics of pre-SVs, we have used the Posterior Lateral Microtubule (PLM) cell of the model organism *C. elegans* that contains a branched neuronal process (White et. al., 1986). Using live imaging, we are investigating the possible role of UNC-104/KIF1A, the primary motor responsible for anterograde transport of pre-SVs (Hedgecock and Hall, 1991, Otsuka et. al., 1991) and associated regulatory proteins in mediating transport of pre-SVs.

Collective behavior in wild type *C. elegans*

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Animals live in a dynamic complex environment. The change in their environment affects the individual behaviors and sometimes new functionalities emerge at a population level due to the change in individual behaviors leading to some interactions among them. Collective behaviors have drawn much interest in the last years because it provides a model example of self-organization in the absence of centralized control. But the mechanism behind these collective phenomena is far from understood.

C. elegans do not normally come to our mind as a social animal but they do interact with each other in certain situations such as dauerformation, mating, population density sensing etc. The standard laboratory strain N2 is known as solitary [1] *C. elegans* in the context of their feeding on bacterial lawn as reported in earlier studies [1, 2]. We have observed some collective behaviors in the wild type young adult such as aggregation in a group in a disk shape and subsequently formation of a stripe under starved condition. It has also been seen that oxygen content [2] in their environment plays a role in their aggregation. As we changed the partial pressure of oxygen in the petri plate, they start to disperse. We also saw the clumping phenomenon of these nematodes in an eppendorf tube filled with a buffer medium and formation of a stripe with a change of oxygen tension in the tube. We then asked the question whether the direction of the stripe is arbitrary in the isotropic environment. Can we provide some bias to the direction of the stripe? We did some standard chemotaxis experiments and we found that the stripe is directed towards the attractant or in other words they align themselves in the direction of the attractant though it lasts for a short-time span. We are doing further investigation for how do worms interact with each other to form clumps? What's the nature of communications? It could be chemical or mechanical. At least we could say that the shape change from the disk to a stripe is an interplay between attractive and repulsive forces. Therefore, what are those attractive and repulsive forces? After understanding the behavioral aspects of this phenomenon, we would like to model these phenomena using multi-agent models.

Caenorhabditis elegans: A versatile model to study Photoaging

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Ultraviolet-A (315-400 nm) irradiated by Sun, cause damage to humans, predominantly in skin which is characterized by wrinkles, sun tan, sun burns and sometimes skin cancer. These changes probably lead to acceleration in aging of skin, which is termed as Photoaging. *Caenorhabditis elegans* could be used as one of the models in aging studies to decipher the molecular changes during UV-A exposure. This was achieved by analyzing the physiological changes through lifespan, pharyngeal pumping and brood size assays and molecular changes through Quantitative PCR. Moreover, transgene coupled with GFP was used for monitoring the level of expression of collagen gene after UV-A exposure. Furthermore, candidate regulatory pathway specific mutants were utilized to confirm the role of specific pathways (IIS and MAPK) during UV-A exposures.

The level of expression of collagen inside the *C. elegans* was found to be altered during UV-A exposure, which was recorded through CLSM analysis. Wild type *C. elegans* and *daf-2* mutants (of IIS pathway) showed reduction in lifespan when exposed to UV-A for 2, 4 and 6 h, continually. IIS pathway, which has a major role in determining the lifespan of the *C. elegans* was found to be negatively regulated during the course of UV-A exposure. Moreover, the normal cognitive functions including pharyngeal pumping and brood size, which interpret the healthspan of the nematode, were also reduced. The p38 MAPK pathway, which is the chief regulator of innate immunity of the *C. elegans* was also analyzed during UV-A exposure using the pathway specific mutants. The mutants (*sek-1* and *pmk-1*) showed a steady fall in lifespan after exposure which indicates that the innate immune system was also altered during exposure. Molecular evidences revealed that changes takes place in DAG (diacylglycerol) signaling pathway, which is essential for the normal healthspan and neuronal development of the nematode. These data revealed that *C. elegans* are susceptible to UV-A radiation and can be used as a model to study photoaging, which is a rising issue in the current scenario.

Therapies based on antioxidants have been routinely employed to UV mediated damages since it triggers oxidation reaction inside the cells, thereby cleaves Reactive Oxygen Species (ROS). Plant extracts isolated from Green tea which are rich in antioxidants have shown to delay photoaging in *C. elegans.* Synergistic action of flavanoids along with Green tea in different combinations showed much higher effect. These combinations which can destroy the ROS and also regulate the DAF-16 mediated IIS pathway, could be employed to treat UV-A mediated damages. Identification of the most suitable combination could pave way for drug discoveries against UV-A mediated damages which will be of high demand in the near future, since the depletion of ozone layer which helps the hazardous rays has an easy route to reach the Earth's crust.

Bis(2-ethylhexyl) phthalate induce larval stage specific reproductive and developmental defects in *C. elegans*

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Phthalate ester plasticizers are accounted for reproductive and developmental toxicity related disorders in higher animals. This group of endocrine disruptors displays high level of estrogenic potential that interrupts functioning of several steroid hormones, thereby increasing the incidence of several growth disorders. Toxic endpoint studies previously carried out using bis(2-ethylhexyl) phthalate (DEHP) in the nematode *C. elegans,* displayed several phenotypic and behavioral defects those linked to mortality, growth, reproduction, and altered gene(s) expression. In the present study we observe larval stage-based sensitivity of the organism in causing developmental arrest together with prolonged reproductive delay on exposure to sub-lethal doses of DEHP and at different temperature conditions, i.e. at 20^{o}C and 25^{o}C, respectively. While L4 stage worms experience interrupted reproductive development in presence of DEHP thus entering into a state of metabolic arrest, L3 larval stage worms were found to be less susceptible under similar conditions. Interestingly, L2 stage animals mimic the phenotype of dauer diapause to enter a stage of reproductive quiescence under similar conditions. Consistent with this observation and in the presence of DEHP, the amount of dafachronic acid (DA), a steroid hormone that is known to bind DAF12/NHR, is found to decrease concomitantly with increase in lophenol, a 4-methyl sterol that is known to promote dauer diapause in L2 stage animals. Corresponding gene expression studies involved in steroid hormone biosynthetic pathway further confirm transcript level modulation for candidates responsible for dauer diapause and larval stage-specific arrests. The present research is thus aimed at understanding the molecular mechanism of larval arrests and dauer diapause under DEHP exposed conditions at the designated temperatures in *C. elegans*. Furthermore it would be interesting to dissect the incidences of such phenotypes that probably could arise either as a consequence of phthalate esters that may perhaps mimic the pheromone signaling of amphid neurons in response to unfavorable signals at the level GPCRs or there may be a presence of negative feedback mechanism initiated from DAF-12/NHR leading to sensory neurons being unresponsive to the favorable pheromones necessary for initiation of normal development in the organism.

Proteomic investigation of *Caenorhabditis elegans* during *Shigellaflexneri* reveals drug targets for bacillary dysentery.

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The enteroinvasive bacterium *Shigellaflexneri* invades the intestinal epithelium of humans, causing an acute mucosal inflammation called shigellosis or bacillary dysentery that is responsible for 1.1 million deaths annually. Ease of high throughput screening, availability of genome and proteome datasets has made *Caenorhabditis elegans* as a preferred model system for drug discovery. *S. flexneri* has been shown to colonize and cause mortality in *C. elegans*. The present study aims to investigate the drug target(s) in model host *C. elegans* against *S. flexneri* infection through proteomic approach.

Survival rate of *C. elegans* WT adult worms exposed to *S. flexneri* were assessed by liquid killing assay. *E. coli* OP50 was used as the control food source. Physiological parameters such as pharyngeal pumping, egg laying and defecation were analyzed. For proteomic approach, 2D- gel electrophoresis followed by MALDI-MS-MS analysis was performed to identify the host regulated proteins during *S. flexneri* infection. DAVID analysis was used to categorize the biological functions of identified regulated proteins. STRING analysis was used to predict the interacting proteins for the identified regulatory protein. Validation of the predicted interacting proteins was confirmed through qPCR analysis, western blotting and “loss of function” mutant worms.

Survival assay showed complete mortality of the host within 48 h of *S. flexneri* infection. 2D- gel electrophoresis of *C. elegans* proteome revealed that 368 and 455 spots were regulated with a threshold of >1.5 fold during 12 and 24 h of *S. flexneri* infection, respectively. By using MALDI-MS-MS analysis, we identified 67 proteins among the differentially regulated spots. DAVID analysis revealed proteins which are important for signal transduction; proteasome activity, membrane trafficking and defecation process. These proteins were majorly enriched among the identified regulatory proteins. STRING analysis predicted that the identified regulatory proteins needed several interacting partners which are important for 26S proteasome degradation process and scaffolding activity inside the cell. Validation studies highlight the interaction among the predicted and identified proteins, which clearly depicts their involvement during S. flexneri infection in the host.

These results suggest that drug molecules that target(s) 26S proteasome and scaffolding proteins can be used against *S. flexneri* infection.

Towards understanding exploratory behavior in *C. elegans*

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Neurotransmitters and neuropeptides are signaling molecules used by neurons to communicate with each other. Both neurotransmitter and neuropeptides act as a neuromodulator in a wide range of neuronal functions and are known to modulate a large number of behaviors in *C. elegans*.

We are interested in understanding the neuromodulators that are involved in the exploratory behaviors of *C. elegans*. Exploratory behavior helps worm to locate food in its environment. During exploratory behavior, worm moves forward with occasional reversals and Omega-turns.

I will be presenting data indicating the role of neuromodulators required for normal reversal behavior in *C. elegans.* Our work will also shed some light on the signaling mechanism of the functioning of the neuromodulators involved in this behavior.

Identification and functional characterization of *pds-20*, a novel gene involved in germline development

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RNA-binding proteins of the PUF family are conserved regulators of germline development in diverse species. The *C. elegans* PUF protein PUF-8 functions at multiples stages of germ cell development including germline stem cell proliferation, mitosis-meiosis transition, sperm-oocyte switch and during the meiotic progression of spermatocytes. In a genetic screen designed to isolate alleles that enhance the *puf-8* mutant phenotype, our laboratory has earlier isolated mutant alleles in a number of genes. We have now mapped one such allele, *kp20* to a specific locus on chromosome II, which encodes a nematode-specific gene with no known function or ortholog in other organisms. We have named it tentatively as *pds-20* (*puf-8*-dependent sterile-20). Our RNAi analysis indicates that *kp20* is a reduction-of-function allele. Transgenic expression of PDS-20::GFP fusion using the pie-1 promoter and 3' UTR suggests that PDS-20 is predominately localized in the nucleus, although it could be detected in the cytoplasm as well. When tethered to promoters in yeast, PDS-20 activates transcription of reporters. Together the above two observations suggest that PDS-20 is possibly a transcriptional activator. Further, PROSITE scanning of the protein sequence reveals the presence of a D domain, which has been characterized as a docking site of the MPK-1 / ERK. In addition, PDS-20 contains a few potential Ser/Thr phosphoacceptor sites nearby the D domain, and PDS-20 interacts with MPK-1 in the yeast two-hybrid assay, which is consistent with the ScanProsite results. These observations suggest that the PDS-20 activity is possibly regulated by the MPK-1 pathway. Experiments testing the ideas that PDS-20 might be a transcriptional activator controlled by MPK-1 and how mutations in *pds-20* enhance the *puf-8* mutant phenotype are currently in progress.

Understanding the function of ubiquitin like protein HUB1 in *C. elegans*

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Hub1 belongs to the family of ubiquitin like proteins and shares remarkable sequence and structural similarity to ubiquitin. Further, Hub1 is evolutionary conserved from yeast to humans. Hub1 interacts with the splicosomal protein Snu66 via a Hub1 interaction domain (HIND). This interaction of Hub1 and Snu66 is important for the usage of non-canonical splice sites in *S. cerevisiae*. Hence, Hub1 is known to be involved in mRNA splicing in *S. cerevisiae*. Hub1 has been studied in *S. cerevisiae, S. pombe* and in HeLa cell lines (1, 2, 3). However, its role in splicing in multicellular organism has not been addressed as yet.

The *C. elegans* genome contains homologs of Hub1 and Snu66. As these protein share remarkable similarity at the sequence level we are interested in seeing if they exhibit functional homology to Hub1 and SNU-66 in *S. pombe*. We will discuss the interaction between Ce HUB-1 and Ce SNU-66 in *C. elegans* and go on to address the role of Ce HUB-1 in the splicing of genes in *C.elegans*. (*equal contribution)

Gardenin B a bioactive phytomolecule from *Gardenia lucida* (Roxb.) delays aging and retards onset of age related neurodegenration in *Caenorhabditis elegans*

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Gardenin B (5-demethyltangeretin), a lipophilic flavonoid that is part of a class of natural compounds known as polymethoxyflavones (PMFs). These compounds have been shown to exhibit a range of biological activities viz. anti-inflammatory, anti-carcinogenic, anti-viral, anti-oxidant, anti-thrombogenic, and anti-atherogenic properties. Gardenin B (GB) is isolated from the plant *Gardenia lucida* (Rubiaceae), which is commonly called as 'Dikamali'. The present study for the first time utilizes well established free living, multicellular model system *Caenorhabditis elegans* to explore the longevity promoting, stress modulatory and neuroprotective effects with different doses (5 µM, 10 µM and 25 µM) of Gardenin B (GB). The 25 µM dose of GB significantly prolonged the mean lifespan significantly by 24 % in the worms as compared to control and other tested pharmacological doses of GB. Additionally, GB enhanced resistance against juglone induced oxidative and heat induced thermal stress in the worms. Furthermore, GB also attenuates age related intracellular ROS level and intestinal lipofuscin aggregation. Additionally, GB (25 µM) significantly extended the mean lifespan of stress hypersensitive mutant (*mev-1*) by 30 %. The progression in age is accompanied by age related neurodegenerative pathologies like Alzheimer's (AD) and Parkinson's disease (PD). GB exposure reduced the alpha synuclein aggregation and delayed Aβ induced paralysis in *C. elegans* transgenic model of PD and AD. In order to investigate genetic mechanism regulating GB mediated lifespan extension, we examined the effect of GB (25 µM) on lifespan of various mutant strains viz. *daf-16, eat-2, skn-1* and *hsf-1*. The GB exposure was found to regulate function of gerentogenes like *daf-16, eat-2, skn-1* and *hsf-1*. The longevity promoting and stress modulatory effects of GB are mediated by up regulation of the stress response genes *sod-3* and *gst-4*. Altogether, our results suggest GB exposure promotes longevity with enhanced stress resistance, improved healthspan and neuroprotection in *C. elegans*. The present findings encourage future investigation for developing therapeutic interventions for managing aging and age related diseases.

Regulation of neuronal microtubule cytoskeleton

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Microtubules are dynamic polymers that are critical for physical transformations that cells undergo in order to divide, develop and generate motility. Neuronal microtubules are unusual in that they are generated and stabilized without the influence of centrosome during development and regeneration. Stabilization of microtubules is limiting in neuronal polarization. Loss of *klp-7* kinesin-13 family microtubule destabilizing factor leads to multipolar neuronal phenotype in *C. elegans* touch neuron, which can be reversed by the destabilization of microtubules with Colchicine. We hypothesized that a genetic screen for the suppressors for *klp-7(0)* mutant will help us identify regulators of microtubule cytoskeleton in neuron. With this in mind, we conducted a genetic screen covering 75% of the mutagenized genome and isolated 7 suppressors. By combining meiotic recombination and whole genome sequencing we have identified candidates such as tubulin genes, post-translation modification factors and other novel factors. We are characterizing the effect of these mutants in neuronal development and their roles in the regulation of neuronal cytoskeleton. Understanding the fine regulation of microtubule dynamics will help us design therapeutic strategies in neurodegenerative disorders and axon regeneration.

Putative role of vesicular cargo adaptors in regulating the transport of mitochondria

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**Guruprasada Reddy Sure is deceased*

In a neuron, mitochondria are distributed throughout the neuronal process and are found in greater density in regions which require high energy like the synapse and Nodes of Ranvier. It has been observed in many model systems that the density of mitochondria along the neuronal process is constant. Such an observation holds true for *C. elegans* as well. The biogenesis of mitochondria primarily occurs in the cell body. The microtubules, motors and adaptor proteins function in concert to transport mitochondria to the regions where they are required. The major anterograde motor which transports mitochondria is Kinesin-1. Kinesin-1 consists of four subunits: two heavy chains (KHC) and two light chains (KLC). A loss of function in either KHC or KLC-2 results in a decrease in mitochondrial density in the neuronal process. This suggests that transport may be one of the ways in which the maintenance of mitochondrial density in a neuronal process is brought about. The regulation of mitochondrial transport in *C. elegans* is poorly understood. We are trying to address how this regulation is brought about. UNC-16/JIP-3 and UNC-76/FEZ-1 are known to associate with Kinesin-1 and transport vesicular cargo. Interestingly, *unc-16* and *unc-76* mutants show an increase in mitochondrial density in the neuronal process. In these mutants, we observe an increase in the levels of KHC and KLC-2. There is an increased bias in anterograde flux in these animals which potentially arise due to the increase in KHC and KLC-2 levels. This may explain the observed increase in mitochondrial density. There is a possibility that the competition between various adaptors for their respective cargo serves as a checkpoint for the transport of mitochondria into the neuronal process. We are also investigating the role played by *miro* genes in the regulation of mitochondrial transport.

Ursolic acid confers stress resistance and extends lifespan in *Caenorhabditis elegans*

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The pharmacological lifespan extension by natural molecules satisfying the need to develop therapies and prevention of age-related diseases has a vivid prospect and significance in human welfare programs. Most of these phytochemicals that extend lifespan also confer enhanced stress resistance indicating a strong correlation between lifespan extension and stress resistance. Since ursolic acid (UA), 3beta-Hydroxyurs-12-en-28-oic acid, a natural pentacyclic triterpenoid has been recently reported to ameliorate oxidative stress, we here aim to determine the pharmaceutical concentration(s) of UA for its influence on the lifespan in Caenorhabditis elegans. We show that UA was able to extend the lifespan in *C. elegans* at various tested concentrations. Furthermore, this pharmacologically active molecule demonstrated significant ROS (reactive oxygen species) attenuation and enhanced percentage survival under sublethal thermal stress. The thermo-resistant phenotype was found to be conferred by the up-regulated heat shock protein expressions. We show that the mammalian Nrf2 orthologue, SKN-1, which directly promotes the expression of a range of detoxification enzymes is required for increased stress resistance of UA treated worms. Together, these data suggest that UA is capable of conferring oxidative stress resistance, ROS attenuation and longevity promotion in *C. elegans* suggesting it might serve as a lead molecule in natural therapeutics that can cope up with the negative physiological aspects of aging. Since the components of stress response pathways, share homology with factors in complex human disease pathways correlating aging and resulted woes. There remains intense interest in understanding how these pharmacological interventions influence aging and age-related disorders. These phytochemicals with substantial implications for the onset or progression of age-related disorders need to be tested on models of age-related diseases available in *C. elegans*. Currently UA is in human clinical trial for its anti-cancerous potential and interestingly, a unified model integrating cancer to aging has been supported by a variety of evidences. We will further delineate the notable clinical implications of UA including underlying signaling pathway demonstrating whether the anti-cancer genes are interacting with anti-aging genes.

***C. elegans casy-1*, an ortholog of the mammalian Calsyntenins is essential for long-term learning and memory**

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While different molecular and cellular components of memory and learning are being identified rapidly using large-scale genetic screens and knockout experiments, a comprehensive view of the molecular mechanisms underlying this phenomenon is still not available. CASY-1 is the *C. elegans*ortholog of the type 1 transmembrane protein Calsyntenin-2, which has been implicated in defects associated with human episodic memory (Hintsch, 2002). This contains two cadherin repeats and a LG/LNS-like domain which has been shown to be critical for learning (Ikeda et al., 2008). CASY-1 is expressed in a number of neurons including neurons in the head.

We tested for learning defects using an olfaction-based associative learning assay. Here worms are trained to avoid the chemo-attractant isoamyl alcohol using nonanone as the unconditioned stimulus. After 24 hours, the amount of learning is quantified using a chemotaxis index to measure the amount of repulsion to isoamyl alcohol. We find that three mutant alleles of *casy-1* (hd33, hd41 and tm718), all containing deletions in the *casy-1* genomic region exhibit learning defects in this assay. These defects are, however, rescued when *casy-1* is expressed under the control of a pan-neuronal promoter rab-3 in the *casy-1* (tm718) mutant background.

We are interested in investigating the molecular mechanism of *casy-1* regulation of learning and long-term memory formation in *C. elegans*.

Impact of the fumigant phosphine on various generations in *C. elegans*

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Phosphine (PH_3, hydrogen phosphide) is a fumigant widely employed to disinfest stored food commodities worldwide. However, extensive usage of PH_3 for the past several years has resulted in the development of resistance among several pest insects of stored products, which threatens the efficient use of PH_3. However, the underlying mechanism/s of PH_3 toxicity has not been well delineated. Hence, recently much emphasis has been laid on elucidating the mechanism/s of PH_3 toxicity to understand the development of resistance. PH_3 is reported to cause a variety of physiological changes in organisms, including lipid peroxidation, production of reactive oxygen species (ROS), depletion of glutathione (GSH) levels, disruption of mitochondrial membrane potential and ATP depletion. Besides inducing lethality, PH_3 has also been reported to prolong the developmental period of survivors or reduce their longevity and adversely affect fecundity, fertility or productivity in several stored product insect pests. Previously, a few studies have demonstrated the advantages of employing *Caenorhabditis elegans* as a model organism in understanding the mechanisms underlying PH_3 toxicity. Earlier studies from our laboratory demonstrated the vital role of GSH and antioxidant defenses among worms developing under PH_3 exposure. The present study aimed to investigate the impact of PH_3 on various generations in *C. elegans* in terms of biochemical and physiological responses to track the development of resistance. We exposed the embryos of *C. elegans* to varying concentrations of PH_3 (0.02 to 0.562 mg/L) and observed for mortality and selected 0.056 mg/L for further studies. Worms were exposed through several generations (up to 30th generation). PH_3 exposure caused a significant delay in the embryonic development (egg to gravid).To determine oxidative imbalance we examined the level of antioxidants and oxidative markers in 10th, 20th and 30th generations. Interestingly, there was a significant decrease in the activities of acetylcholinesterase (AChE) and carboxylesterase (CaE) (12 and 14 %) and an increase in glutathione-S-transferase (GST) and superoxide dismutase (SOD) activities (23% and 25%) in the 30th generation worms. There was no significant change in the activity of catalase throughout the generations. No significant alterations in egg-laying rate were evident, but there was a significant increase in the brood size and locomotion in the 30th generation worms (35 and 27 % respectively). Our data demonstrated that the worms under continuous PH_3 exposure through generations developed resistance to PH_3 in terms of enhanced antioxidant defenses.

Towards understanding the molecular role of *Caenorhabditis elegans* Actin Related Protein 6 (Arp6)

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Remodelling of chromatin structure is one of the important cellular event which regulates different DNA transaction processes such as replication, repair, transcription, and recombination, DNA accessibility is modulated by chromatin modifications for instance, acetylation to increase accessibility, methylation to decreases access, or/and chromatin remodelling. Chromatin remodelling includes nucleosome eviction, nucleosome sliding and histone variant exchange. The catalytic subunit of all chromatin remodelling complexes belongs to SWI/SNF2 superfamily of ATPase that use energy of ATP hydrolysis for remodelling the chromatin. Depending upon the catalytic subunit of the complex, these remodellers are categorised into four families i.e. - 1) SWI/SNF, 2) ISWI, 3) CHD, 4) INO80 family. Among chromatin remodellers, INO80 family has been found to be involved in all major DNA dependent processes (replication, DNA repair, transcription and recombination, telomere maintenance). Yeast and human INO80 family contains two important complexes (INO80-C and SWR1-C). The SWR-C recruits H2AZ/H2B dimers in the nucleosome, which is essential for maintaining genomic stability, whereas INO80-C replaces H2A/H2B dimers into H2A.Z containing nucleosome that ensures the right composition of H2AZ and its removal in the chromatin. These complexes contain actin and several Actin Related Proteins (ARPs).

It has been observed that INO80-C is not found in *C. elegans* is that INO80-C whereas; SWR1 and its components are present *C. elegans*. As we know that, SWR1-C and INO80-C are known to play a major role in maintaining the homeostasis in histone variant exchange dynamics during DNA damaging conditions by opposing activities. The absence of INO80-C raises an important question that how *C. elegans* regulates the homeostasis of H2A.Z. Further, *C. elegans* contains only one nuclear ARP i.e. Arp6. We are set to understand the role of nuclear Arp6 in *C. elegans*. Here we present our results on the localisation pattern of Arp6 and its knockdown studies in *C. elegans*. This research towards understanding the mechanism of chromatin dynamics in relation to Arp6, a component of SWR1-C will provide us information regarding complexity of the chromatin, histone dynamics and their role in regulation of DNA repair.

Understanding the function of Claudins in the *C. elegans* Nervous System

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Cell adhesion molecules (CAMs) are known to play various assembly and interconnection functions in vertebrate systems but their role in nervous system has not been fully elucidated. We are interested in studying Claudins, a class of cell adhesion molecule implicated in normal functioning of epithelial cells. Claudins are a family of proteins which are an important component of tight junctions, where they maintain paracellular permeability and barrier function. The tetraspanclaudins superfamily of proteins displays diversity at the sequence and functional level but structurally they are conserved across different animal species. However, the role of claudins in maintaining tight junction structure and function is extensively studied, how claudins function at synapses remains largely unknown. A screen performed in our lab showed that one of the claudin homolog T28B4.4 is required at the *C. elegans* neuromuscular junction (NMJ) for normal synaptic functioning and it is expressed in a subset of cholinergic neurons of the animals. Although the claudin mutant does not cause any obvious developmental defects in the animal, the mutant *C. elegans* show increased acetylcholine receptor levels at the NMJ. Since alterations in Acetylcholine receptor trafficking is responsible for many brain diseases, how T28B4.4 is involved in acetylcholine receptor trafficking /signaling could provide a deeper insight in to the possible role of claudins in the human brain.

Proteome analysis of *C. elegans* during consecutive pathogenic exposures modulates the innate immune response

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Immunodeficiency has become a major risk factor in the current scenario and has alleviated the death toll up to several thousands. Acquired immunodeficiency is more common than the congenital immunodeficiency. With a wide range of bacterial infections growing it has become a big challenge to the research field to combat the new diseases emerging. Immuno-compromised patients are vulnerable to opportunistic infections, in addition to normal infections that could affect everyone. The effect of opportunism was studied with the help of model organism, *Caenorhabditis elegans*. Proteus mirabilis (PM), an opportunistic pathogen infects the nematode when the immune system is compromised. In the present study, the *C. elegans* was pre-exposed to *Staphylococcus aureus* (SA) for a short term, and then consecutively infected with *P. mirabilis*.The primary infection caused by *S. aureus* weakens the immune system of *C. elegans* and the subsequent exposure to *P. mirabilis* colonizes the same, thereby stimulating the immune system of the nematode.

The advent of various proteomic tools has led us to understand both the quantitative and qualitative analysis of proteins. In this study, the *C. elegans* exposed to the pathogens [SA 4h/ PM 40h and SA 8h/ PM 60h time points] with various time points showed a substantial differences in the SDS-PAGE banding patterns, when compared to their respective OP50 fed controls. The protein samples with the above time points were taken for further separation by two dimensional gel electrophoresis. Totally 524 spots were matched with the SA 4h/ PM 40h in which 266 spots have >1.5 fold regulation and 609 spots were matched in the SA 8h/ PM 60h in which 162 spots have >1.5 fold regulation. The regulated protein spots were taken for MALDI-TOF-TOF analysis and found that significant numbers of proteins were involved in the regulation of MAPK immune pathway in addition to the other molecular and biological processes. The colonization of *S. aureus* and *P. mirabilis* in *C. elegans* as a single infection and as sequential infections was also monitored at the above conditions and time points and investigated through confocal laser scanning microscopy too, wherein, the sequential infections had higher colonization when compared to the single infection. The survival of the *C. elegans* MAPK mutants during the sequential exposure of the pathogens were also moniotored and observed to be having a higher mortality rate than that of the wild type *C. elegans*. More studies are needed for understanding the regulation of proteins confined to the *P. mirabilis* infection.

A fluoride resistance gene defines a new paradigm of longevity assurance in *C. elegans*

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Aging is the single largest risk factor for debilitating diseases like atherosclerosis, neurodegenerative disorders and cancer. Although it is a universal phenomenon that is controlled through conserved pathways, the complex molecular mechanisms of aging are only beginning to be understood. *C. elegans* has evolved as a powerful model system to study the molecular mechanisms of aging, which has helped define the role of nutrient sensing pathways like Insulin/IGF-1 and TOR signaling in controlling this process. Research using *C. elegans* has also helped us to understand why Dietary restriction (DR), a non-genetic intervention of reducing food intake without malnutrition, robustly enhances life span and delays susceptibility to age-related disorders.

Our lab has recently shown that a serine/ threonine kinase *drl-1drl-1* in *C. elegans*, when knocked down via RNA interference, displays DR-like phenotypes characterized by better health span, lower fat content and an extended life span. These worms shift metabolism towards fatty acid oxidation, generate lower levels of ROS and activate the xenobiotic detoxification machinery. *C. elegans* possesses another putative serine/ threonine kinase, *drl-2* that has significant homology to *drl-1drl-1* and is known role to play an undefined role in fluoride resistance. We characterized DRL-2 with the expectation that it is also a DR-associated gene.

Similar to *drl-1*, *drl-2* knock down using RNA interference also leads to extension of life span and reduced fat content of worms. We show that *drl-2* works in the intestine/adipocytes and has to be knocked down early in development for extending life span. Similar to DR worms, *drl-2* also requires pha-4/FOXA but not other transcription factors to regulate longevity in *C. elegans*. Interestingly, the life span extension on *drl-2* knock down is dependent on the type of bacteria that the worms feed on. Unexpectedly, genetic analysis revealed that *drl-2*-mediated longevity does not require metabolic reprogramming, unlike DR. Knocking down *drl-2* can still extend life span of and reduce fat content in nhr-49, nhr-62 and nhr-80 mutants that are compromised in fatty acid oxidation. On the other hand like DR worms, transcriptome analysis revealed that *drl-2* knock down leads to increased expression of xenobiotic detoxification genes, similar to *drl-1*. Thus, DRL-2 represents a class of longevity assurance genes that has overlapping as well as distinct genetic signatures when compared to DR.

Determining the Significance of Kinesin-3 family Specific Novel Motility Outputs in the *Caenorhabditis elegans* Axonal Transport and Function

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Kinesins are a large superfamily of microtubule based motor proteins with individual family members playing essential roles in cell division, cell motility, intracellular trafficking and ciliary function. Most of the focus on diversity between kinesin families has been on the distinct non-motor regions and their roles in regulation and cargo-binding of each family. How the mechanical properties of distinct kinesin motors are tailored to their cellular roles, however, the cellular significance of these properties and how mutations alter transport properties and cellular functions to cause human diseases remains unknown. The kinesin-3 family is one of the largest among the kinesin superfamily and its members play important roles in neuronal transport, cell signaling, development, and cytokinesis. Defects in kinesin-3 transport have been implicated in a variety of genetic, developmental, and neurodegenerative diseases and cancer. We recently discovered at single molecule level that upon dimerization, kinesin-3 motors are inherently fast and remarkably superprocessive, being more processive than any previously characterized kinesin motor and 10-fold more processive than kinesin-1 motor (the founding member of the kinesin superfamily). We also discovered that the K-loop, a signature feature in the loop 12 of kinesin-3 motor domains, does not influence the processivity, rather, endows kinesin-3 motors with a high affinity (10-40 folds as compared to kinesin-1) for microtubule surface while transporting cargo. These motility properties are reflected in the motion of known kinesin-3 cargoes in neurons. We thus hypothesize that family-specific evolutionary adaptations to the kinesin-3 motor domain endowed these motors with distinct mechanical outputs critical for their neuronal transport and functions. In my startup lab, we will rigorously test this hypothesis from *in vitro* single-molecule to ensemble level on cellular cargo by employing *Caenorhabditis elegans* as a model system. The KLP-4, a *C. elegans* homolog of mammalian kinesin-3 motor KIF13A regulates the localization of the glutamate receptor GLR-1 in the worm ventral nerve cord, a critical event for animal behavior in response to glutamatergic signaling. We will generate mutant versions of CeKLP-4 with decreased on-rate, processivity and velocity and examine their effects on GLR-1::mCFP transport and animal behavior.

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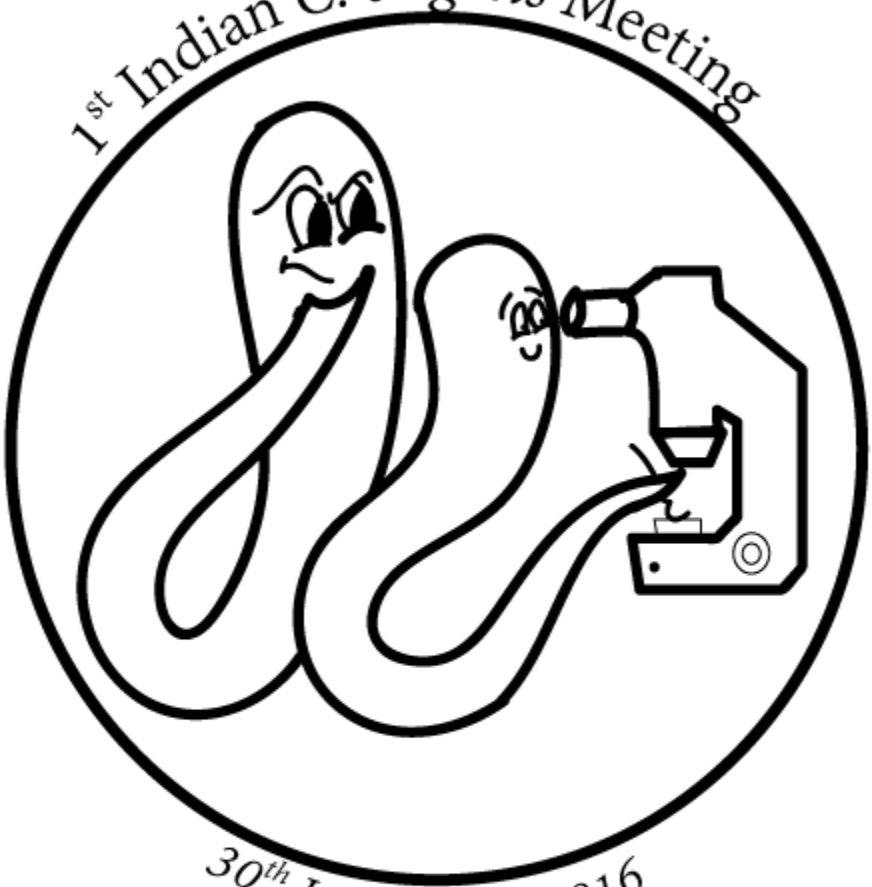

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