Understanding the role of molecular motors in living cells: an odyssey from physics to biology

Dr Roop Mallik from the Department of Biological Sciences (DBS), Tata Institute of Fundamental Research (TIFR), Mumbai was recently awarded the Infosys Prize 2018 in Life Sciences for his 'pioneering work on molecular motor proteins, which are crucial for the functioning of living cells'[1]. The award citation further reads that 'Mallik has identified and measured forces needed to transport large particles inside cells, and demonstrated their role in fundamental processes such as targeting pathogens to their destruction and moving lipid droplets for fatty acid regulation in the liver'[1]. In this article, I hope to summarize Roop's journey from an aspiring physicist to an eminent cell biologist who has made significant inroads into our understanding of motor proteins.

Roop completed his Master's in Physics in 1993 from the University of Allahabad, Uttar Pradesh, and as he mentions in a very intriguing article entitled 'Non-Fermi liquids to endosomes, via pH jumps' describing his journey from physics to biology[2], that upon completion of his Master's degree, he was playing a lot of cricket and waiting for something to happen. Fortunately for Indian science, his uncle from Kolkata sent him a newspaper clipping of an advertisement suggesting that he apply to TIFR Mumbai for graduate school. In 1994, after a successful interview, he joined E. V. Sampathkumaran's lab in the Department of Condensed Matter Physics to pursue his Ph D, where he studied heavy fermion behaviour in rare earth alloys, giant magneto-resistance in manganites, and other layered lattices[3]. It is during his Ph D that he learnt how to conduct independent research, develop hypothesis and most importantly do science his own way. Not surprisingly, Roop was productive as a Ph D student, co-authoring over 20 research papers and graduating with a Ph D in 1999. During his time as a graduate student at TIFR Mumbai, he was very intrigued and increasingly attracted to different biological processes that he read about in scientific journals such as *Nature* and *Science*, and would gather as much information as he could on topics of interest. It was then that he realized that he wanted to apply principles learnt in physics to complex biological systems, and consciously decided to transition into biological sciences. Upon completion of his Ph D, he did a first postdoctoral stint jointly with G. Krishnamoorthy (Department of Chemical Sciences, TIFR Mumbai) and Jayant Udgaonkar (National Centre for Biological Sciences, Bangalore) from 2000 to 2001. Here, he used rapid laser induced changes in pH of the solution to determine how protons released during this process make their way to the core of a protein, and used the green fluorescent protein (GFP) as a case example for this study[4].

It was during this time that Roop came across an e-mail from Steve Gross (himself a physicist turned biologist) from the Department of Developmental and Cell Biology, University of California at Irvine. In 2000, Steve had just completed his postdoc from Princeton University studying the *in vivo* function of molecular motors, and had just set up his laboratory. Steve was in search of a postdoctoral candidate with a physics background and training, interested in studying biological processes. Seeking this opportunity, Roop joined Steve's lab for a second postdoctoral stint from 2001 to 2005 as a Human Frontiers Science Program (HFSP) long term postdoctoral fellow, and performed *in vitro* characterization studies on the cytoplasmic molecular motors' dyne in and kinesin. Here, Roop got his first taste of molecular and cell biology and quite quickly found his footing in biology. He candidly admits that he was never concerned about the lack of biological knowledge and training, and took it in his stride to understand topics of interest very deeply. His postdoctoral work resulted in a seminal paper published in *Nature*, where he showed using elegant optical trapping experiments that the motor protein cytoplasmic dynein changes step size (analogous to gears in a car) depending on the cargo load that it has to transport[5]. On completion of his postdoctoral tenure in 2006, Roop returned to India as a faculty in DBS, TIFR Mumbai, this in spite of him never taking an advanced biology course in his life!

Today at DBS, Roop's lab focuses broadly on the biological functions of two motor proteins, namely dynein and kinesin, and aims to understand their role in (1) phagocytosis and (2) lipid homeostasis during feeding–fasting cycles (see Figure 1 for his current group)[3]. His lab first showed in a *PNAS* paper that during the process of endocytosis, there exists a tug-of-war between kinesin and dynein motor proteins that eventually enables the transport and subsequent fission of the cellular cargo to the endosomes[6]. Next in a remarkable study published in *Cell*, his lab developed elegant optical trapping methods to measure pico Newton forces on single phagosomal particles inside immune cells, and in doing so showed for the first time that solitary strong kinesin motors were unable to generate enough cellular force to transport phagosomal particles, but in contrast dynein motors worked collectively in larger teams to generate enough force within cells to efficiently facilitate this process[7]. Following up on this study, in another landmark paper published in *Cell*, his lab further showed that during phagocytosis, early aged phagosomes (EPs) have bidirectional motion, while late aged phagosomes (LPs) have unidirectional motion that enables transport of cellular debris and pathogens to the lysosome for subsequent degradation[8]. This phenotype was attributed to the clustering of dynein motors on cholesterol rich microdomains present on LPs, but absent on EPs[8]. Finally on the phagocytosis related stories from Roop's lab, in a recent study published in *Current Biology*, his lab makes one of the first attempts in understanding the biological basis of the opposing activity of microtubule motor proteins kinesin and dynein, and their effect on the polarized distribution of organelles within cells, and postulates factors that might be relevant in this phenomenon[9].

While optimizing quantitative optical trapping methods for single organelles in cellular and tissue extracts, Roop's lab serenedipitously found that lipid droplets isolated from the livers of rodents that were fasted had extremely sluggish motion compared to their fed counterparts. An effort to mechanistically understand this phenotype led to the finding that kinesin-1 was responsible for the motion of the lipid droplets, and the levels of kinesin-1 was significantly lower on lipid droplets isolated from fasted rat liver. This finding was the first implication of the involvement of a motor protein in regulation of lipids in feeding–fasting cycles, and their homeostasis from the liver, and led to a very fascinating paper in *Nature Methods*[10]. In a follow up study, his lab has shown that kinesin-1 regulates the transport of lipid droplets to the endoplasmic reticulum, and thereby the release of triglyceride rich VLDL particles from the liver through an insulin dependent pathway. Under fasting conditions, as fats are metabolized, lipid droplets are sequestered in the liver and thus triglyceride rich VLDLs were prevented from circulating in the blood by reducing the kinesin-1 levels on these lipid droplets. This study also explains how the hepatitis-C virus replicates inside liver cells, and this finding was published in *PNAS*[11]. Finally, Roop's expertise and wide knowledge of molecular motor proteins, has led him to write several seminal review articles on this topic[12–14].

For his research, in addition to intramural support from TIFR Mumbai, Roop was first financially supported by the Wellcome Trust (UK) as an International Senior Research Fellow (2006–2012), which was followed by support from the Wellcome Trust DBT India Alliance (Senior Fellow, 2013 – today). For his pioneering contributions to the field of biophysics, he was awarded the Shanti Swarup Bhatnagar award in Biological Sciences in 2014 by the Council of Scientific and Industrial Research (CSIR), Government of India. He is also a Fellow of the Indian Academy of Sciences, Bengaluru. Outside his lab and research, Roop is an avid traveller and especially loves hiking. He routinely hikes to the historical forts in the Western Ghats of Maharashtra, and maintains a nice photographic log of all his travels on his website[15]. It is during these travels, that he was inspired by tribal Warli arts, and this led to the design of his website depiction for the ongoing research in his lab (Figure 2). He is also a sports enthusiast, routinely plays badminton, table tennis and follows cricket closely. He is a very strong advocate and practitioner of science outreach, and aspires to make science education and temperament more reachable to the masses. During his frequent travels to interior Maharashtra, he routinely interacts with school children from the small villages, and spends hours talking to them about the meaning of science, working in a laboratory setting, and the importance of education. A testament of this, is the effort he has taken to write his research in layman terms in both Hindi and Bengali, so that a larger audience within India can understand and follow his research[16].

Lastly, on a personal front, I have known Roop for the past few years. He serves as a mentor on my Wellcome Trust DBT India Alliance Intermediate Fellowship, and in this role, has constantly provided constructive feedback on research programs. Roop's advice in several aspects of setting up of our lab towards streamlining our research has been greatly beneficial. Given our mutual interests in lipid metabolism, a very enriching and productive collaboration with Roop's lab has emerged. A testament to our ongoing collaboration is a recent paper published in *ACS Chemical Biology* (that appeared on the cover of the August 2018 issue) where we show that along with cholesterol, the waxy ceramide lipids are also enriched on late phagosomes, have functional relevance in phagosomal maturation and this process is orchestrated by the enzyme ceramide synthase[17].

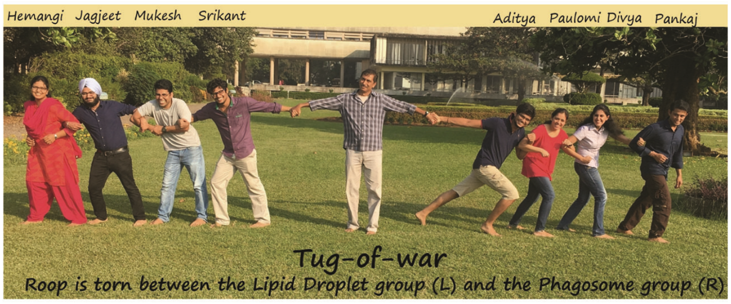

Figure 1. Roop's current lab members are engaged in two major areas of work in the lab (sourced from Roop Mallik's webpage)[3].

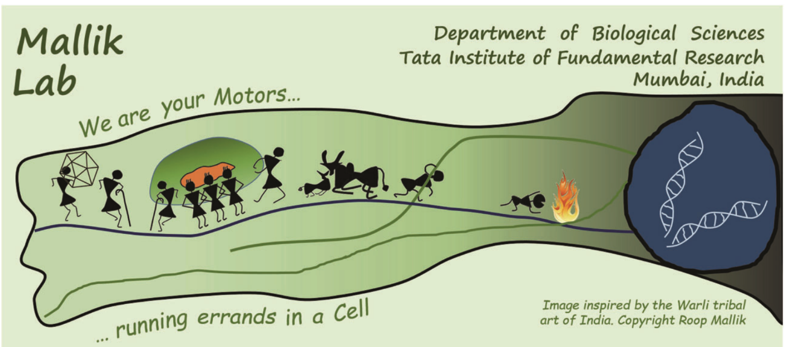

Figure 2. A rendition of the ongoing research in Roop's lab inspired from Warli tribal art (sourced from Roop Mallik's webpage)[3].

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Much More than Moore – a journey from VLSI to disease biomarkers

The Infosys Prize 2018 for Engineering and Computer Science has been awarded to **Dr Navakanta Bhat**, Professor and Chairperson, Centre for Nano Science and Engineering, Indian Institute of Science (IISc), Bengaluru, for his work on the design of novel biosensors based on his research in biochemistry, and gas sensors that push the performance limits of existing metal-oxide sensors. The prize recognizes his efforts to build state-of-the-art infrastructure for research and talent training in nanoscale systems, and for developing technologies for space, atomic energy, and national security applications.

Bhat obtained the B E degree in Electronics and Communication in Mysuru (1989) and the M Tech degree in Microelectronics from IIT Bombay in 1992. He then entered Ph D program at Stanford University, where he worked under the guidance of Krishna Saraswat, one of the leading experts in semiconductor physics and technology. After graduating from Stanford in 1996, Bhat worked on sub-micron VLSI device and process design at the R&D facility of the Motorola Company, in Austin, Texas. He returned to India in 1999 to a faculty position in the Department of Electrical Communication Engineering (ECE), IISc and began his work in the Microelectronics Laboratory in the small annexe to the ECE building.

When he joined IISc faculty, Bhat knew that the Institute had no facilities to fabricate microelectronic devices of the kind that he had made and studied at Stanford or the kind produced by Motorola. Even devices of *circa* 1970 could not be made with the facilities available: India had famously missed the 'microelectronics bus' and, now, nanoelectronics and nanotechnology were on the horizon. Determined not to miss the bus again, Bhat and Rudra Pratap (then of the Department of Mechanical Engineering) led an interdisciplinary group of kindred spirits among the faculty and began discussions on establishing a state-of-the-art facility for fabricating and studying micro- and nano-electronic devices, which would also be the enabler of R&D into the emerging domains of nanoscience/technology, including nanomaterials, microelectromechanical systems (MEMS), and biology. It was an opportune time and the idea found resonance with R. Chidambaram, the then Principal Scientific Advisor to the Govt of India. With his advice and encouragement, a proposal to establish Centres of Excellence in Nanoelectronics at the IISc and IIT Bombay was submitted to the Department of Electronics and Information Technology, DeitY. With the proposal funded, Bhat tapped his Stanford and Motorola experience to design a nanofabrication facility in the new structure built expressly for it, empowered by strong support from Balaram (then Director, IISc, and funding from the DST also. Determined and dedicated team effort ensured that the facility could be benchmarked against the best in the world in academia. Fully operational in 2011, the National Nanofabrication Centre (NNfC) has won plaudits from experts from around the world and is presently the largest and most versatile such facility in an academic setting anywhere. NNfC became the anchor of the Centre for Nano Science and Engineering (CeNSE), a new academic unit established in 2010.

From the very beginning, it was the intent of DeitY and the team led by Bhat and Pratap that the unique and expensive NNfC should truly be 'national', accessible to researchers from across India. The Indian Nanoelectronics Users Program (INUP), also funded by DeitY, was designed to meet this goal and, over two five-year phases since 2008, has enabled training and project work of thousands of academic researchers from the farthest parts of the country. It has been hailed as one of the most successful academic R&D projects in the country for sharing advanced facilities, with Bhat presently as its leader at the IISc. NNfC has of course, been crucial to advanced in-house research projects on developing devices and technology based on gallium nitride, MEMS and NEMS devices, silicon photonics, aspects of 5G technology, and 3D integrated electronic systems.

Anticipating the importance of detecting gases with sensitivity, Bhat led from the front, the effort at CeNSE in designing, developing and fabricating gas sensors for monitoring hazardous gases, such as NO_2, SO_2, CO and H_2S. Detecting these gases is crucial to air pollution monitoring, but is important also to strategic agencies like ISRO, where, for example, monitoring the pre-launch level of NO_2 is critical. Toward this end, Bhat's group has been working closely with ISRO, DRDO and the DAE. Deploying the full processing capability of the NNfC, the group has recently designed and developed a metal oxide-based 'single-chip gas sensor array' capable of simultaneous, sensitive detection of CO, CO_2, NO_2 and SO_2; the array can be integrated with a CMOS-based platform. In collaboration with a multinational company, Bhat's group has developed a device that can sense H_2S at parts-per-billion (ppb) level, potentially enabling medical diagnosis based on