Connect

WITH THE INDIAN INSTITUTE OF SCIENCE

Volume 7 | Issue 1 | March 2020

Snakebites
Why treatment needs to change

Mission to Mars
The inside story

Veeragallu
Local history set in stone

ISSN 2454-6232

IN THIS ISSUE

EDITORIAL

IISc came into being through the efforts of JN Tata, among others. What is not so well known is his unsuccessful attempt to foster medical research at IISc. Those who followed Tata, however, did succeed in supporting medical research elsewhere in India. We track this story in this issue of *Connect*.

Despite this history, IISc today does contribute to medical research, especially on afflictions for which India bears a heavy burden, such as tuberculosis, and the often neglected problem of venomous snakebites. Scientists at IISc are also developing life-saving vaccines and diagnostic devices.

Underlying the treatment of diseases is our knowledge of the fundamental processes of life, not least the biochemical reactions in the human body. The Department of Biochemistry at IISc, which is celebrating its centenary in 2020-21, has made notable contributions in this regard, with faculty members who have done pioneering work and trained students who have gone on to have successful research careers. A collection of photos from the Department and the IISc Archives in this issue gives a glimpse into its 100-year history. PR Krishnaswamy, who was a student at the Department, also recalls his time there in the 1950s, in the first of a two-part profile.

We also feature two other prominent alumni of the Institute, Ritu Karidhal and Jay Yagnik, of ISRO and Google respectively. Karidhal was part of India's Mission to Mars, while Yagnik leads Google's research efforts in developing technologies that use artificial intelligence.

Biochemistry may be one of the oldest departments at the Institute, but the land on which the Institute was built has a much longer history. Among the historical artefacts that tell us about our rich heritage is a veeragallu or memorial stone on IISc's campus. Read all about it in this issue of *Connect*!

TEAM CONNECT

Deepika S, Karthik Ramaswamy, Kaushal Verma, Kavitha Harish, Manu Rajan, Nithyanand Rao, Ranjini Raghunath

CONTACT

Email: connect.apc@iisc.ac.in

Phone: 91-80-2293 2066

Address: Office of Communications,
Indian Institute of Science, Bangalore 560 012
http://connect.iisc.ac.in

Design: Magnetyz

Cover illustration: Ipsa Jain

Printer: Sri Sudhindra Offset Process

Taking on TB

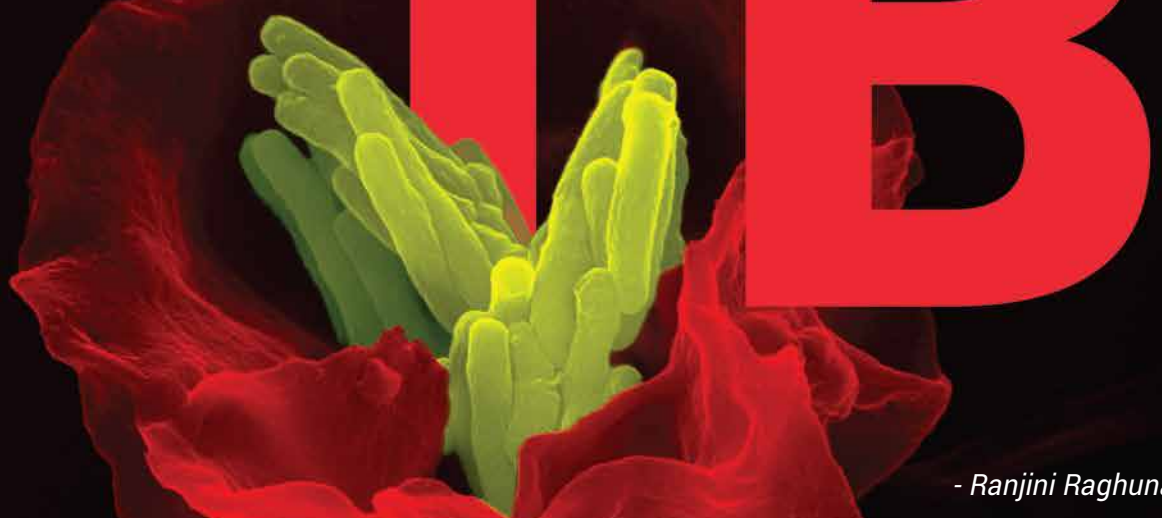


Image courtesy: Volker Brinkmann

- Ranjini Raghunath

India is the world's tuberculosis capital, accounting for 27 percent of the 10 million patients worldwide. Understanding how drug resistance emerges and improving vaccine efficacy are key to fighting this disease.

In 1890, Robert Koch believed he was going to take the world by storm. Again.

Eight years earlier, the German physician had made a stunning discovery. The "great white plague" that had ravaged the continent for centuries was not caused by "bad air" or genes, but by a microscopic killer: *Mycobacterium tuberculosis*.

Macrophage (red) engulfing tuberculosis bacteria (yellow), taken with ZEISS FE-SEM

On 6 August 1890, Koch made a sensational announcement. He had found a remedy for tuberculosis: a mysterious formulation he called tuberculin.

Excitement and hope spread. Patients and journalists flocked to Berlin. Among them was a little-known English physician and soon-to-be famous author named Arthur Conan Doyle.

According to reports, Conan Doyle was unable to meet the scientist or attend his lectures. Yet, he managed to visit patients who had been given tuberculin, and browse through notes from Koch's lectures. Unlike others, he was unconvinced that the remedy was working. In a letter to *The Daily Telegraph*, he singled out the fact that tuberculin was not fighting the bacterium itself, only removing traces of infected tissue.

Soon, it became clear that tuberculin wasn't making patients better; in fact, some were getting worse. Criticism mounted, and Koch was eventually forced to publicly admit that his remedy was a failure.

More than a century after Koch's debacle, TB is now considered fully curable, thanks to the development of powerful antibiotics such as isoniazid and rifampicin. But the fight is far from over.

Battling drug resistance

Although Koch discovered the bacterium only in 1882, some forms of TB infection have existed for millennia. The oldest known case is from a 9,000-year-old skeleton of a woman and her baby found off the coast of Israel. Signs of infection have also been spotted in 5000-year-old Egyptian mummies.

The fact that the bacterium has managed to escape from being eradicated for so long has stumped scientists.

"It is a very successful pathogen," says Nagasuma Chandra, Professor at the Department of Biochemistry, IISc. "It has been able to survive the immune system at various stages, and has survived people's efforts to combat it."

For one, the bacterium can stay dormant inside a host for decades. Once it enters the lungs, it can take on either a *Mr. Hyde*-like aggressive form, or a mild-mannered *Dr. Jekyll*-like form. While *Hyde* goes on a rampage, multiplying aggressively, attacking immune cells, and spreading to other organs, *Jekyll* stays quietly hidden inside the immune cells for years, waiting to transform one day. About a quarter of the world's population is thought to have the latter form of infection, called latent TB.

What makes the bacterium more dangerous, however, is its growing ability to resist being killed by antibiotics.

What makes the bacterium more dangerous, however, is its growing ability to resist being killed by antibiotics

For decades, a potent and safe antibiotic called isoniazid has been used as the frontline drug to treat TB, in combination with two or three others. But bacterial strains resistant to isoniazid are fast emerging.

A few years ago, Chandra's lab started investigating how this drug resistance arises, using a lab-grown isoniazid-resistant strain of a close relative called *Mycobacterium smegmatis*. Instead of looking at only a few pathways or proteins, they mapped entire networks of proteins inside the bacterium, and used computational tools to tease out which mechanisms were activated in the resistant strain. This is akin to building a roadmap of the city to track which roads show unusual activity when there is a roadblock.

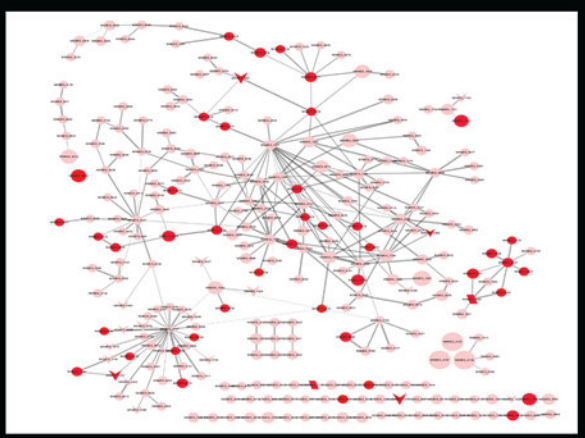


Image courtesy: Jyoti Padiapu et al./ACS Infectious Diseases

Emerging drug resistance: Mapping protein interaction networks

"We found that multiple mechanisms are active simultaneously," says Chandra. Most of them were involved in fighting oxidative stress induced by the drug – they were helping the bacterium defend itself against toxic oxidant molecules. With multiple mechanisms turned on, the bacterium's threshold to handle stress had gone up.

Once the researchers learnt this, all they had to do was raise the oxidative stress beyond this threshold, using the right type of drugs. "Let us say that the bacterium has twenty soldiers that are ready to fight the stress. All twenty are now deployed. If you give additional stress, there are no soldiers left," says Chandra.

Working with Amit Singh, Associate Professor at the Department of Microbiology and Cell Biology, IISc, Chandra's lab screened existing drugs that are known to induce oxidative stress and picked three: ebselen, vancomycin and phenylarsine oxide. Combining isoniazid with any one of these dramatically increased the bacterium's vulnerability to the antibiotic.

The researchers are now beginning to test the vancomycin-isoniazid combination in animal models. "Vancomycin is already used in the clinic for Methicillin-resistant *Staphylococcus aureus* (MRSA) infection," says Chandra. "We thought it would be easy to go to clinical trials."

Purging the persisters

Even before Koch's time, what fueled TB's rampage across Europe was the overcrowding, poor sanitation and malnutrition that mushroomed during the industrial revolution. Today, people in poor living conditions continue to be at a greater risk of infection. They also suffer the most financially because the treatment can be long-drawn-out and expensive.

"If a farmer or a daily wage worker gets TB, and they have to take 2-4 pills everyday for 6-9 months, that is a big burden on their resources," says Singh. There's another danger: if they stop taking the drugs abruptly, the bacteria that are not yet killed will likely grow resistant.

Singh's lab has been trying to cut down this treatment time. Recently, they zeroed in on a subset of TB bacteria displaying tolerance to anti-TB drugs. When TB bacteria enter the body, they are engulfed by white blood cells called macrophages dispatched by the body's immune system. Inside the macrophages, the bacteria are walled off and bombarded with digestive enzymes and lethal molecules. Most of them die. But a subset – about 30 percent – somehow survive inside the macrophages, and grow tolerant to drugs. Getting rid of these tolerant bacteria early on could help reduce the treatment time.

"What is so different in these 30 percent?" says Singh. "How are they generated? Are they generated in response to the macrophage environment? If so, what is that environment which allows them to become drug-tolerant?"

Last year, Singh's lab had a breakthrough. They found that the macrophages containing these tolerant bacteria were different from others: their internal environment was more acidic.

An acidic macrophage environment can induce redox stress in the bacterium by freeing up toxic metals such as iron and copper. Freely available metals can seep into the bacterial cell causing a metal overload and unleashing toxic free-radicals. To survive, the bacterium turns on mechanisms that help it fight the stress caused by these free-radicals. The same mechanisms can help it become drug-tolerant, says Singh.

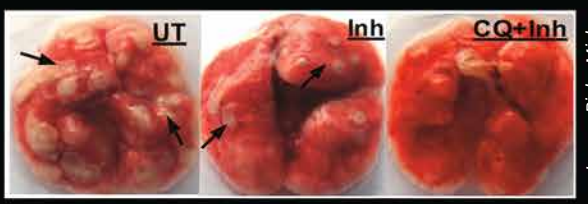


Image: Richa Mishra

Lungs from untreated infected mice, infected mice treated with Isoniazid alone, treated with isoniazid (Inh) + chloroquine (CQ). Arrows indicate presence of granulomas, lesions formed by immune cell aggregates in lungs of TB patients

To reduce the acidity, the researchers gave infected mice chloroquine, a weak base, along with isoniazid. "The results were dramatic," says Singh. Within eight weeks, the lungs of infected mice were completely clear of bacteria.

Chloroquine is a safe drug that is already being used to treat malaria. "If it is given together with anti-TB drugs, we might be able to reduce the therapy time from 6 months to 4," says Singh.

Reviving BCG

If Koch's discovery of *M. tuberculosis* was a turning point in TB history, the development of the first and only vaccine was another.

Spurred by the success of the smallpox vaccine, French scientists Albert Calmette and Camille Guerin took a deadly strain of *Mycobacterium bovis* – responsible for TB in cows – and spent 13 years weakening it until it could no longer cause disease. In 1921, their new vaccine, called Bacille Calmette-Guerin (BCG), was given to humans for the first time. BCG made its way to India in 1948, and is now part of the dozen vaccines mandated under the government's Universal Immunisation Programme.

The vaccine is effective in protecting infants from tuberculosis meningitis and miliary disease, but its protection wears off after a few years.

"BCG, while extremely safe, is a poor vaccine, with very poor efficacy against adult pulmonary tuberculosis. By the time a [vaccinated] person turns 15, they are just as prone to getting TB as an unvaccinated person," says S Vijaya, Professor at the Department of Microbiology and Cell Biology, IISc.

In recent years, researchers have begun to ask if giving BCG once again in adulthood might help. A trial of 990 individuals in South Africa published last year offers some answers. It found that revaccination can not only reduce the chance of infection, but also potentially eliminate bacteria in those with latent TB.

"There is now a lot of interest in trying to see if revaccination of young adults in the age group of 18-22 years is capable of boosting anti-TB immunity," says Annapurna Vyakarnam, Visiting Scientist and Ramalingaswami Fellow at the Centre for Infectious Diseases Research, IISc.

Researchers have begun to ask if giving BCG once again in adulthood might help

To see if revaccination could work in India, Vyakarnam and her colleagues recruited 200 people, most of whom were young nursing students at an old TB sanatorium in the city of Madanapalle, Andhra Pradesh. All of them had been given BCG at birth. They were split into two groups: those who had latent TB, and those who did not carry the bacteria. Within each group, half were revaccinated with BCG. Blood samples were extracted and analyzed over nine months, and detailed flow cytometry investigations were carried out to check for the presence of up to 256 immune cell subsets.

What the researchers found was encouraging. Revaccinated individuals had twice as many immune cells belonging to specific subsets called CD4 and CD8 T-cells. These cells produce signalling proteins called cytokines that rally the body's immune responses against TB. Revaccination was also found to boost the numbers of innate immune cells that form the first line of defense against TB.

"We are able to demonstrate for the first time that revaccination is immunogenic in the Indian context. It induces the right type of immune cells," says Vyakarnam. "What our study proved in addition was that it is putatively safe to vaccinate individuals who aren't infected...[it is] not going to accelerate disease in the individual."

Developing new vaccines

Given how poor BCG is at preventing TB in adults, can new vaccines be developed that offer longer lasting protection?

The answer, many believe, lies in understanding how some people who have been exposed to TB for years – such as hospital staff or caregivers – continue to remain healthy. "These individuals, we know, have naturally acquired protective immunity to the disease," says Vijaya.

A few years ago, her team found that the immune system in these individuals was explicitly targeting certain proteins that the bacterium produced, which the diseased individuals were unable to. Two proteins called Rv1860 and Rv3881c were found to trigger a particularly strong immune response in those who were healthy. Vijaya's team took the genes encoding these proteins, added it to BCG, and gave this to guinea pigs that were then infected with TB.

"We showed that this improved BCG is able to control the disease much better than the parent BCG," says Vijaya. "In one of our experiments, we found that a couple of animals actually had sterilising immunity...[the added genes] were improving BCG to an extent that the bacterial load was below limits of detection."

But translating these lab results to a commercial vaccine is not easy, Vijaya points out. "To take it to human clinical trials, you need large amounts of funding...in India, nobody has the political will or the technical expertise."

Photo courtesy: S Vijaya

S Vijaya showing the Biosafety Level-3 facility, which she helped set up at IISc, to former Director P Balaram and former Associate Director N Balakrishnan. A major part of tuberculosis research at the Institute is carried out here

Some steps are, however, being taken to improve the current state of vaccine development. The Indian Council of Medical Research recently launched an extensive clinical trial of two vaccine candidates – a German BCG recombinant and a leprosy vaccine that produces proteins similar to the TB bacterium. These are being tested in more than 12,000 healthy household contacts of TB patients.

In addition, the government is pumping Rs 12,000 crore into its National Strategic Plan for TB Elimination, to ensure improved access to quality diagnosis, treatment, and support. It also claims that it will eliminate TB in India by 2025.

From pipette to patient:

Tools for better disease diagnosis

- Neelima Basavaraju

Image: Arek Socha from Pixabay

An overview of IISc labs involved in developing novel diagnostic tools for infectious diseases

With the recent emergence of the coronavirus infection, the world has been reminded of the lethal nature of disease outbreaks. Infectious diseases, caused by bacteria, viruses, protozoa, and other parasites, can be transmitted to a healthy individual from another infected individual, or via disease vectors. As a first step towards fighting any infection, diagnosis is critically important. Early detection of infected individuals helps in inhibiting further transmission. Diagnostic tests also help a physician decide whether antimicrobial treatment is necessary in a particular case or not, thus reducing the misuse of antimicrobial medications and the evolution of drug resistance.

India is particularly vulnerable to the spread of infectious diseases such as tuberculosis, malaria, dengue, and pneumonia. In a tropical country like India, which is densely populated and has a large part of the population living in poverty, early diagnosis provides crucial assistance in stopping the infection from spreading and preventing a possible epidemic. However, the challenges of developing diagnostic tools are different compared to those in economically developed countries. India requires highly sensitive devices that are inexpensive, can process a large number of samples, and are easy to carry to rural areas for point-of-care tests. The development of such devices is being actively pursued in some labs at IISc.

Low-cost device for rapid testing of tuberculosis

While working as a postdoc at the University of Washington in Seattle, Bhushan Toley, now an Assistant Professor at the Department of Chemical Engineering, got introduced to paper-based microfluidic devices for biomedical diagnosis. Microfluidic devices, also known as lab-on-chip devices, process and analyse fluids in micro-channels. Paper-based materials are conventionally used in immunoassays, where the presence of a specific protein is detected by a change in colour; a famous example is the home pregnancy test. The porous nature of the paper enables fluid transport on its surface simply by wicking, eliminating the need for bulky pumps. Paper-based assays are particularly advantageous in limited-resource settings, owing to their low-cost and easy portability.

Early this decade, the University of Washington lab was one of the first to perform nucleic acid amplification tests (NAATs) on paper, successfully detecting bacteria that cause respiratory infections, a project in which Toley was involved. NAAT involves segregating DNA or RNA sequences of the microbe from the infected sample and amplifying them to detectable levels. When Toley joined IISc in 2016, he wanted to use this approach to detect other infectious diseases and chose tuberculosis (TB). "TB being a major problem in India and urgently needing a rapid and inexpensive solution for diagnosis, I felt that paper-based TB diagnostics would be a very valuable solution," he says.

Caused by *Mycobacterium tuberculosis (Mtb)*, TB claims 1.2 million lives every year – the highest number for any single infectious disease. An estimated 10 million people were diagnosed with TB in 2018; India alone accounted for 27 percent of all TB cases detected. The Indian government launched the TB-free India campaign in early 2018, setting a target to completely eliminate the disease by 2025.

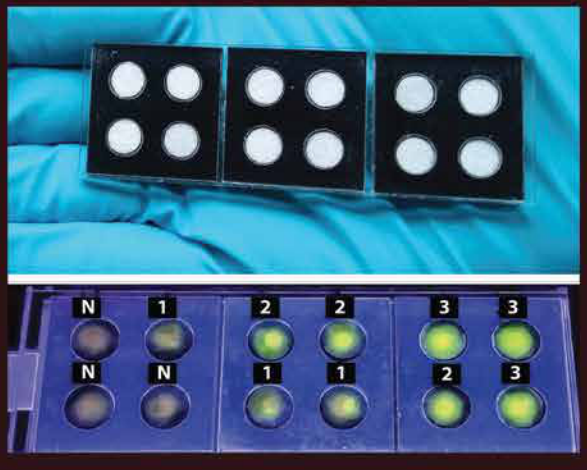


Photo: Navjot Kaur

(Top) Tuberculosis diagnostic kit fabricated in Toley's lab. Paper pads fit inside precisely cut black acrylic sheets. (Bottom) Fluorescence detection images. Numbers indicate increasing concentration of Mtb DNA.

Toley wanted to create a low-cost diagnostic device that would work in the Indian setting. "I wanted to build a device that is uncomplicated, which even a minimally trained user can operate," he says. Indian diagnostics labs and hospitals use smear microscopy as the first step to screen TB patients, which is not very sensitive. The current gold standard for diagnosing TB is the GeneXpert machine, which works on cartridge-based *Mtb* DNA amplification and is fully automated. But the machine is very expensive and a single test costs around Rs 2,000.

Along with his PhD student Navjot Kaur, Toley started developing a paper assay using inexpensive materials. They came up with a suitable design that fitted circular paper pads inside precisely cut black acrylic sheets. Purified *Mtb* DNA is added to the paper surface along with necessary reagents and incubated for 80 minutes at 63°C to achieve DNA amplification. The presence of *Mtb* can be confirmed by shining a UV torch on the paper. "Once this device goes for commercial production, each sample test would cost less than Rs 300," says Toley.

An analysis of clinical samples obtained from a hospital revealed 100 percent accuracy in detecting TB-positive cases. A few negative cases also showed up as positive, a problem which Toley's group is working to resolve. They are also working on the dry storage of pathogen samples on paper for longer durations to facilitate transport of DNA samples.

'One Health' for animals and humans

"Our interaction with animals is changing," says Utpal Tatu, Professor in the Department of Biochemistry. "We share not only the environment but also the diseases," he adds, emphasising the need to keep animals healthy. Many emerging infectious diseases – SARS, bird flu, Ebola, and possibly COVID-19 – originated in animals.

Tatu joined IISc in 1997 and has been involved in studying the proteomics of pathogens causing neglected infectious diseases such as malaria, amoebiasis, and giardiasis. Proteomics, or identifying and analysing proteins produced by an organism, is beneficial in developing drugs that target and disable key proteins, inhibiting growth and virulence. It also helps identify specific protein antigens produced by the pathogen that can be used as biomarkers for diagnosis. "Among all the diseases studied, our laboratory has achieved significant progress in bringing two potential diagnostic studies to fruition in the form of kits: for trypanosome infection in animals, and for trichomonas infection in humans," he says.

Tatu's association with animal diseases started when one of his friends asked him to take a look at his sick horse. It was unclear what the horse suffered from; after vigorously nodding its head due to pain for a day, the horse died the next day. Over time, with more animals across India succumbing to this unknown sickness, Tatu was approached by the animal husbandry department to help identify it. Analysing blood samples collected from sick cattle, he found that they were infected with a protozoan called *Trypanosoma evansi*, a parasite which had eluded detection. Once the cause was determined, the cattle could be treated with medication.

In India, trypanosome infection predominantly affects cattle, resulting in a significant loss of livestock and is a huge economic burden on farmers. Tatu collected animal blood samples from across India and analysed the proteins of the infecting microbe. Eventually, antigen-based rapid detection kits were fabricated to detect *T. evansi* presence. "The kit, which relies on a drop of blood, can diagnose if the animal is infected or not within ten minutes," he says. Tatu's lab is currently supplying these low-cost kits to many veterinarians and turf clubs. In the near future, with funding from the Biotechnology Industry Research Assistance Council (BIRAC), Tatu aims to reach farmers directly by scaling up marketing.

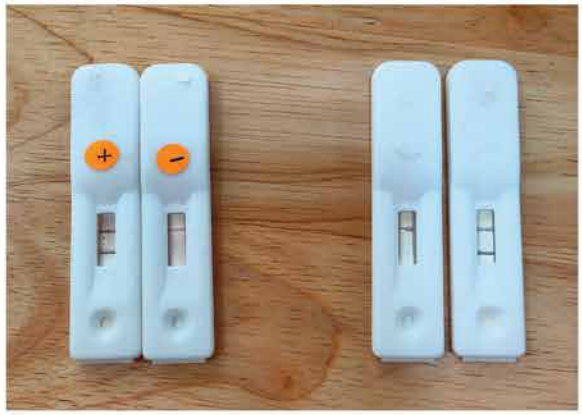


Photo: Neelima Basavaraju

Antigen-based rapid diagnostic kits fabricated in Tatu's lab for trypanosomiasis (left) and trichomoniasis (right). Two coloured lines in the assay indicate the presence of infection

Tatu's lab has also developed a diagnostic kit for trichomoniasis, a sexually transmitted disease (STD) caused by another protozoan *Trichomonas vaginalis*, which infects the human genitourinary tract. Trichomonas infection mainly affects women. However, there were no effective detection methods for this disease. Collaborating with gynaecologists in Bangalore, Tatu obtained infected genital secretion samples to analyse the proteins of the pathogen. He successfully identified the biomarker needed to diagnose this disease. These kits, after successful clinical evaluations, are currently being used by clinicians in Bangalore.

Malaria diagnosis by trapping red blood cells

Vasant Natarajan, Professor in the Department of Physics, joined IISc in 1996 after working at AT&T Bell Labs, New Jersey. "[I wanted] to do research relevant to the needs of Indian society, and not the kind of esoteric research that happens at Bell Labs," he says. At IISc, he chose to work on malaria.

Malaria is caused by single-celled *Plasmodium* parasites, and transmitted by the bite of an infected female *Anopheles* mosquito. Globally, 228 million people were diagnosed with malaria in 2018, almost all of them in tropical and subtropical countries. In 2017, India recorded 8.8 million malaria cases. To detect malaria infection, two methods are widely employed: blood smear microscopy and antigen-based rapid diagnostic tests.

"Natarajan came up with a totally new idea for diagnosing malaria. Up until now, biologists were interested in looking at microscopes and developing biomarkers in a conventional way," says Tatu, who is one of the collaborators on this project. "Natarajan decided to explore the change in physical properties of the infected human cells." Malarial parasites enter red blood cells (RBCs) and multiply, changing the shape and size of infected RBCs. The parasites also secrete numerous proteins to help them survive, resulting in increased rigidity of the RBC membrane and increased adhesion of RBCs to vascular surfaces.

Natarajan probed these changes by trapping the blood cells optically, using focused laser beams to apply force and physically hold a single RBC, similar to mechanical tweezers. "The idea was to see whether the malaria infection changes the corner frequency of the RBC," says Apurba Paul, a former PhD student who worked on this project and is currently a postdoc at Clemson University, South Carolina. Corner frequency gives a measure of the stiffness of the trapped molecule and varies based on the change in the molecule's physical properties.

Photo: Apurba Paul

RBC from a healthy person (top) vs Plasmodium-infected RBC (bottom). When optically trapped (right), the cells fold. Time taken to completely fold is marked on their pictures.

Natarajan's team found that the corner frequency noticeably increased for infected RBCs, compared to healthy ones. They also found that infected RBCs showed an increase in corner frequency even if it didn't contain the parasite, a finding that they termed as 'bystander effect'. "This effect may be caused by the substances secreted into the bloodstream by the parasite or the infected RBCs," explains Paul. "We have tried to isolate these substances, and the results suggest that cyclic adenosine monophosphate (cAMP) could be one of them," he adds. This effect enables the detection of malaria earlier than existing methods, even when the parasite count in blood is very low. The group has validated this technique on clinical samples obtained from malaria-infected patients.

Point-of-care diagnostics: taking the lab to the field

To diagnose malaria, blood smear microscopy is the most widely used method. But its reliability depends largely on the proficiency of the technician performing it, especially when the pathogen count in the blood is low. Accurately detecting infection through microscopy takes a few hours. A wholly automated machine used for complete analysis is often bulky and expensive.

"For malaria diagnosis, we have picked up the gold standard of microscopy, and we are trying to translate it into a point-of-care device by bringing in end-to-end automation," says Sai Siva Gorthi, Assistant Professor at the Department of Instrumentation and Applied Physics. Gorthi's lab has developed an automated device consisting of a single unit with a microscope, sample holder, optical setup and computational tools, all inside a compact box, making it easily portable. In an actual clinical setting, the technician would just have to mix the blood sample with the reagents, drop the fluid onto the provided microfluidic slide, and keep it inside the device.

"The end-to-end automation of our device avoids the requirement of a skilled technician," points out Gorthi. The machine uses algorithms to focus on infected RBCs, acquire images, and present the result. "The result can be known within ten minutes," says Gorthi. The device is equipped to check for both the life-stage of *Plasmodium* as well as the parasite count. It can also be used to detect an array of other RBC-related disorders, such as sickle cell anaemia and spherocytosis, and can easily be extended for routine tests of blood cell counts.

Photo: Neelima Basavaraju

Students from Gorthi's lab (Aravind Venukumar, Prateek Katare, and Roopa Ashwath) loading samples on their lab-built device and analysing the images

After clinical validation supported by BIRAC, Gorthi aims to commercialise the device through a startup incubated at the Society for Innovation and Development, IISc. He is also working with the Indian Council of Medical Research to take the device to North East India for large-scale malaria detection.

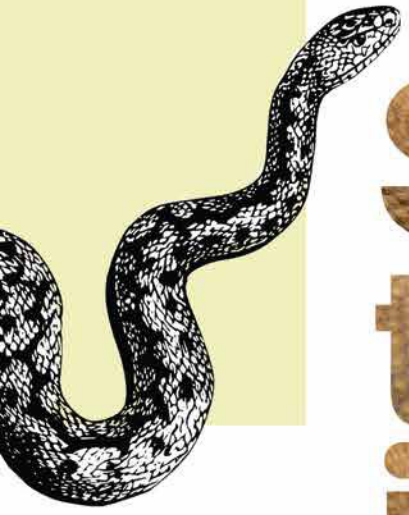
Neelima Basavaraju, a former postdoctoral researcher at IISc's Solid State and Structural Chemistry Unit, is a freelance writer.

Photo: Chandini Chhabra

A Russel's viper being milked for its venom by Gerard Martin

Why traditional antivenom therapy is inadequate in treating this neglected tropical disease

Humans have always been fascinated by snakes. In some cultures, snakes are considered divine because they are indispensable to humans in controlling rodent pests that can otherwise cause enormous damage to food crops. But snakes can also be deadly to humans, and have come to symbolise evil in mythology and popular culture. For instance, in the Book of Genesis in the Old Testament and the Torah, Satan takes the form of a serpent and talks Eve into eating the forbidden fruit from the tree of knowledge in the Garden of Eden.



Snakebite treatment in India

(and what we can do about it)

- Kartik Sunagar

Several species of snakes are venomous (*venomous* animals actively inject toxins into their victims as opposed to those that are considered *poisonous*, which only harm animals that bite or eat them), and are capable of causing harm to humans through a process called envenomation. Snake venom is a toxic cocktail of proteins produced in modified salivary glands, also called the venom glands. Snakes inject this complex biochemical concoction into the target animal using specialised fangs, which, in some species, resemble hypodermic needles.

Indian subcontinent: Ground zero of snakebites

In India, over 300 species of snakes have been described to date, living in a myriad of habitats, both on land and in water. Nearly 60 species among them are thought to be capable of delivering venomous bites that are clinically significant for humans. Of these, the 'big four' snakes are infamous for causing the majority of venomous bites that lead to death and disability: the common cobra (*Naja naja*), Russell's viper (*Daboia russelii*), the common krait (*Bungarus caeruleus*) and the saw-scaled viper (*Echis carinatus*).

More people suffer from snakebites in India than anywhere else in the world. In fact, more than half the global snakebite deaths occur in India.

In addition to killing an estimated 46,000 people annually, Indian snakes are responsible for nearly 140,000 morbidities every year. This unsettling figure comes from a study published in 2011 in *PLOS Neglected Tropical Diseases* by Bijayeeni Mohapatra from the Shri Ramachandra Bhanj Medical College in Cuttack and her collaborators. The study, based on a nationwide survey, revealed, for the first time, the true burden of snakebites in India. The Indian government's figure on snakebite fatalities in the country up until that point was less than 1,000 a year. However, the actual number of snakebite deaths and disabilities may be even higher than the estimate reported by Mohapatra's study, as it did not cover several states in India, especially in the northeastern region. Moreover, the problem of underestimation of data is made worse because snakebite is not a *notifiable disease* in India.

Snakebite victims are almost always from low- and middle-income sections of the society and they tend to be the primary breadwinners of their families. Once bitten, most victims visit quacks, who resort to unscientific snakebite treatment practices. This is because people in rural India lack access to hospitals or fear not being able to afford the treatment. While the treatment of snakebites is free in government hospitals and Primary Health Centres (PHCs), its cost in private hospitals can be worth a king's ransom. And because snakebite is a rural phenomenon, it mostly affects farmers, thus hurting the nation's agrarian economy.

Despite at least 200,000 Indian families being affected annually by this socio-economic malaise, the scientific and financial resources that are devoted to research on snakebites in India is shockingly low. A similar scientific neglect towards this problem in the rest of the world led the World Health Organisation (WHO) to declare snakebite as a *neglected tropical disease* in 2017.

Antivenom

The only scientifically validated remedy to treat snakebites is the use of antivenom. To make antivenom, venom from the target species is first collected, following which animals, such as horses and sheep, are injected with it in sublethal (incapable of killing) and subtoxic (incapable of causing harm) doses. The resulting antibodies (IgGs) produced by the animal's immune system against venom proteins are collected, purified, and packaged in vials along with preservatives before being marketed.

Photo courtesy: ANET

The Andaman cobra (N. sagittifera) is genetically closer to its southeast Asian counterpart

The use of antivenom has saved millions of lives since it was first developed in 1895 by Albert Calmette, a French scientist at the Pasteur Institute, against the common cobra (*N. naja*). However, this technology has not changed since then, and there are several issues associated with how snakebites are treated even today.

Problems with antivenom

For the manufacture of commercial Indian antivenoms, animals are immunised with crude 'whole' venoms that contain antigens, bacteria, viruses and other impurities. In addition to toxins that could cause disease with severe symptoms in humans, snake venom cocktails also contain components that target the non-mammalian prey and predatory animals. Therefore, using crude venoms for immunisation results in the inclusion of antibodies against impurities and medically unimportant toxins, thus diluting the lifesaving antibodies in the marketed product. Studies have shown that the proportion of therapeutically relevant antibodies in an antivenom vial may be lower than 10-15 percent of the content, necessitating the use of a large number of vials for effective treatment. When excessive quantities of therapeutically redundant antivenom are administered to a snakebite victim, it can lead to further complications, including serum sickness and severe allergic reactions. But there is an even more pressing issue with antivenom, particularly in India, where the problem is already acute.

As a consequence of millions of years of an evolutionary arms race with their prey and adversaries, snakes have rapidly diversified their venoms in terms of structure, function and composition

Evolution bites

Venom is thought to have evolved in the common ancestor of all snakes. This claim is supported by several lines of evidence. In fact, in a study by my colleagues and me, published in 2013 in *Molecular and Cellular Proteomics*, we recovered three-finger toxins (3FTx) from the saliva of an evolutionarily ancient lineage of constricting snakes, such as boas and pythons. 3FTx is amongst the most potent neurotoxic proteins that enriches the venoms of many 'advanced' snakes, including cobras and kraits. Thus, the discovery of these neurotoxins in ancient groups of snakes points to a single early origin of venom in this lineage.

Furthermore, as a consequence of millions of years of an evolutionary arms race with their prey and adversaries, snakes have rapidly diversified their venoms in terms of structure, function and composition. Consequently, geographically distinct populations of the same snake species can exhibit dramatic differences in venom composition, which imposes a serious problem for the production of effective antivenoms. For example, in a study on the Southern Pacific rattlesnake (*Crotalus oreganus helleri*), published in the *Journal of Proteomics* in 2014, we unravelled stark variability in the venoms of geographically close populations of this species, considered the most medically important snake in all of North America. While three of the investigated populations produced venoms rich in haemotoxins – proteins that destroy blood cells – the fourth population secreted large amounts of a potent neurotoxin – a component that targets the nervous system and causes paralysis. Since antivenom was not produced by sourcing venoms of all populations, such dramatic intrapopulation venom variation was found to severely limit its effectiveness.

The problem with antivenom seems even more profound in India. For one, the 'big four' snakes – whose venoms are used to make antivenom – are not found in all regions of the Indian subcontinent. Northeast India, for example, is nearly devoid of the 'big four' species. This region, however, is home to many other species of medically important snakes. Similarly, while the Andaman and Nicobar Islands are politically a part of India, biogeographically speaking, they belong to Southeast Asia. Therefore, venomous snakes on these islands, such as the Andaman cobra (*N. sagittifera*), the Andaman krait (*B. andamanensis*) and the Andaman king cobra (*Ophiophagous hannah*), are evolutionarily more closely related to the Southeast Asian snakes than to their congeners on mainland India. But since the distribution of many of these snakes is restricted to relatively smaller geographical regions, commercial antivenoms are not manufactured against them, and clinicians administer the 'big four' antivenoms for treating bites from even such 'neglected species'. It has been assumed that these antivenoms would be effective in treating bites by other venomous snakes, but this assumption has been largely untested.

The magnitude of the problem

To better understand the problem, researchers from my lab, in collaboration with our counterparts from the Gerry Martin Project and the Madras Crocodile Bank Trust and Centre for Herpetology, carried out a study that was published in 2019 in *PLOS Neglected Tropical Diseases*. In the study, we evaluated the effectiveness of commercial Indian antivenoms in negating the toxic effects of snakebites by the 'neglected many' – medically important yet neglected snake species. We compared the venom compositions, biochemical and pharmacological properties, and the potencies of the major neglected species of snakes with their 'big four' counterparts.

For example, we compared two populations of monocled cobra (*N. kaouthia*) in the eastern and northeastern part of the country (West Bengal and Arunachal Pradesh respectively) with venoms from a southwestern population (Maharashtra) of their closest 'big four' relative, the common cobra (*N. naja*). Similarly, venoms of two subspecies of saw-scaled vipers (*E. c. carinatus and E. c. sochureki*) and three species of kraits (*B. sindanus, B. fasciatus, and B. caeruleus*) from various parts of the country were examined.

Photo: Vivek Sharma

The common cobra, one of the 'big four' snakes in India

Our results unravelled dramatic venom variations both between and within species. For instance, while the venom of the West Bengal population of monocled cobra was rich in neurotoxins, the venom of the Arunachal Pradesh population had more cytotoxins (toxins that destroy cells). And because of distinct feeding ecologies, differences were also observed in their venom potencies. While tests on lab mice identified the Sind krait (*B. sindanus*) as the most toxic snake in India (it only requires 0.37 µg of venom to kill a mouse!), and amongst the most toxic snakes in the world, the venoms of the banded krait (*B. fasciatus*) and Sochurek's viper (*E. c. sochureki)* were found to be least potent. Such dramatic differences in potencies were explained by the differences in prey preference. The banded krait feeds voraciously on other snakes, including certain members of the 'big four' species, while the preferred prey for Sochurek's vipers are scorpions. Hence, the venoms of these snakes may be highly potent against their non-mammalian prey, but they were found to be less potent against mammals.

Our study revealed alarming shortcomings in contemporary snakebite therapy in India

The way forward

Unfortunately, nearly all antivenom manufacturers in India produce antivenoms by sourcing venoms from just one part of the country. These venoms are collected by the Irula Snake Catchers Industrial Cooperative Society from mostly two districts in Tamil Nadu – Kanchipuram and Thiruvallur. In the face of this spectacular geographic venom variability, how can we ever address the snakebite crisis in India?

The solution may lie in new approaches and cutting-edge technologies being adopted by toxinologists and venom biologists from around the world – from producing venoms in plates with the help of venom organoids (organs grown on plates) to the mass production of antivenoms in cell cultures. One such unconventional approach is being pursued by our lab. Using our understanding of venoms, we are seeking to produce broadly neutralising antivenoms – antidotes that are effective against geographically distinct populations and/or species of snakes. Our pursuit to innovate Next Generation Antivenoms (NGA), amongst other strategies, involves the discovery of antibodies against the evolutionarily conserved regions in toxin proteins that are shared between distinct populations and species across India. Broadly neutralising antivenoms generated this way will be inexpensive, dose efficacious, and effective in treating snakebites across the country. Unfortunately, India needs to wait a bit longer for its NGA as such recombinant antivenoms will require human clinical trials.

Kartik Sunagar is an assistant professor at the Centre for Ecological Sciences where he leads the Evolutionary Venomics lab (https://www.venomicslab.com/)

The TATA and Medical Research in India

- *Shirish N Kavadi*

Tata medical philanthropy in colonial India was not confined to investing in bricks and mortar but also aimed at creating a culture of medical research

The emergence of modern philanthropy and the expansion of modern medicine in colonial India were closely intertwined, as medical historians have recorded. They note that medical philanthropy was simultaneously part of the colonial 'civilising' and nationalist modernising projects, and that Indian philanthropists, with encouragement from the colonial authorities, were engaged in a "joint enterprise" in founding permanent public utilities such as medical colleges, dispensaries, and large hospitals. Hospitals were in fact seen as the pre-eminent symbol of modern medicine. However, government officials gradually became suspicious of Indian charity, less amenable to cooperation, and even reneged on their commitments, revealing the fault lines in the "joint enterprise."

From 1890 to 1932, the Government of India was engaged in organising medical research and founding of bacteriological laboratories and medical research institutes. The focus of these was primarily the manufacture of vaccines and sera for protecting army personnel. As Indians began to demand the Indianisation of the Indian Medical Service (IMS), medical research became a site of contestation and anti-colonial struggle. The IMS, already experiencing a decline in European recruits, attempted to retain its European character by emphasising prospects and opportunities for medical research.

JN Tata

Image courtesy: Tata Central Archives

Medical research was a state responsibility and imperial preserve with the Medical Research Department dominated by European doctors from the IMS and the Royal Army Medical Corps (RAMC). Indians were employed in subordinate positions, and the Indian National Congress, Indian nationalists, and medical professionals such as Jivraj Mehta decried inadequate or lack of Indian representation in senior scientific positions and in the Governing Bodies of medical institutes.

Nevertheless, medical research institutions established to protect and promote IMS interests – the Indian Research Fund Association, the Pasteur Institutes and the Calcutta School of Tropical Medicine (CSTM) – all received generous donations from Indian philanthropists. Despite this, the perception prevalent among British officials and even educated Indians was that Indian philanthropy neglected medical research. For instance, IMS officers WB Bannerman and Leonard Rogers, who proposed CSTM, bemoaned the absence of interest amongst educated well-off Indians, with Rogers suggesting that an 'Indian Rockefeller' come forward to advance genuine medical research throughout the country. Editorials in *Current Science, Calcutta Medical Journal* and *Science and Culture* lamented the lack of awareness among affluent Indians of the benefits of promoting medical and scientific research and underscored their responsibility to support and inculcate in Indians an interest in medical research. Meanwhile, the AV Hill Report (1945) pointed out that some wealthy Indians had indeed made considerable benefactions to science, medicine and technology, and mentioned in particular the Bombay-based Tata family.

The Tata Research University and medical research

Jamsetji, the founder of the Tata business and industrial house, was also a well-known philanthropist who believed in constructive and purposeful gifting. "What advances a nation or a community is not so much to prop up its weakest and most helpless members," he wrote, "as to lift up the best and most gifted so as to make them of the greatest service to the country. I prefer this constructive philanthropy which seeks to educate and develop the faculties of the best of our young men." He aspired to create a culture of research that would benefit the country and, during his life, he set up technical training and science research institutions. Jamsetji's sons Dorabji and Ratan would also go on to will their property for the advancement of education, science and medicine.

The Tatas were particularly keen on medical philanthropy; to institutionalise and professionalise medical research, Jamsetji Tata and his son Dorabji proposed various schemes. The first of these was the Research University proposed as a "joint enterprise" with the colonial government in Bombay (1896) incorporating scientific, technical and medical research. This marked the beginning of Tata's various endeavours to endow medical research in India. The principal ideas underlying the Tata schemes, drawn from an exceptional world-view discussed above, challenged the narrow colonial conception of bacteriological research restricted to the production of sera and vaccines, and contested imperial control over medical research. This caused much consternation among colonial authorities and the schemes were met with a mixed response.

Photo courtesy: Tata Central Archives

JN Tata (left) with his sons – Dorabji (facing him) and Ratanji (standing) – and RD Tata, father of JRD Tata

Rev Machichan, a member of the University Committee, observed that the University was not meant to be a "mere handmaid to industrial progress" but a "seat of intellectual and scientific culture" dedicated "to the cultivation in India of the spirit of research." The objectives of the University were "to provide for advance [sic] instruction and to conduct original investigations into all branches of knowledge… likely to promote the material and industrial welfare of India" that included: scientific and technological education; medical and sanitary education, including research in bacteriology; and studies in what are currently termed humanities and social sciences.

Jamsetji's scheme coincided with a proposal by some Indian princes to commemorate the Diamond Jubilee of Queen Victoria's coronation in 1897 by setting up a "medical research institute which would investigate the unsolved problems of health and disease in India." The Government agreed that there were benefits. The princes recommended Waldemar Haffkine, the Russian bacteriologist then employed with the Bombay Bacteriological Laboratory (BBL), as Director. Jamsetji invited Haffkine to negotiate an amalgamation of the proposed medical research institute with the Research University and to expand its scope beyond bacteriology to include hygiene, and pathological and physiological chemistry. Jamsetji, inspired by German research universities, wrote to Haffkine, "Our whole Bill has been drafted on the assumption that it is best for the interests of Higher Education to leave the Professors unfettered in teaching and research. *Lehrfreiheit* [academic freedom] is the most important lesson that we have learnt from Germany." The model was, however, the Johns Hopkins University, the first university in the US to introduce postgraduate teaching and which enshrined a great deal of autonomy and academic freedom.

Both Tata and Haffkine envisioned a role for medical research beyond the laboratory, aiming at creating a culture of scientific research in India

Haffkine sought government sanction for medical postgraduates of the Research University to be chosen to study and work in the BBL. This move, he pointed out, would provide them with opportunities to develop their scientific skills and conduct pure research in India – instead of sending them abroad – that would be "used for the study and combating of Indian diseases" and through them spread the interest in medical research among the wider Indian community. The aim "was to give Indian students the opportunity of achieving fame in the world of science, and also to assist the people and the country in various departments of life." Among the students, "those who displayed more than ordinary gifts might look forward to being placed on the staff of the Bacteriological Institute of the Research University when such an independent branch came to be established. On the other hand, a class of men would be created from amongst whom the Government and the country could recruit officers for special problems and appointments…such as the plague."

Jamsetji passed away in 1904, but his sons Dorabji and Ratan continued pursuing plans for a medical faculty at IISc

Haffkine pointed out that in France the *Ecole des Hautes Etudes* alumni were the foci for the radiation of scientific culture in the country and Indians needed to bear this in mind. Both Tata and Haffkine envisioned a role for medical research beyond the laboratory, aiming at creating a culture of scientific research in India.

There were differences of opinion within the Government, with some officials arguing that bacteriological and medical research should remain in the government domain. On the other hand, AHL Fraser, the Home Secretary, noted that the part that most appealed to him about the University concerned "training doctors and facilitating research in respect to problems connected with health and disease." Jamsetji's scheme was viewed by the Indian elite and middle class as a patriotic act and one that would confer lasting benefit on the people of India. William Ramsay, the British advisor to Tata's University scheme, wanted it to concentrate on scientific research alone. Around the same time, the Viceroy Lord Curzon unfavourably viewed the Princes' Health Institute and turned it down. He also considered Ramsay's proposals for the Tata University as too ambitious and narrowed down its scope to basic sciences and technical research. It was, however, eventually established as the Indian Institute of Science (IISc) in Bangalore. The vesting order for IISc was passed in 1909 and the foundation stone of its Main Building laid in 1911.

Dorabji's persistence

Jamsetji passed away in 1904, but his sons Dorabji and Ratan continued pursuing plans for a medical faculty at IISc. They unsuccessfully attempted to persuade Charles Martin, Director of the Lister Institute of Preventive Medicine, to take over as the Director of IISc to ensure that medical research would acquire prominence in the Institute. Ramsay, fearing a medical bias and a shift from the technical focus that

he had been consistently espousing, argued that enough medical research was being done in India. Martin himself declined the offer, observing that the scope of the Institute was too narrow and it appeared unlikely that medical work would ever become part of the Institute.

Image courtesy: Tata Central Archives

Dorabji Tata

Dorabji also sought opinion from Rogers of CSTM and Glen Liston of the BBL (who had proposed a School of Tropical Medicine in Bombay for Indians), and from other experts in Britain on how he could best endow medical research in India. In September 1912, he wrote to Morris Travers, the first Director of IISc, seeking to ascertain how his bequest for two medical chairs in IISc could be utilised for research in tropical medicine and in a manner that would be "valuable alike to the cause of science and the progress of India." Dorabji did not want to invest in 'brick and mortar,' but believed that the money would be best utilised to pay the professorial staff recruited for their ability, temperament, knowledge and skills for research to engage unfettered in the production of knowledge. But Travers put up stiff resistance.

Dorabji persisted, and in 1917 invited R McCarrison (IMS) to prepare a scheme for medical research. McCarrison recommended that Indians themselves establish an "Indian Institute for Medical Research" on the lines of the Rockefeller Institute of Medical Research (established in 1901). India, he noted, had her Rockefellers and millionaires who he felt confident would respond generously to achieve in medical research what other countries had. He also argued that the future of western medical science in India lay with Indians.

Dorabji offered endowments to both the Bombay School of Tropical Medicine and the Central Medical Research Institute in Delhi, medical institutes which the Starling Report (1920) had recommended establishing. The schemes ostensibly had to be abandoned due to the recommendations of the Retrenchment Committee (1922) on government expenditure. However, as Dorabji explained to WS Carter of the Rockefeller Foundation, who was conducting a survey of medical education and research in India, the real reason in both cases was government unwillingness to accept his conditions: that the government match his endowment with a contribution of its own; that these should be postgraduate institutes; faculty recruitment not be restricted to the IMS; appointments be made by a Committee of the Royal Society; faculty salaries be higher than those prevalent in government institutions; and, a ban on private practice, which caused much disquiet among European IMS officials.

In 1941, the Sir Dorabji Tata Trust inaugurated the Tata Memorial Hospital

Dorabji sought Carter's opinion on "the possibility of doing something to develop medical research in Bombay for the good of all of India and independent of Government" and the best means of promoting research. Carter suggested the establishment of fellowships to train Indians as research workers. In 1928, Dorabji donated a grant for a Pathology Laboratory at Bombay's Grant Medical College. When his wife passed away due to leukaemia, he set up the Lady Tata Memorial Trust in 1932, the first Indian Trust to offer private funding to individual medical researchers in India. Its London-based Scientific Advisory Committee offered research grants and scholarships to leukaemia and cancer researchers globally. Some of Europe's leading researchers were recipients of this benevolence. In 1941, the Sir Dorabji Tata Trust inaugurated the Tata Memorial Hospital, incorporating a cancer research centre. Today, this hospital continues to remain a symbol of the Tatas' enduring commitment to endow medical research in India.

Shirish N Kavadi is a researcher with interests in the history and politics of health and medicine, and a Visiting Professor at the Symbiosis School for Liberal Arts, Pune. He is presently working on a book manuscript on Tata philanthropy and medical research in colonial India.

How a Hepatitis B vaccine was made in India

- Madhura Amdekar

P N Rangarajan is currently the Chair of the Department of Biochemistry, IISc. He obtained his PhD from IISc in 1989 and carried out his postdoctoral work at the Salk Institute for Biological Studies, USA. Since joining IISc as an Assistant Professor in 1993, he has carried out research in the field of eukaryotic gene expression and vaccine development. Besides being an elected fellow of three major Indian science academies, he was also awarded the Shanti Swarup Bhatnagar Prize in 2007 in recognition of his outstanding scientific contributions.

During the late 1990s, Rangarajan developed an indigenous recombinant Hepatitis B vaccine which was subsequently marketed by multiple companies. This vaccine has been a huge commercial success, with hundreds of millions of doses sold so far. Rangarajan spoke to **Connect** ***about how the vaccine was developed, how it was taken to the market, and the impact that it has had. Here are excerpts from the interview.***

Photo: Ujjual

P N Rangarajan

Why did you decide to do research on Hepatitis B?

I joined the Department of Biochemistry in 1993 as an Assistant Professor. Like everybody else, initially, I also focused on extending my postdoctoral work which was on transcriptional regulation by retinoic acid receptors. But in the back of my mind, I always wanted to do work that has some benefit for the country. I was greatly influenced by my PhD mentor, Prof G Padmanaban, who played a key role in the establishment of the Astra Research Centre in Bangalore, and by my postdoc mentor Prof Ron Evans at the Salk Institute, San Diego, who had a tie-up with a company called Ligand Pharmaceuticals through which his research was translated to developing drugs. I always thought that, in addition to my basic research, I should also do something that is of relevance to the country.

Such an opportunity came in 1998, when a company called Bharat Biotech approached me for developing the indigenous recombinant Hepatitis B vaccine. In the 1990s, India was importing this vaccine from abroad for immunisation. However, because it was expensive, the government was unable to purchase large volumes of this vaccine required for the Universal Immunisation Programme. Additionally, in 1996-98, the Ministry of Human Resource Development introduced a scheme called Technology Development Mission (TDM) under which scientists were encouraged to collaborate with industry to develop indigenous products that are useful for the country.

Even though I had no prior experience in working with yeast, I took up this challenge and collaborated with Bharat Biotech to develop the recombinant Hepatitis B vaccine under the TDM.

How did you develop this vaccine in your lab and how does it work?

As I mentioned earlier, in the late 1990s, India was importing this vaccine and the major market share was for a brand called Engerix B which was made from *Saccharomyces cerevisiae* or Baker's yeast. The technology for the vaccine was already available, but what we did was indigenisation of this technology.

We decided to use a different type of yeast called *Pichia pastoris* which can grow to higher cell densities compared to *S. cerevisiae* and can therefore produce greater amounts of the recombinant protein. We cloned the gene encoding the Hepatitis B virus surface antigen (HBsAg) and expressed it in *P. pastoris*. Recombinant *P. pastoris* strains expressing high levels of HBsAg were selected. We also standardised a four-step protocol for purifying HBsAg from the yeast cell extracts. This purified HBsAg, when adsorbed onto aluminium hydroxide and

injected into humans, generates anti-HBsAg antibodies in the body. These antibodies bind to the virus and prevent it from infecting liver cells, thereby conferring protection. This was the recombinant Hepatitis B vaccine that we developed.

> *The technology for the vaccine was already available, but what we did was indigenisation of this technology*

Before we could complete the project, a company called Shantha Biotech introduced a *P. pastoris*-based Hepatitis B vaccine (Shanvac-B) in the market. However, since this vaccine had a huge market, several companies wanted to manufacture the vaccine in India using indigenous technology. Therefore, I transferred the technology to three companies in Hyderabad, of which two acknowledged our contribution.

How did this vaccine reach the market from the lab?

After the vaccine was developed, the technology was transferred to Bharat Biotech and the company launched the product. Unfortunately, it did not acknowledge IISc's contribution. After this misadventure, two other companies in Hyderabad, Biological E Limited and Indian Immunologicals Limited, approached me because they knew that I had a commercially viable technology.

After getting the recombinant *P. pastoris* yeast strain from us, both these companies carried out the necessary clinical trials, obtained the regulatory approvals, and launched the vaccine under the names BEVAC and Elovac-B, in 2004 and 2006, respectively. Both these vaccines are called monovalent vaccines since they have only one component: the Hepatitis B virus surface antigen. When this monovalent vaccine is combined with four other vaccines – Diphtheria, Pertussis, Tetanus (DPT), and Haemophilus Influenzae B (HiB) – you get a pentavalent vaccine. In 2011, Biological E Limited brought out a pentavalent vaccine called ComBE Five, and in 2018, Indian Immunologicals Limited brought out their pentavalent vaccine called Vaxtar-5.

Both the companies not only brought out these vaccines and duly acknowledged IISc's contribution in the vaccine development programme, they also paid one percent royalty on total sales and fully honoured the terms and conditions of the MoU we signed with them. In fact, after the successful completion of this project, Indian Immunologicals Limited signed another MoU with my lab via the Society for Innovation and Development (SID), IISc, to develop a DNA rabies vaccine, since they wanted me to support their company's R&D. They actually gave me Rs 50 lakh per year as an R&D grant for five years. During the next five years, we had a very good collaboration and I helped them establish a recombinant DNA laboratory.

Photo courtesy: PN Rangarajan

The recombinant Hepatitis B vaccines developed using the strains provided by Rangarajan (clockwise from top-left): BEVAC, Elovac-B, Vaxtar-5, and ComBE Five

What has been the impact of these vaccines in the market?

The indigenous manufacture of these vaccines by several companies in India led to a drastic reduction in their prices, enabling the Government of India to announce their inclusion in the universal programme of immunisation. In 2016, Biological E Limited obtained an order of Rs 895 crore, while in 2018, Indian Immunologicals Limited obtained an order of Rs 210 crore from the Government of India to supply their pentavalent vaccines for the Universal Immunisation Programme.

When I asked these companies whether they are still using the yeast strain provided by me, they both told me in writing that yes, both of them are still using the *Pichia* strain received from IISc for the production of their Hepatitis B vaccines. Biological E Limited has sold more than 110 million doses of the BEVAC brand since 2010-11 and more than 200 million doses of the pentavalent vaccine since 2012-13. Indian Immunologicals Limited has sold more than 110 million doses of the Elovac-B brand since 2006 and more than 3 million doses of the pentavalent vaccine (Vaxtar-5) since 2018.

It is very gratifying that a technology that I transferred in 2002 is still being used for making millions of doses of vaccines. Millions of children are being immunized against Hepatitis B with a vaccine made from a yeast strain developed in my lab. This vaccine is an example of making a global technology work locally, resulting in the reduction of the vaccine's cost and its introduction in the Universal Immunisation Programme. We, at IISc, have made a small contribution towards this effort.

Personally, what were the major challenges you faced during the development of this vaccine?

In the 1990s, very few faculty members in the Division of Biological Sciences at IISc were engaged in collaboration with industry. The mandate was to carry out basic research, publish high-quality papers, and train graduate students. I was probably the first Assistant Professor in the Division who collaborated with the industry before being promoted to Associate Professor. I chose to travel down the road not taken. It was quite disappointing when IISc refused my promotion to an Associate Professor at that time, since, in my excitement to develop the vaccine, I had not published enough papers.

It is very gratifying that a technology that I transferred in 2002 is still being used for making millions of doses of vaccines

The second challenge was when Bharat Biotech, the first company to get the technology from us, did not acknowledge our contribution. I had to spend a lot of time convincing the IISc administration that we should give this technology to other companies because of its national importance. I am grateful to Prof G Padmanaban, the then-DBT secretary Dr Manju Sharma, Prof M Vijayan, who was the Associate Director at that time and also in-charge of TDM, and of course my family for their help, encouragement, and for supporting me in difficult times. Looking back, I did go through tough times. But in the long run, my decision to work with companies and develop an indigenous vaccine gained appreciation in the country.

In addition to the Hepatitis B vaccine, you have also worked on developing vaccines against rabies and Japanese encephalitis. Could you briefly tell us about those?

Along with the Hepatitis B vaccine project, I had also started a research programme on developing a DNA vaccine in which, instead of a protein, a plasmid DNA encoding a viral antigen is directly injected into the body. Unlike the recombinant Hepatitis B vaccine, which is an example of indigenisation of available technology, the DNA vaccines were very innovative products since nobody had launched a DNA vaccine for human use in the market. While we published good papers and even obtained a patent, unfortunately, we did not succeed in bringing out the Japanese encephalitis vaccine or rabies vaccine into the market.

Are there any more vaccines in the pipeline from work that is currently being carried out in your lab?

I have stopped the vaccine work right now as it was becoming very difficult for me to do both basic as well as applied research. When I was working on *Pichia pastoris*, I realised that it is a wonderful yeast because many aspects of its biochemistry and metabolic pathways are very different from *Saccharomyces cerevisiae*, the yeast on which most of the research work was being done. I thought that this is a goldmine for basic research.

Therefore, my entire lab is now focusing on understanding the regulation of metabolism of *P. pastoris*. We have identified several transcription factors and novel regulatory mechanisms and have had good publications in the past 10 years. We are now beginning to see some interesting leads which have the potential to contribute to a novel expression system.

What do you see as the major challenge in the field of vaccine development?

India has become a major player in the global vaccine market through the indigenous manufacture of vaccines. But, to the best of my knowledge, we are yet to bring out an innovative, blockbuster vaccine into the global market through our own R&D efforts. This, in my opinion, has not really happened and is the major challenge. For example, the rabies vaccine that I had developed was a home-grown technology for which we got a patent, but somehow it could not be converted into a commercially successful product. Now, there is a lot of encouragement and a number of programmes to support academia-industry interactions, biotech startups, and entrepreneurs. It is up to the faculty members to take up this challenge and develop commercially successful products.

Madhura Amdekar is a former Research Associate at the Centre for Ecological Sciences, IISc.

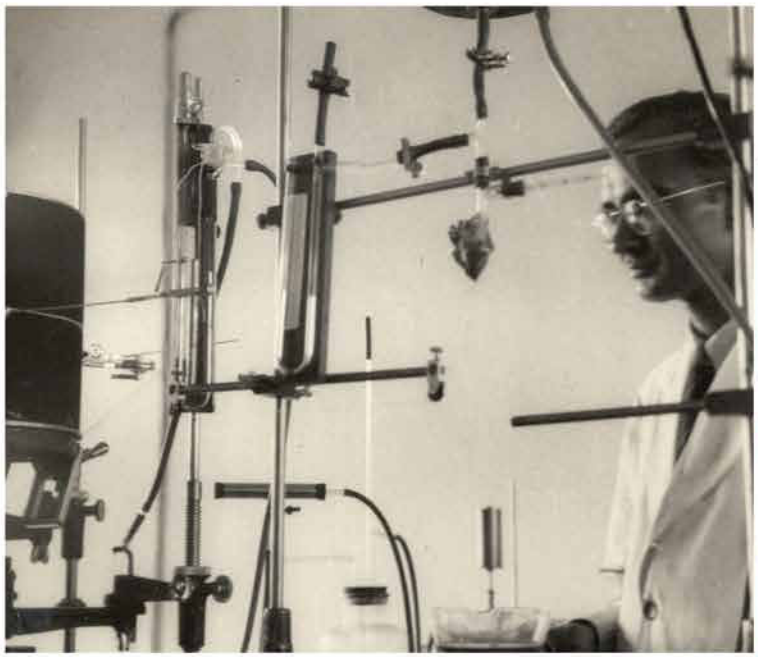
Celebrating a century

The Department of Biochemistry at IISc began its year-long centenary celebrations on 21 February. Here are some photographs from an exhibition it is hosting to mark the event.

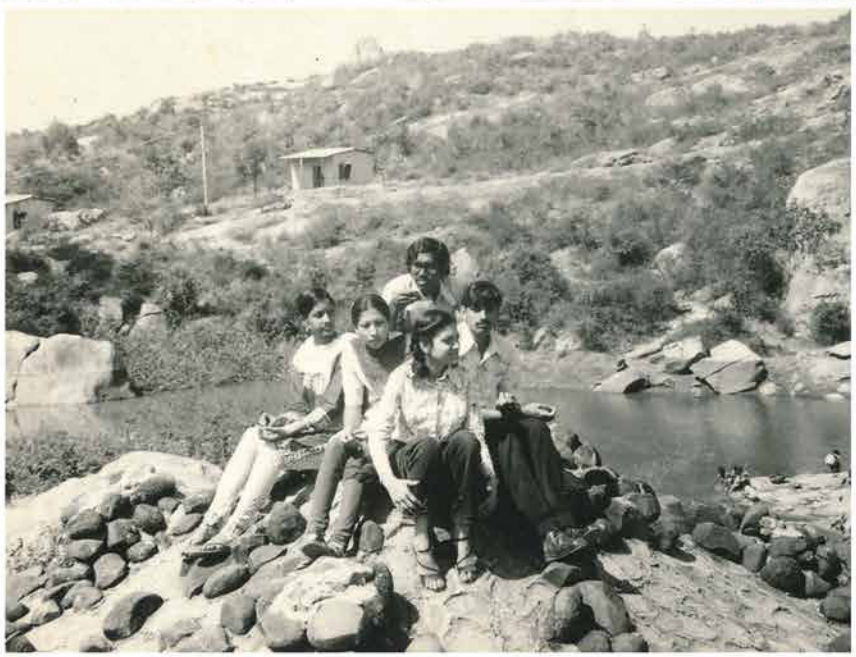
Artist's sketch of the original department building, commissioned for the centenary celebrations

Alumni reunion to celebrate the department's Golden Jubilee in 1971

Research at the department's Pharmacology Laboratory (seen here in 1941) led to the discovery of antitubercular and antibacterial properties of essential oils, isolated from traditional Indian medicinal plants such as tulsi



Students enjoying a lighter moment in the corridors of the old building



Students from PR Adiga's lab on a picnic to Mekedatu in 1982

Vani Iyer, Sandhya Visweswariah and PB Seshagiri, alumni of the department who continue to work at IISc, sharing lunch in 1986.

‘They were beautiful experiments that gave me

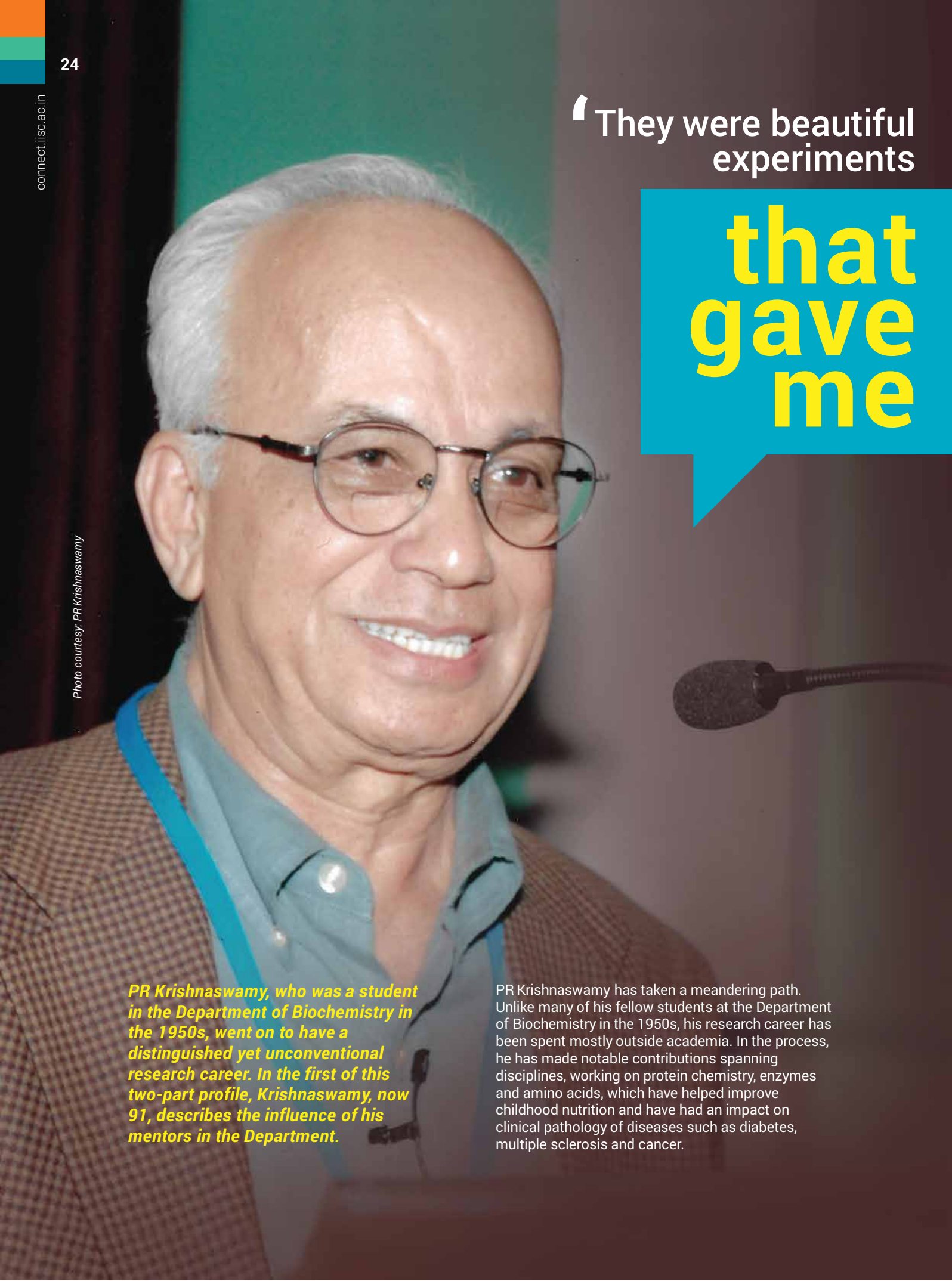


Photo courtesy: PR Krishnaswamy

PR Krishnaswamy, who was a student in the Department of Biochemistry in the 1950s, went on to have a distinguished yet unconventional research career. In the first of this two-part profile, Krishnaswamy, now 91, describes the influence of his mentors in the Department.

PR Krishnaswamy has taken a meandering path. Unlike many of his fellow students at the Department of Biochemistry in the 1950s, his research career has been spent mostly outside academia. In the process, he has made notable contributions spanning disciplines, working on protein chemistry, enzymes and amino acids, which have helped improve childhood nutrition and have had an impact on clinical pathology of diseases such as diabetes, multiple sclerosis and cancer.

an insight into life'

- Nithyanand Rao

This interest in work that not only satisfies scientific curiosity but also has practical applications is a predilection that he attributes to the influence of his mentors. Among them are the faculty members with whom he worked at the Department, particularly M Sreenivasaya and KV Giri, whose own work straddled the presumed divide between basic and applied sciences. "Their approach," says Krishnaswamy, "influenced me in whatever I have done later."

After completing his doctoral work in 1957, Krishnaswamy worked at the lab of Alton Meister, a renowned biochemist at the Tufts University School of Medicine in Boston, USA. But when Krishnaswamy came back to India in 1963, he did not have a job. He eventually found a temporary position at the Central Food Technology Research Institute, Mysore, before heading the Protein Foods and Nutrition Development Association of India. Later, he founded and led the pathology laboratories at Jaslok Hospital and Research Centre, Mumbai, and the Vittal Mallya Scientific Research Foundation in Bangalore – where his work led to one of the first patents for recombinant insulin in India. He also simultaneously served as the Executive Director at Mallya Hospital before joining Manipal Hospital as Director of its Diagnostic Services and Research division, where he trained many students. He is now a visiting scientist at the Centre for Nano Science and Engineering, IISc, consulting for PathShodh, the startup that is developing devices for monitoring diseases like diabetes.

Krishnaswamy, born in 1929, grew up in a Bangalore where child mortality was common; his own parents lost four children. Plague was a pervasive fear, with people evacuating their homes at the sight of a dead rat. Food was scarce, healthcare facilities were meagre, and even basic medicines – at a time when cholera, diarrhoea and amoebic dysentery were common – were not readily available.

> *"Their [Sreenivasaya and Giri's] approach influenced me in whatever I have done later"*

The education system, however, was different. Because of the Great Depression at the time and the lack of job opportunities, many who were highly educated chose to become teachers. Krishnaswamy remembers that many of his teachers at Malleswaram High School were Master's degree holders. "We had great teachers and also beautiful labs," he says.

After completing high school and Intermediate, he joined Central College for his BSc. During this time, he was already familiar with IISc through his uncle CN Acharya, a microbiologist, who had worked at IISc with Gilbert Fowler (the first chair of the Department of Biochemistry) on sewage treatment and compost. While at college, his interests started veering towards biology, sparked by the book *Microbe Hunters* (by American microbiologist Paul de Kruif, published in 1926), that presented the discovery and study of

microbes as a scientific adventure. For Krishnaswamy, the book was, in some ways, a preview of all the advances that were yet to come in the chemistry of life. "For example, at the time I was a student, most of the vitamins were discovered," he says, "and amino acids which make proteins were discovered." But nucleic acids and enzymes were just beginning to be intensely studied.

After college, Krishnaswamy joined the Department of Biochemistry at IISc in 1951 to work towards his Master's degree in Sreenivasaya's Fermentation Technology laboratory. He had heard about Sreenivasaya from reading the journal *Current Science*, of which Sreenivasaya was the editor (1942-50). "He would come to the lab at 7:30 am, lecture for an hour and then for an hour show us a lot of techniques including glass blowing to make our own pipettes," says Krishnaswamy. "You had to make everything yourself since you didn't have these disposables." Sreenivasaya would spend time in the morning helping his students prepare the protocols for the experiments they were to perform that day. "All this laid the foundations for our later work," says Krishnaswamy.

Through such close interaction, Krishnaswamy came to know of Sreenivasaya's pioneering work, beginning in the 1920s, spanning biochemistry, microbiology, plant virology and enzymology. "I was thrilled to see the equipment he had used for his earlier classic experiments in these areas," says Krishnaswamy, "which he had carefully preserved."

> *"Sreenivasaya, in my view, was an intellectual giant"*

Skilled as he was at making new instruments, Sreenivasaya had developed dilatometry as a method for assaying enzymes and measuring enzyme activity. He was also an expert in estimating amino acids using *Lactobacilli* which are deficient in single amino acids, which is the work that Krishnaswamy initially did.

With a fellow student, GD Kalyankar, Krishnaswamy was soon asked by Sreenivasaya to study the nitrogen metabolism in the growing silkworm, from the egg to the pupa stage. This involved, among other things, drying, powdering and estimating nitrogen using micro-Kjeldahl methods that Sreenivasaya taught them. He also wanted them to find what amino acids the proteins they found in the silkworms were made of, using 2D chromatography. "We must have done nearly 2000 Kjeldahl estimations," says Krishnaswamy, "and the analysis took about six months." And he learned a whole suite of techniques. All of this, to him, was work which was new and topical. "They were beautiful experiments that gave me an insight into life, and remain so fresh in my mind."

Sreenivasaya retired in 1952, but left a lasting impression on Krishnaswamy. "Sreenivasaya, in my view, was an intellectual giant," he says. "His knowledge and ability to perform experiments hands-on, his knowledge of instrumentation needed for these experiments and more importantly, his ability to put all these things together to articulate an idea and execute it, was incomparable."

M Sreenivasaya

Photo courtesy: PR Krishnaswamy

But Sreenivasaya was not the only faculty who inspired Krishnaswamy. His uncle Acharya had worked with SC Pillai who had, for instance, painstakingly isolated the microorganisms found in Bangalore's sewage. Another faculty, MK Subramaniam of the cytogenetics lab of the Department, says Krishnaswamy, was a "brilliant biologist and a great and eloquent teacher," who had produced mutant yeasts, one of which turned out to secrete the vitamin riboflavin. Krishnaswamy measured this secretion using the only fluorimeter in the department, and went on to study its biosynthesis.

The combined influence of these faculty members in the Department convinced Krishnaswamy that his passion lay in studying amino acids, proteins and enzymes. He focused on studying the enzymes associated with riboflavin derivatives for his doctoral work with KV Giri, Chair of the Department, whom he remembers as "a very benevolent person, almost child-like as a scientist."

Krishnaswamy was a keen reader, but the only access to the latest literature in those days was through the *Chemical Abstracts* published by the American Chemical Society, which used to arrive in India by ship. It would carry abstracts of papers from various journals, along with the author names and addresses. "We used to buy ruled cards, write the title and summary of the papers we were interested in, and at the back, note the author's address," says Krishnaswamy. "Every single day I would make about 10-20 cards." If one wanted a copy of the paper, one had to send a postcard, by sea mail, to the author. "After three months, if you're lucky you'd get a reprint. This would go on continuously, so every week you'd get two or three reprints."

As he completed the work that led to his DSc, he was looking for a job. Krishnaswamy had gotten married after his MSc, and the couple now had a child. (His wife, Rukmini, is an educationist working with children with special needs, and is the Founder-Director of the Spastics Society of Karnataka.) Around that time, Giri received a letter from Alton Meister, an MD who had switched to a research career, becoming a well-known enzymologist at the Tufts University School of Medicine in Boston.

Meister had written to Giri after seeing some of Krishnaswamy's papers, enquiring if Krishnaswamy would like to work with him on protein synthesis. Meister had perhaps read Krishnaswamy's paper on isolating adenosine triphosphate (ATP) from rabbit muscles, in work that he did with Appaji Rao (now an emeritus professor in the Department). "It was a lengthy process involving washing, centrifuging, separating, freeze-drying, all without the kind of facilities that are available now," he says. "He must have been impressed with that. At the time, even in Meister's laboratory, ATP was a very precious chemical that had to be rationed out."

Photo courtesy: PR Krishnaswamy

Krishnaswamy with Rukmini

Giri wrote back, recommending Krishnaswamy, who got a fellowship to join Meister in January 1958. He took his wife and young daughter with him, undertaking a 25-day voyage in the cabin of a freighter ship, the cheapest way to travel to the US at the time.

Meister was interested in studying protein synthesis, specifically amino acid activation, the first step in the process, focusing on the amino acid L-tryptophan as an example. The aim was to study the reaction that makes tryptophanyl adenylate from L-tryptophan, ATP and magnesium. Upon arrival, Krishnaswamy began intense work on purifying that activating enzyme to study the reverse reaction. This required making purified preparations of the enzyme, and synthesising and purifying nearly 20 amino acyl adenylates. The known method for preparing the enzyme was using beef pancreas. "I made many trips to a slaughterhouse close to the medical school with a big ice bucket," he says, "to get 15-20 pounds of beef pancreas." The process of purification was a lengthy one, involving some 15 steps that would take a week each time, yielding only 20-30 mg of the purified enzyme.

But he was able to publish this work within four months of having arrived in Boston. "That gave me a big thrill, though I lost 10 pounds!" he says. "Within a year, I had four or five publications. I was fortunate to go to an extraordinarily stimulating and rewarding lab." He also had the opportunity to interact with well-known enzymologists who visited Meister's lab. "These were people who had contributed to the study of protein synthesis from its very beginning – among them were Arthur Kornberg, Hans Krebs, Fritz Lipmann and John Edsall."

> *"Books now refer to that study as a classic and remark on the originality of our 'isotope chase' approach"*

He then moved on to studying the enzyme that converts glutamic acid to glutamine. Glutamic acid is the most abundant of all the amino acids in the body, present in every organ. Krishnaswamy chose to source this amino acid from sheep brain, which entailed more visits to the slaughterhouse. "We chose the brain as a source," he says, "where glutamate-glutamine interconversion is important and glutamic acid and its derivatives play a very important role, because it may have some ramifications for brain function."

He had to develop a method for obtaining the enzyme glutamine synthetase from sheep brain, and devise a method to prove the stepwise binding of the constituents in the synthesis of glutamine. "Our work, which showed that it was a stepwise reaction, has stood the test of time," he says. "Books now refer to that study as a classic and remark on the originality of our 'isotope chase' approach. This method that involves trapping isotopically labelled intermediates is well recognised and used for several other enzyme mechanistic studies."

Giri died within a year after Krishnaswamy left for Boston. "Had he been around, I would have come back to IISc and joined him again," says Krishnaswamy. Instead, when he came back to India in 1963, he struggled to find a job. Eventually, he worked at several research institutions and headed research labs at major private hospitals. He credits this willingness to take opportunities as they arose to his time at IISc. "I think those seven years [at IISc] gave me, intellectually, an opportunity to sharpen my skills to address basic curiosities in science and also, when demanded, be equally willing to try and apply them to challenging problems in other fields."

With inputs from Sangeetha D and Debraj Manna

The race for FIVE MILLION DOLLARS

Photo: Ayush Ranka

- Deepika S

IISc-TCS was the only Indian team to compete in the Mohamed Bin Zayed International Robotics Challenge 2020

The competition was only a few days away. With one drone having crashed already, all eyes were locked nervously on the two drones over the airfield outside the Department of Aerospace Engineering. During the final testing at the Department before leaving for the competition, one drone flew high with a red ball trailing beneath it, while another drone with a hoop and net followed it to try and catch the ball. But getting this right was only one of several challenges the team from IISc would have to get through at the competition. And once this final phase of testing was over, the team would have to pack up all their materials and instruments, ship them away, manage to get some sleep (which had so far proved elusive), and get on a flight to the United Arab Emirates to vie for prizes worth five million dollars. Two years of preparation would boil down to just minutes in the arena.

The Mohamed Bin Zayed International Robotics Challenge (MBZIRC), hosted by the Khalifa University of Science and Technology in Abu Dhabi, took place between 23 and 25 February 2020, followed by a symposium in which participants presented papers about their work in robotics. IISc was participating for the first time, in partnership with Tata Consultancy Services (TCS). In the first round of the competition, IISc-TCS was among 14 teams to receive sponsorship based on the proposal they submitted: they were awarded $100,000, disbursed in instalments (though this amount wasn't sufficient to prepare for the competition – additional funds of Rs 86 lakh came from the Robert Bosch Centre for Cyber-Physical Systems at IISc, and Rs 40 lakh and equipment worth over Rs 1 crore came from TCS). Collaborations were allowed with industry, between universities, and even across countries.

Though IIT Kanpur was also initially among the teams selected to participate this year, IISc-TCS was the only Indian team to make it to Abu Dhabi. Among the competitors were teams from universities like Virginia Tech, University of Bonn, Beijing Institute of Technology, Carnegie Mellon University, and Osaka University.

The Challenges

The teams could participate in three challenges: the first was based on unmanned aerial vehicle (UAV) safety and involved attempting to capture and neutralise intruder UAVs within a given area. To do this, teams would have to demonstrate that one of their UAVs could identify a moving target (in this case, a ball trailing from a drone), navigate towards it, capture it, and drop it off in a given location. The second challenge involved using UAVs as well as unmanned ground vehicles (UGVs) to build a structure by identifying large blocks by their colour, and picking, transporting and assembling them. The third challenge involved using three UAVs and a UGV for firefighting. The vehicles would have to autonomously sense and extinguish fires simulated in a building with multiple floors.

In addition, teams could take part in a Grand Challenge – a triathlon that involved taking on all three challenges simultaneously. The IISc-TCS team went in for the three individual challenges as well as the Grand Challenge, with IISc participants primarily focusing on the first two, and TCS primarily handling the firefighting challenge. The team's best performances in the competition were in Challenge 2, in which they were ranked sixth out of 19 teams, and in the Grand Challenge, in which they were ranked ninth out of 17 teams. They also received a $1,000 cash voucher as a special recognition for the technical diversity involved in their solutions and for leading a large team.

Photo: Rolif Lima

Members from the IISc-TCS team in Abu Dhabi

IISc-TCS team members preparing for the international robotics competition at IISc's airfield

A large team it certainly was: 60 people, with 40 from IISc, led by Principal Investigator Debasish Ghose – a professor at the Department of Aerospace Engineering – and 20 from TCS, co-ordinated by Kaushik Das – a scientist at TCS Innovation Labs. The team was divided into five groups working on different aspects of the challenges, and comprised PhD students, postdocs, project assistants and project associates from IISc, and scientists and researchers from TCS based in Bangalore and Kolkata. "We agreed to this partnership [with TCS] because they were willing to invest trained manpower and equipment to this large scale competition," says Ghose. "Their expertise in building vehicles, which we need[ed] for the competition, was invaluable to us. The last, but certainly not the least, [important] factor that played a role in forging this excellent collaboration was that some of the top TCS scientists and engineers who were actively involved in this work were IISc alumni."

The technical diversity they were lauded for was in Challenge 1, where they were ranked 13th out of 25 teams. "For Challenge 1, all other teams used the same type of manipulation mechanism to catch and pop the balloon [which was part of a secondary task]," says Lima Agnel Tony, Student Co-ordinator for the team and a PhD student at the Department of Aerospace Engineering. "We went with two approaches – one was the same forward-facing basket kind as the others, while the second one was a manipulator that extended sideways. Our drone was within the volume specified by the organisers, unique in design, and effective." An additional advantage of their sideways manipulator was that the same drone could be used to pop the balloon, instead of requiring a separate drone for it, as most other teams did.

Photo: Rolif Lima

A drone carrying the blocks required to build a structure as part of Challenge 2 in Abu Dhabi

Technical trouble

But the IISc-TCS team faced a major hurdle after reaching Abu Dhabi. Until that point, they had faced minor glitches in the form of delays in delivery from hardware suppliers, a mismatch between performance using software simulation and using actual hardware, and a crash during testing that meant having to borrow a drone from another department at the last minute. They had been able to overcome these to prepare for the challenges in Abu Dhabi, but one aspect threw them off balance after they arrived: "Because of the Telecom Regulatory Authority rules in India, several of the 20-plus channels in the 5.8 GHz frequency are not accessible by our devices, which could access only six or seven of them," says Ghose. "This would not have been a hindrance but for the fact that the organisers had spread the 20-plus channels selectively over the large challenge arena, and so many channels that we could not access covered large parts of the arena."

This created issues in deploying the autonomous codes, Tony points out, as the architecture they developed depended on inter-vehicle communication. They had to shift between manual mode and autonomous mode for some tasks, for which they lost points. In the second trial, they were unable to use their drone with the novel design for Challenge 1 and had to revert to the same method as the others. "I am pretty sure that we would have been placed way above other teams if communication worked the way we wanted," says Tony – a sentiment that Ghose echoes.

Despite the whirlwind of the last month, Ghose points out that even though IISc-TCS didn't walk away with first place, they learned that their technology was no less innovative than that of other teams. He says, "In the second challenge we were supposed to identify, locate, pick up and place several long bricks, one over the other, autonomously. Our algorithms could do this so perfectly that the brick wall we built was perfect and looked like a wall that a mason has laid! On the other hand, none of the other teams could demonstrate this." He credits the superior image processing and vision techniques that the team employed, integrated with the operation of a UGV-mounted manipulator arm, for their success.

"We developed many new technologies in designing grippers of various kinds, autonomous algorithms for multi-vehicle coordination which were implemented and shown to work, search algorithms, vision-based techniques, development and effective use of artificial intelligence and machine learning techniques, etc. Many of these are patentable and most will appear in journal and conference publications. In fact, in the symposium which followed the event, we had the maximum number of papers on new ideas," says Ghose.

The experience of participating was an incredible opportunity, says Tony. "Every difficulty gave us an opportunity to learn and progress. Interactions with other teams and their mentors were meaningful. We met many acclaimed professors in our field. They were quite open and were ready to answer any of our queries."

Though the last few days of testing in the airfield at IISc were certainly nerve-racking, Tony says that the time spent there was "beyond doubt" the most fun part of the preparations. "It was indeed a joy seeing the autonomous codes working flawlessly," she says. "Irrespective of the end result, the two-year journey means so much to us as it moulded our team into one big family."

The beauty of quasicrystals continues to attract me

- Srinivasa Ranganathan

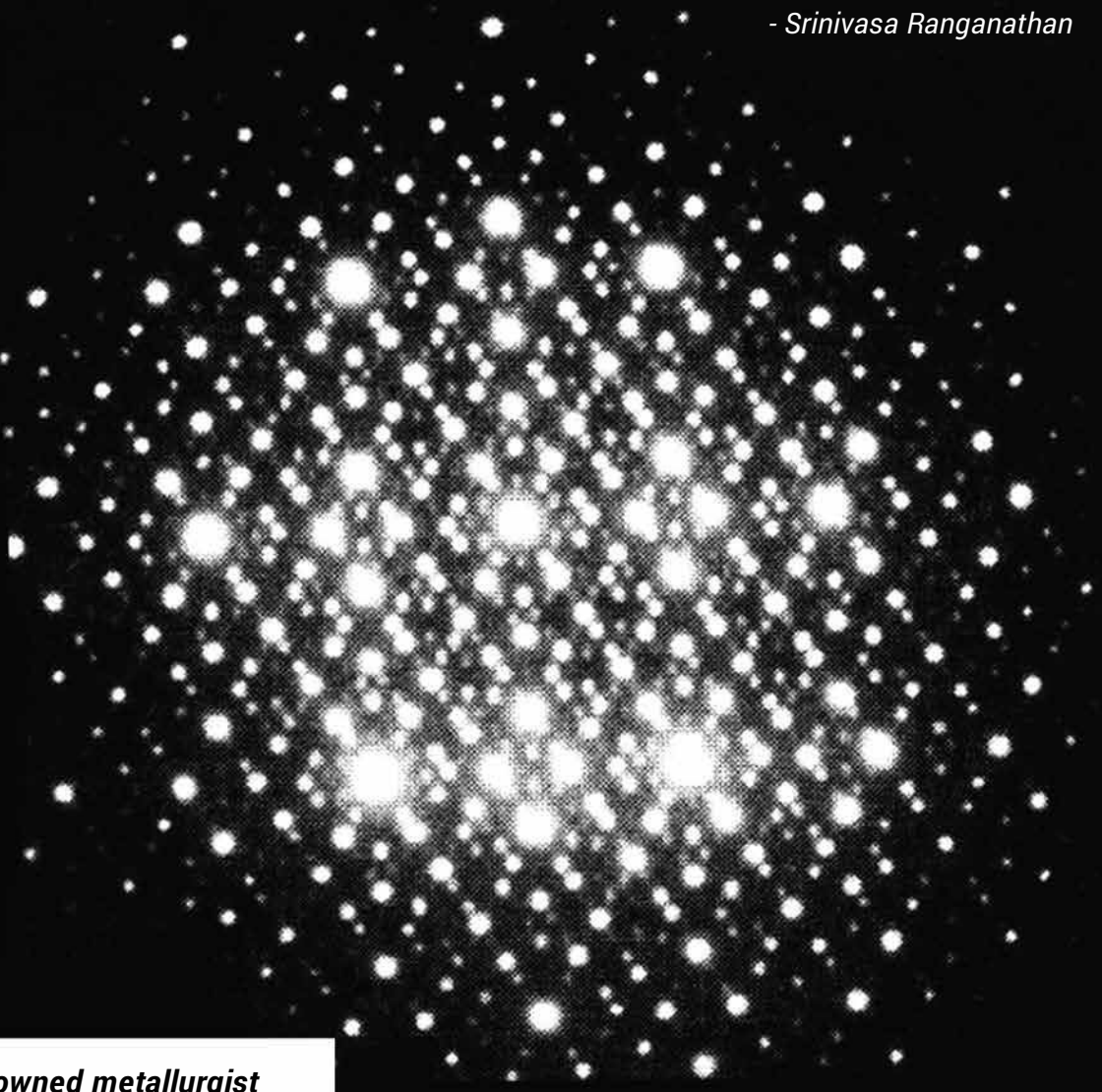


Image courtesy: Alok Singh

A renowned metallurgist on his relationship with geometry, Japan and more

Electron diffraction patterns of Al-Cu-Fe quasicrystal, the first stable and perfect quasicrystal known

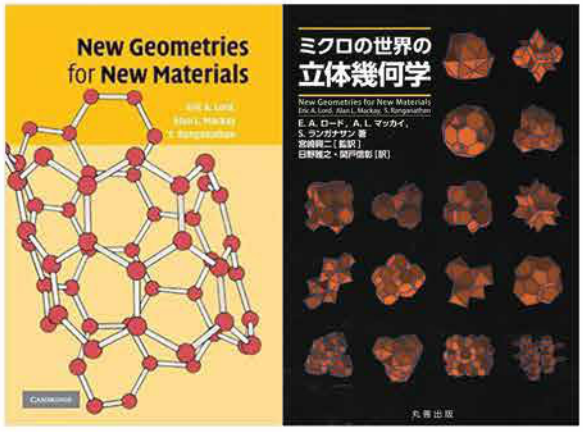
My work has involved studying the geometries of materials such as crystals, glasses, twin boundaries, grain boundaries, and quasicrystals. Quasicrystals open new windows into the architecture of solids. Their beauty continues to attract me and I have worked on them for close to 36 years.

Quasicrystals or quasiperiodic crystals are important because they tell us how matter is organised. Scientists used to believe that solid matter existed in only two states – crystalline and amorphous. Crystals, especially minerals, have fascinated humans from early times. Their beautiful shapes were attributed to periodic and ordered arrangement of atoms. But quasicrystals mark a paradigm shift – they are ordered but quasiperiodic. They follow the Fibonacci sequence and can repeat a motif upto infinity, without being identical. We see examples of quasicrystals in Islamic art like the Alhambra palace in Spain, where geometry is used so beautifully. It has been shown that they can also occur in meteorites.

We see examples of quasicrystals in Islamic art like the Alhambra palace in Spain, where geometry is used so beautifully

In 2006, a book that I co-authored with Eric A Lord and Alan Mackay, *New Geometries for New Materials*, was published. Soon after, it was translated into Russian, and most recently in December 2019, another translation was published in Japanese.

There were many influences that led to the point where I got involved in contributing to the book. I have been fortunate to have worked with a large number of mathematicians without any of them figuring out that I was not a mathematician myself! They could tell that I had a feel for it, perhaps. But the truth is that I did not study mathematics beyond Intermediate. I obtained my BSc (Hons) in Chemistry from the University of Madras, BE in Metallurgy at IISc, and PhD in Metallurgy from the University of Cambridge in the UK.



(Left) The 2006 edition by Cambridge University Press. (Right) The 2019 Japanese edition published by Maruzen

It was while I was at Cambridge between 1962 and 1965 that the book *Introduction to Geometry* by HSM Coxeter drew my attention. Coxeter is believed to be one of the greatest geometers of the 20th century, and his book was so lucid that I was able to clearly grasp what he said about concepts like polytopes – geometric objects extending polygons and polyhedra to higher dimensions. I even corresponded with him and was thrilled to receive a reply. From his work I learned that geometry links not just inorganic materials, but biological materials too, like DNA.

My first paper, "A field-ion microscopic study of the atomic configuration at grain boundaries in metals," published in 1964, became a citation classic. In writing about the genesis of the paper, my doctoral supervisor at Cambridge, David G Brandon, made a reference to me having been inspired by Coxeter's polytopes.

Brandon had also been supervisor to Dan Shechtman, the Israeli metallurgist who in 2011 won the Nobel Prize in Chemistry for the discovery of quasicrystals. In 1984, Shechtman published a paper on the quasicrystalline configuration in a metallic alloy. And nobody believed him. It took 30 years for the Nobel Prize committee to recognise his work. Shechtman and I didn't just share a supervisor – we also share the same birth date, month and year! When I was a child, my parents changed my date of birth on paper by a few days so that I could gain admission to Loyola College, Chennai. I like to joke that if they hadn't, I might have won the Nobel Prize too!

Dan Shechtman and I didn't just share a supervisor – we also share the same birth date, month and year!

In addition to Coxeter, I was deeply influenced by articles in the Mathematical Recreations section of *Scientific American* by Martin Gardner, the English mathematician Roger Penrose's 1974 paper on tiling which contributed to the eventual modelling of quasicrystals, and by the British metallurgist Cyril Stanley Smith, who emphasised that the information contained in the structure of materials is vital. In 1981, I returned to IISc where I collaborated with Kamanio Chattopadhyay in the Department of Metallurgy and we discovered decagonal quasicrystals. We published our first paper together in 1985, within months of the appearance of Shechtman's seminal paper. Over the years, a number of gifted students, including Alok Singh who now works at the National Institute for Materials Science, Japan, also did their theses on quasicrystals under my supervision.

Photos courtesy: Shounak Roy; Koji Miyazaki; Wikimedia Commons, CC BY SA 3.0; Eric A Lord

(Clockwise from top left) S Ranganathan, Alan Mackay, Koji Miyazaki, and Eric A Lord

In 1987, I met Shechtman at a quasicrystal conference in Beijing. There, I also met the British crystallographer Alan Mackay. Numerous papers by Mackay on generalised crystallography and discussions with him influenced me tremendously. His 1981 paper on "De Nive Quinangula" predicted structures that traditional crystallography did not allow – like quasicrystals. This was reminiscent of Johann Kepler's "De Nive Sexangula", which in 1611 tried to describe why snowflakes have a hexagonal symmetry. It ignited my mind.

Back in Bangalore, I met Eric A Lord, a mathematician who was a visiting scientist at IISc, and had the good fortune of collaborating with him. Eric and I wrote a paper on Truchet tiles and another on the transformation of polyhedral grains. He translated several of my ideas, in particular those on quasicrystals and biological helices. His ability to visualise geometry and shape is unparalleled. Alan and Eric worked on periodic minimal surfaces and published several papers together.

The book *New Geometries for New Materials* came about because I was teaching classes at IISc on geometries – on intermetallics and so on. I took Eric's help because I had the metallurgical concepts, but needed to put them into mathematical form. After all, geometry is all-pervasive in our studies of materials. Alan joined us too. Cambridge University Press published the book in 2006. Years later, Koji Miyazaki, from the Graduate School of Human and Environmental Sciences, Kyoto University, made the Japanese edition possible.

I have had a long and enduring relationship with Japan, beginning in 1966 when I was on a personal visit to Kyoto. In 1993, I was invited to Japan by Akihisa Inoue, a scientist at Tohoku University who made seminal contributions by inventing bulk metallic glasses. My collaboration with Motoko Kotani at Tohoku needs to be highlighted as it is perhaps the first time that the fusion of mathematics and materials science has been central. My collaboration continues with Miyazaki, whose insights into geometry are phenomenal. He generously gifted me several books, including his *Adventure in Multidimensional Space: The Art and Geometry of Polygons, Polyhedra and Polytopes*, which has been an important influence in my career. Since Japan is the foreign country I have visited the most – over 20 times – the publication of this new edition is an extremely pleasing development and cements my relationship with Japan and Japanese scientists. Its title in Japanese is "Solid Geometry for the Microcosm".

It seems appropriate that while the earlier editions of the book appeared in the Heisei era, the translation into Japanese appears in the Reiwa era which has just dawned, and stands for harmony and beauty.

(As told to Deepika S)

Srinivasa Ranganathan is a metallurgist and former Chair of the Department of Materials Engineering and the Division of Mechanical Sciences, IISc, and Honorary Homi Bhabha Chair at the National Institute of Advanced Studies.

A Martian Odyss

- Ritu Karidhal

Ritu Karidhal completed her MTech from the Department of Aerospace Engineering, IISc, in 2003. A senior scientist at the Indian Space Research Organization (ISRO), she has participated in many of its critical missions, including the recent Chandrayaan-2. As a Deputy Operations Director, Karidhal played a key role in steering the Mars Orbiter Mission (MOM), India's first interplanetary mission. MOM, also called Mangalyaan, was launched on 5 November 2013 and has been successfully orbiting the Red Planet since 24 September 2014.

For her contributions, Karidhal received the IISc Distinguished Alumna Award in December 2019 at the Institute's annual alumni reunion. The following is an edited transcript of the talk she gave at the event.

Indian astronomy was at its peak in the 5th century under the great astronomer Aryabhatta. Then, due to waves of invasions and colonisation, India faced a decline in science. Not until independence in 1947 could we make a fresh start.

The story of India's space programme goes back to the 1960s, to the vision of the great physicist Dr Vikram Sarabhai who wanted to use space technology to solve the problems of the common man and society. But it was not an easy task for him to convince the government of the day about the relevance of the space programme to the nation's development. Eventually, he obtained the funds needed for the programme to begin.

The Indian space programme had very humble beginnings with extremely limited resources. In the present, we see so many sophisticated labs and testing centres. At that time, we did not have good infrastructure. All the work started in a little shed.

In 1975, we had our first satellite launch, but that was with the help of the USSR. We had our first major breakthrough with Chandrayaan-1. This mission detected water on the Moon for the first time, thus creating history, and proved that India's and ISRO's satellites could also contribute to major discoveries in space.

After this, our next goal was Mars.

Why Mars?

I've heard many people, even students and small kids, asking why we should go to Mars or the Moon. I see three main reasons why.

One, there are many unanswered questions about Mars. Is there any life on Mars? Is there water? Is colonisation possible in the near future? Most importantly, can we learn something about the Earth's past or predict its future? Billions of years ago, Mars had an abundant amount of water and a sufficiently thick atmosphere. But then, over the years, while our planet flourished with life, Mars lost all its features which could sustain life. The data which we can collect using our instruments can tell us something more about why this happened.

Photo: Jagadesh

ey

Ritu Karidhal at IISc's annual alumni reunion in 2019

The second reason is improving the quality of life on Earth itself. For example, a computer algorithm that was developed for one of the space programmes to take X-ray images did a better job of detecting breast cancer in its initial stages than the conventional method. When we do some work in one field, it may lead to a revolutionary change in another field. This cross-pollination can lead to a better quality of life.

The third reason is to inspire the next generation of space explorers who can contribute to the growth of the nation.

This is why ISRO's next venture was the mission to Mars.

Uncharted territory

One of the toughest challenges was completing this project in 18 months, when we did not have any legacy. We had been to the Moon, and we had the satellite that revolved around it. But that mission was limited to operating in Earth's gravity. We did not have any experience in how to leave Earth's gravity-well and enter a different one.

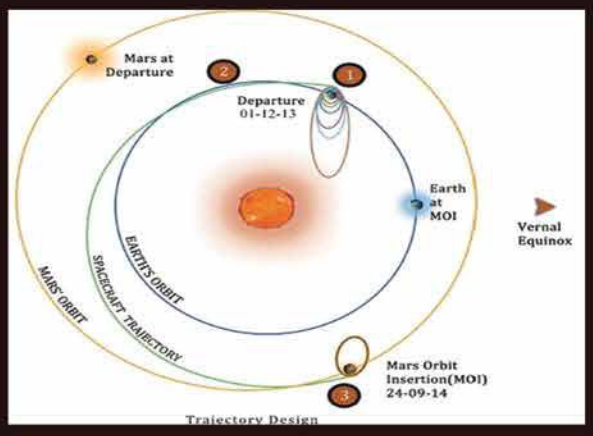
Another challenge is that, the farther we go, the longer it takes for the signal to reach us. The maximum distance from Earth to Mars can go up to 400 million kilometres. At this distance, the signal may take 20-40 minutes to reach us.

> It meant that we had to build systems that are capable of self-diagnosis and self-recovery, because micromanagement from the Earth is not possible. Onboard autonomy was a totally new venture for us. We had many brainstorming sessions with engineers from all fields: mechanical, computational, thermal, structural, sensors, and so on. We built a network of autonomy with different levels of fail detection, isolation and recovery. Thousands of lines of code were implemented on the onboard computers, thoroughly tested and reviewed.

At this time, 51 such missions had already been attempted in the world and only 21 had been successful. No one had done it in their first attempt. We were also really struggling hard to get the hardware and software in place. But in the end, within 10 months, we could achieve the target.

Made in India

Image courtesy: Ritu Karidhal



Designing the precise trajectory that would take MOM to Mars

All the parts of the satellite were indigenously developed. One was the propulsion system, which provides the thrust and energy to leave Earth's gravity-well and enter Mars' gravity-well. The engine used was adapted from one of the earlier geosynchronous satellites. The main challenge was that it had to work after sleeping for 10 months of cruising, and re-ignite at the correct time.

Other major elements were the antennas, the "ears" of the spacecraft. We had three different types of antennas: low gain, medium gain and high gain. The low-gain antenna has a bigger beam, for short distances. Once we go deep into space, the antenna size increases and the beam width decreases. The main challenge was to perfect the sensitivity of the high-gain antenna to work and respond at a distance of 400 million km. This is similar to hearing a person's whisper across a soccer field.

Another challenge was to maintain the orientation of the satellite so that it is always in line with the Earth, to ensure that communication is not lost. The antenna had to respond at all times, at both nearest and farthest distances from Earth.

We also had to plan a precise trajectory that would take the satellite from Earth to Mars. Our main requirement was minimum fuel use, because we had to limit the weight of the spacecraft to a given amount or else the launch vehicle will not be able to lift off.

At the Sriharikota Range, when any launch vehicle lifts off, it injects the satellite either over Mauritius or near the east coast of Australia. But here, our requirement was that the launch vehicle should inject the satellite over the west coast, in the Pacific region. The injection point would have to be over the ocean, but we did not have any ground station, control centres or antennas over the ocean. So we decided to deploy two ships, which took two months to reach their destination.

Very close to the launch dates, bad weather conditions over the Pacific delayed us by 10 days. We were racing against time. Finally, on the 5th of November 2013, our mighty PSLV [Polar Satellite Launch Vehicle] took off and put the spacecraft into its first parking orbit successfully.

Photo courtesy: Ritu Karidhal

Launch of the PSLV carrying the MOM spacecraft from the Satish Dhawan Space Centre SHAR, Sriharikota

The next unique part was the slingshot trajectory [a slingshot uses the gravity of a planetary object to give the satellite speed and save fuel]. With each operation, each burn, every time the satellite comes close to Earth, we impart some extra energy so that the orbit's maximum distance keeps on increasing. Each operation demanded accurate performance. If we missed anything here, there would be a fuel penalty and we may not have been able to leave Earth's gravity.

Twenty-five days later came the final manoeuver: a final energy transfer to the satellite to leave Earth's gravity. Many missions of NASA, or from Russia, Japan and China, have failed at this stage. But India and ISRO made history on 30 November 2013 when the satellite left Earth's gravity in its first attempt.

The satellite had to follow the direction and path precisely. NASA scientist Charles Elachi [Director, Jet Propulsion Lab] described our challenge with an example: If you hit a golf ball from India towards a hole located near Los Angeles, the ball has to fall straight into the hole. To make it a little bit more challenging, the hole is moving.

We had to track the path and the direction very closely, and also watch for any disturbances such as solar radiation pressure, using technologies that were new to us, such as two-way doppler and delta-DOR technology.

21 minutes of terror

After travelling 650 million km in 10 months, the spacecraft finally reached within 500 km of Mars. But this did not mean we had completed the mission.

When a satellite nears a planet, the planet exerts its gravitational force on it and the satellite's energy increases. When the energy is increasing, it cannot fall into the planet's gravity-well. It will merely fly by. So we had to perform a precise manoeuvre where we had to kill the satellite's velocity to a very precise value so that it falls into Mars' gravity-well.

Photo courtesy: Ritu Karidhal

Ritu Karidhal at the ISRO Control Centre during insertion of the PSLV into Mars' orbit

Then, D-Day arrived. As the deputy operations director, my team and I were responsible for ensuring that this operation takes place as planned. There would be no second chance.

On the 24th of September 2014, around 7 am IST, we got the first signal from the satellite indicating the correct start of the onboard sequence. Twenty one minutes later, the engines started firing, and that was the time when everyone thought that, yes, 50 percent of the mission has been achieved.

But then, four minutes later, the signal stopped. What had happened?

Actually, the satellite had gone behind Mars. The geometry was such that when this operation was happening, Mars was blocking the antennas. We were not getting any signal.

For those 21 minutes, all eyes in the control centre were glued to the screen, waiting for the signal to come back. There was utter silence in the whole centre. And then, at 8 am IST, history was made. The Mars Orbiter Mission successfully entered the Martian orbit.

Mission with many firsts

This Mission had many firsts:

This was the first Mars mission to succeed in its first attempt.

It was the most economical interplanetary mission in the world (Rs 450 crores; other contemporary missions are estimated to have cost ~Rs 6000 crores).

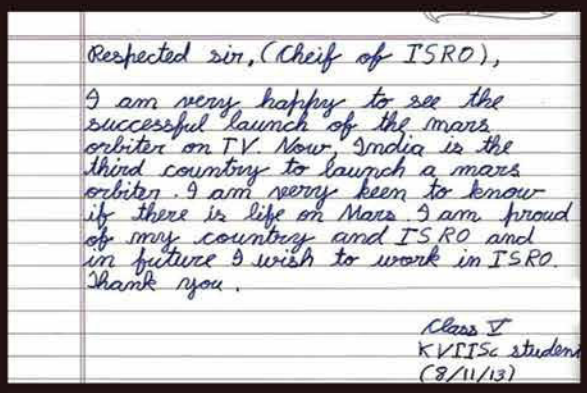
It was realised in the shortest time – within 18 months.

It was the first Indian satellite that had full-scale onboard autonomy.

The youngest team of women and men scientists worked for this mission.

Now the Mars Orbiter Mission has completed five years. It is continuing to send huge amounts of data. With a bird's eye view, we can capture both the north pole and the south pole of Mars, and also see how the dynamics of the atmosphere change. It has many instruments that keep sending data, and all this data is available for research students to analyse.

But I feel that the most important contribution of the Mars Orbiter Mission can be seen in a letter written by a young boy to the Chairman of ISRO, stating how proud he feels of ISRO and how he desires to join ISRO.



Respected sir, (Cheif of ISRO),

I am very happy to see the successful launch of the mars orbiter on TV. Now, India is the third country to launch a mars orbiter. I am very keen to know if there is life on Mars. I am proud of my country and ISRO and in future I wish to work in ISRO.

Thank you.

Class V
KV IISc student
(8/11/13)

Photo courtesy: Ritu Karidhal

Letter written by a young boy to the Chairman of ISRO praising the successful launch of the Mars Orbiter Mission

This Mission created and stirred inspiration in the mind of every Indian student. It created awe and fervour towards science in the whole country. The biggest thing that the Mission achieved is empowering 1.3 billion people, and making them realise the inner strength and power of Indians to reach a far-off planet, and showing to the whole world that we are second to none.

What is AI good for?

- Pratik Pawar

Photo courtesy: Jay Yagnik

In his 15 years at Google, Jay Yagnik has led many foundational research efforts in machine learning and perception, computer vision, cybersecurity, quantum AI, and more. He has contributed significantly to the success of some of Google's most popular projects, like Google Photos, YouTube, Search, and Maps.

An alumnus of IISc, Yagnik was back at his alma mater for a public talk on 4 December 2019. Following the talk, in a brief sit-down, he spoke about artificial intelligence (AI), his work at Google AI, the ethical and moral concerns of this technology, and on the apocalyptic notions often associated with the predicted disruption.

Tell us a bit about yourself and your journey from being a student at IISc to Google.

It has been a good journey. Back when I was at IISc, I used to work on machine learning and computer vision. My thesis had an intersection of both, and I'd imagined working for some biometrics company, doing facial recognition and related things. Through a series of coincidences or [because of] people I met with an open mind, I ended up talking to Yahoo Labs at the time. I figured if I'm talking to one search company, why don't I talk to the other, and that's how I ended up talking to folks at Google. I walked out of those conversations with a very distinct impression: there was a lot of intellectual bandwidth. I was forced to think hard, even in real-time as the topics were evolving, and I took that as a very positive sign for the work environment I would have if I were to join them. So I took a leap of faith and ended up making that move.

When I joined Google, the number of people who spoke [about] computer vision, machine learning and those domains, you could fit them all in one conference room, which we did back in the day. As we were starting on the early projects, I made a conscious choice to do projects that were different from what I had worked on. So some of the early projects I took on were in the video analysis domain, and those ended up panning out. As I gained more exposure to the Google environment, I saw very clearly that we were sitting on some very unique assets. We were a search company, so we had all this web data, text data, we had Google Video and YouTube afterwards. I drafted a research agenda of building systems that look at images, read the surrounding text, look at videos and learn automatically, and that ended up being a good long-term trend. Over time, that led to some 18-20 projects that made many interesting things happen.

I then ventured outside [computer] vision into graph algorithms, into mainstream machine learning, and computer science theory. Every time I switched to a new domain, it gave me a chance to think afresh. Over time, [it] helped me to get a good top-down view of these technical fields and gave me this realisation that we are solving roughly the same set of problems over and over in different disciplines with slightly different names and slightly different variants and environmental constraints.

Can you tell us what artificial intelligence is, perhaps by contrasting it to natural intelligence?

Actually there is more than one definition of AI, but they all point in roughly the same direction. I guess in layman's terms, it is to build systems that exhibit behaviour that people would say is intelligent and is beyond a set of simple rules that are prescribed. If you go deeper than that, there are notions of what we call artificial general intelligence (or AGI), which is to build systems that, when put in arbitrary environments, can exhibit intelligent behaviour given the constraints of the environment. They're not task-specific but task-agnostic. We are still far from realising those versions of AI. The things that are working very well today are what we call task-specific AI, where you're building say, natural language understanding systems or machine perception systems or systems that are making recommendations or ranking or personalisation of various forms. They end up being very useful in practice, but they are built for a [specific] task or set of tasks.

> *When you talk about research, there's a lot of activity around AGI [Artificial General Intelligence]*

So that's state of the art today. When you talk about research, there's a lot of activity around AGI. There are teams that pursue the reinforcement learning view of the world, which is task-agnostic. You put the agent in an environment, and you give the agent reward signals, [and] it learns to gain more reward and [do] whatever it takes to get there. There are other approaches like extreme multitask learning – if you build one system that understands images and video and also understands the text and is also a dialogue system, eventually it's forced to learn intermediate representations that are shared across all of these, and that would lead to this notion of general intelligence over time. All of these are active research trends. But what you see in products and practical applications are more of the narrow AI because it's easier to integrate [it] into the context of a product which requires a specific question to be answered.

Can you give us a sense of some of the areas where AI is being used today and what sort of problems it is being used to address?

In any place where we are trying to associate some input with either a numerical value or a tag or a natural language outcome, [we] use machine learning and AI systems today. The examples I gave in the talk were in the context of AI for social good. For example, flood forecasting – predicting which specific terrain is likely to be flooded if a river overruns. Another would be in detecting diseases in plants, where you take a picture of the leaf, and categorise that picture into [either] a healthy leaf or one with a specific disease. If you look at Google Assistant, there you are providing a natural language interface. So your input is raw audio samples which in the intermediate state get converted into text, and through a variety of other machine learning transformations, then leads to a response in natural language, which is hopefully the answer to the intent you were expressing.

Let's say you have a problem, like detecting the likelihood of developing cancer based on MRI scans. When an AI system arrives at a solution, we don't have a sense of how it solves the problem – it is essentially a black box. How do we trust such a black box?

First of all, the AI system doesn't have to be a black box. That is often a stereotypical characterisation, but AI systems can be made to work with people in the loop. We have many demonstrations of the same. If you look at our work in the health space, where we use medical records to predict the possibility of adverse outcomes in a hospital setting, the AI doesn't just predict the probability of an adverse outcome, it then goes back to the case history and picks out a small number of things so that the doctor can actually look at [and determine] which of them are statistically significant. So the way it manifests itself in practice is that the system says: "Looks like there is a greater than 80 percent chance something might go wrong with this hospitalised patient, and from their entire lifelong case history, here are five things you should really look at."

So, in that case, AI, in a way, is not replacing the doctor but rather augmenting their ability to diagnose.

Yes, it's both augmenting the person and also scaling and leveraging their abilities. If you take our work on diabetic retinopathy, we find this to be pretty much the case. Expert ophthalmologists are very rare [in many places]. Over two to three years, we managed to get that to work to a level where the accuracy of that system is on par with experts in the domain. When we look at countries like India or Indonesia, where we are actually using these systems, the ratio of ophthalmologists and people who need to be screened is very skewed. So here's a way in which ophthalmologists can use their knowledge to look at cases which are borderline and require more nuanced expert opinion. And even when those cases come to the ophthalmologists, it doesn't come as a black box; the system has already attended to parts of the image. It also explains the output that it is giving.

Alongside these medical use cases, you alluded to a few other applications where AI can have societal impacts. Can you tell us a bit about that?

Yes, if I stick to AI for social good, we've been doing some on-device machine learning. We open-sourced parts of it, which an NGO, Rainforest Connection, picked up. They did this fascinating thing where they took old recycled Android phones, ran audio processing models on them, connected them to solar chargers and put them up on trees in the Amazon rainforest. These things look out for audio of bulldozers and chainsaws. And in real time, they alert the authorities to illegal deforestation activity. These kinds of interventions are only possible with the technical capabilities that AI is uniquely unlocking.

Image courtesy: https://unsplash.com

Google Home, a smart speaker, employs AI and natural language processing to understand spoken language and answer queries in real-time

In the Indian context, we've recently funded the Wadhwani AI Institute. I mentioned [in my talk] the project around the cassava plant imaging; they are doing something similar for agriculture in India. We've funded that through our Google.org AI impact challenge grant. We're also doing work on the analysis of satellite imagery, which over time can lead to a better understanding of agriculture patterns, resource allocation and so on.

Another compelling use in the Indian context is this product called Google Lens, where you can point your camera at what you're looking at and it will bring up an

experience that is relevant to the picture. People who cannot read can use Google Lens and point at a piece of text. It will recognise the text, OCR it, and if necessary, translate it into a language that they understand and read it to them. This is now also allowing people who are illiterate to actually transact in the real world because they are able to read and understand what's happening through this augmentation.

These are all cases where AI can be used for social good. But many commentators have also discussed the potential threats of AI – that we could lose control over the very things we have built. What are your thoughts about such concerns?

A lot of those narratives are coming from science fiction. What we find is that people tend to be very bimodal when they make these assessments. For example, a lot of people assume that if you achieve AGI, then it will have some version of a consciousness of its own. But if you look at the research, the more formal notions of AGI do not require these things to be present. It's unclear if they are necessary for intelligent behaviour. Really well-meaning people, because they are not practitioners in the field, can take two or three of these questionable assumptions and then jump to these conclusions. What we see in practice is that these things, when done with the right product mindset, can unlock some tremendously useful capabilities.

Barring apocalyptic notions of AI, there's also a moral concern. For instance, if a self-driving car gets into an accident with another car, one model of morality could make the car save as many lives as possible. But if you were driving your own car, your first instinct would be to save your life first and not necessarily worry about other lives.

If I were to be precise, I wouldn't use the term *morality*. I would say *ethics* because morality is an overloaded word and depending on perspective and population group, it has different meanings. The question of ethics in AI is an important one, and at Google, we wrote down our AI principles. It's a collection of seven principles that practitioners need to be cognisant of in all of the macro decisions that they are making in building a system. There are things like fairness. [For instance, we could ask], "Is the machine learning system that you're building producing equitable outcomes for different population groups?" And if you are careful algorithmically in building these systems, they can actually lead to more equitable outcomes.

So it's not just things that could potentially go wrong. There is a tremendous amount of opportunity to reduce societal bias and bring equitability in societal processes through this. Ethics as a field has had more than two centuries to develop. It has a lot of models to offer us in this context. We've also drawn red lines on some of the applications we will not pursue because they are not in line with these principles. For example, we have said that we will not pursue AI applications in autonomous weaponry or things that are directly intended to cause harm in one form or another.

Where do you think AI stands currently and where it will be in the next 20-25 years?

Take the evolution of photography as a technology. There have been several inflexion points, where photography merged with other disciplines. A lot of those inflexion points have to happen with AI, like AI and healthcare, AI and social sciences, AI and programming. I think those have to fully play out over the course of more than a decade. AI itself, in a technological sense, has to develop much more. Because if you look at the parts of AI that are really working well, it's the subset that we call supervised machine learning: you collect data, you then apply a class label to this data, and eventually train a machine learning system to map from input to the class label. That explains a vast number of use cases that are successful today. If we had this talk 10 or maybe 15 years from now, we would be at a point where AI and machine learning is more like a turnkey system that is not too data-heavy, and you can talk to it for a little bit, and it starts exhibiting intelligent behaviour. That would be a pipe dream today, but hopefully a reality a decade from now.

Google AI recently started a lab in Bangalore, India. Can you tell me a bit about the lab and what it intends to do going forward?

Yes, we recently started an AI lab in Bangalore. Google has a presence in India and in Bangalore, where lots of product development happens, but the emphasis of the AI lab is research. The goal of this lab is to be a world-class research lab, and it will be a peer to all of our other research outlets worldwide. Over time, it will also engage in some Google product development but driven by research activities.

(This interview was jointly conducted for *Connect* and *Current Science*, where a version of this interview has also appeared)

Pratik Pawar is an S Ramaseshan Fellow at Current Science

'I had developed an emotional attachment with the Institute'

- Kavitha Harish

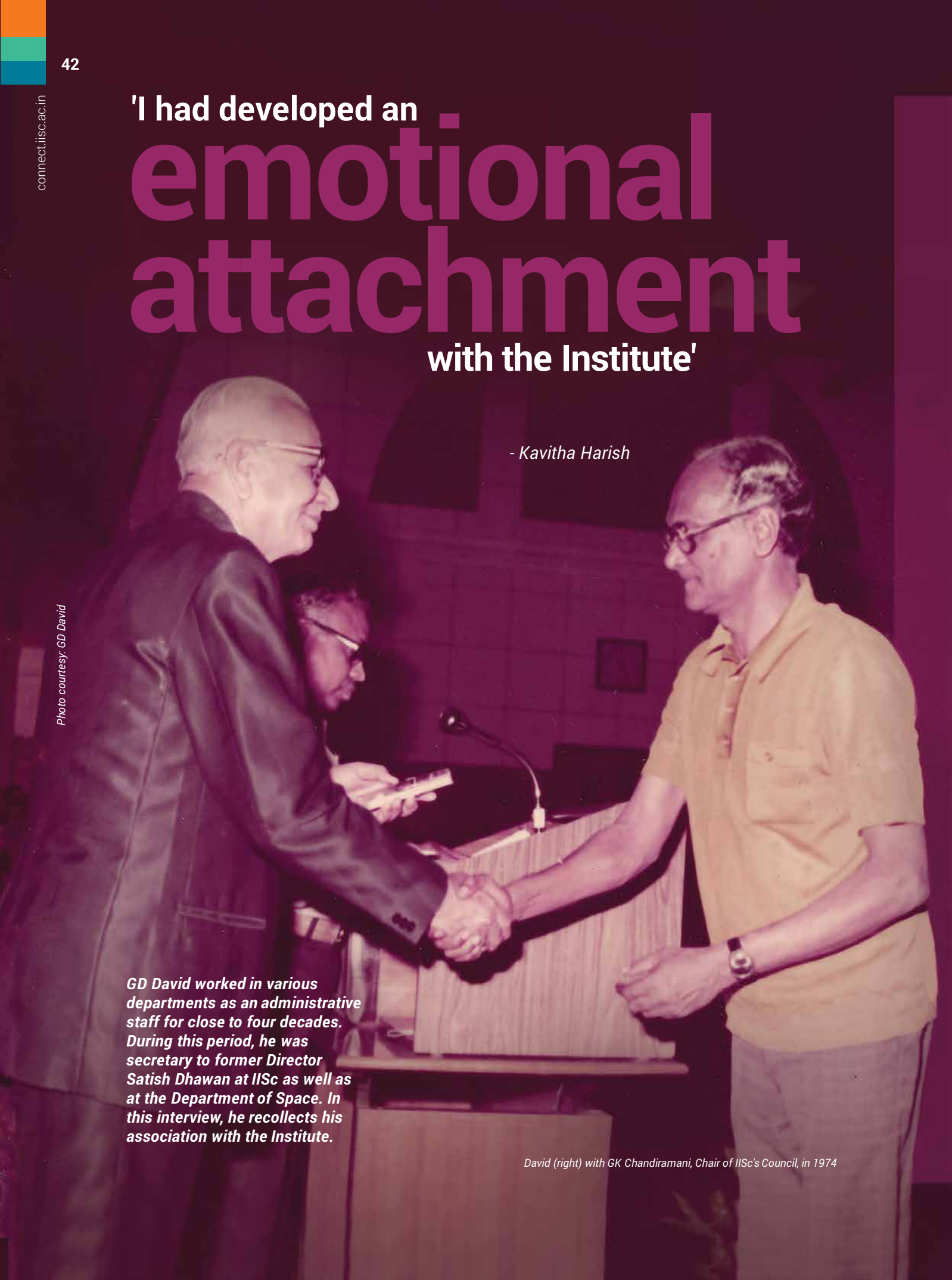


Photo courtesy: GD David

GD David worked in various departments as an administrative staff for close to four decades. During this period, he was secretary to former Director Satish Dhawan at IISc as well as at the Department of Space. In this interview, he recollects his association with the Institute.

David (right) with GK Chandiramani, Chair of IISc's Council, in 1974

When and why did you choose to join IISc?

I joined IISc in 1949. Before that, I was working for the state government. My father, the late Mr G Devaneson, who was then working at the Department of Aeronautical Engineering, informed me about an advertisement for administrative staff positions at IISc. As I had the requisite qualifications and a few years of relevant experience, I applied for the position and was selected.

What did your work involve?

My first posting at IISc was to the Registrar's Office. Mr AG Pai was then the Registrar of IISc. After working for three or four years there, I was transferred to the Students' Section, where I handled the theses and dissertations submitted by the PhD and MSc (Engineering) students for further processing. My work at the Students' Section was highly challenging. I had to maintain a high level of confidentiality in contacting the external examiners, and coordinating with the IISc Council and the Senate. But I thoroughly enjoyed this work. Working in the Students' Section enabled me to interact with many of the faculty members and students, which helped me develop a good rapport with many of them.

After serving for four or five years at the Students' Section, I was transferred back to the Registrar's Office. By then, Mr Prabhu had taken over as the Registrar. I was transferred to the Director's Office in 1974, when Prof Satish Dhawan was the Director. He was also the Chairman of the Indian Space Research Organization and Secretary to the Department of Space (DoS), Government of India. I served as the private secretary to Prof Dhawan both at IISc and the DoS, between 1977 and 1981. I had an opportunity to continue my remaining service period at ISRO with a much higher position than the one that I was holding at IISc. However, I decided against it as I had developed an emotional attachment with the Institute.

What are your recollections of working at the Director's Office?

On several occasions, I had the opportunity of receiving high-level dignitaries, heads of states, and other renowned people who visited the Institute. I was particularly fortunate to welcome and receive several people associated with the Tata Group, including Mr JRD Tata, Mr Ratan Tata and Dr JJ Bhabha during their frequent visits to IISc.

Did you work in any of the departments other than admin offices in the Main Building?

After Prof Satish Dhawan superannuated in 1982, I was transferred from the Central Office. I worked as the Superintendent at the Guest House; I also worked at the Centre for Scientific and Industrial Consultancy, and the Department of Computer Science and Automation. I was due for retirement in 1987. Around that time, the National Institute of Advanced Studies (NIAS) was started by the Tatas on the IISc campus. The late Dr Raja Ramanna was appointed as the first Director of NIAS, and he was on the lookout for an executive secretary. Prof CNR Rao, the then Director of IISc, recommended my name to Dr Ramanna. With less than a year's service left at IISc, I opted for voluntary retirement and took up the offer from NIAS to work as the executive secretary to Dr Ramanna from 1987 to 2002. I am thankful to Prof Rao for recommending my name to Dr Ramanna, and to NIAS for providing me an opportunity to work there.

After completing my term with Dr Ramanna I had several other offers but I did not accept any of them. After having had a long career of more than five decades, I have been thoroughly enjoying my post-retirement years with family and friends, and taking part in religious activities.

Photo courtesy: GD David

David (centre) at NIAS, with (from left to right): CV Sundaram, Maj. Gen. (Retd.) MK Paul, Raja Ramanna, and MN Srinivas

What did you do outside of work?

Although my job kept me fully occupied, I used to take time off at the Institute clubs, initially at the Tata Memorial Club (TMC), playing tennis and bridge. I was part of the TMC Managing Committee as its general secretary for three years. Later, when I got the membership for the Staff (Faculty) Club and Gymkhana, I used to enjoy playing billiards, snooker and bridge. I have represented IISc in a number of billiards, snooker, and bridge tournaments in Bangalore.

What are your best memories of your time at IISc?

From 1967 to 1987, I stayed on the campus at staff quarters No 10. My family and I thoroughly enjoyed our stay on campus. All our neighbours were more of an extended family than merely neighbours. For example, if we ran out of essential kitchen items – the nearest shop selling these items being at least two kilometres away – invariably our immediate neighbours would come to our rescue. The help and support extended by our neighbours was remarkable.

The

IISc's neighbourhood has a long and rich history

Hulibete veeragallu in IISc

Photo: KG Haridasan

In the late 1890s, JN Tata was hunting for a suitable location for what eventually came to be known as the Indian Institute of Science (IISc). By the early 1900s, Bangalore had become the frontrunner to host the research institute, not least because of the wholehearted support it received from Mysore State. Besides startup capital and an annual grant, the State promised to provide land in the city for Tata's ambitious initiative, an offer both Tata and the Government of India found hard to resist. And thus IISc found a home in Bangalore. While the story of how the Institute came to occupy 371 acres and 11 guntas of prime real estate in the north of the city has been well chronicled, we are only now beginning to piece together a deeper historical account of the land in and around IISc.

land on which we stand

- Udaya Kumar PL and Karthik Ramaswamy

Hulibete veeragallu in IISc

One day, in the late 1970s, young Vibhavaree and Sameehana excitedly dragged their father through thorny shrubs in the northeastern part of the campus of IISc, where the family lived from 1976 to 2002. "I was truly shocked that the children were wandering around snake-infested areas in the campus," recalls their father SN Balasubrahmanyam, who was then a professor in the Organic Chemistry Department. Still recovering from the shock, he followed his children as they scurried along the unkempt terrain. He was eventually led to a stone, which Vibhavaree and Sameehana had accidentally stumbled upon. The children's excitement was justified – this was no ordinary stone. It was a veeragallu.

A veeragallu – or hero stone – is a stone sculpture erected in honour of a person martyred in an act of extraordinary valour. Most veeragallus commemorate civilians and rarely soldiers or royalty. The sculpture typically depicts the martyr in action: defending his or her town against enemies (ooralivu veeragallu), fighting a boar (handibete veeragallu), fighting off cattle raiders (turugol veeragallu), defending a woman's honour (penbuyyall veeragallu), entering the funeral pyre of a dead husband (sati veeragallu), or fighting a tiger (hulibete veeragallu). "There are many reasons for which a person may have sacrificed his life. And in their names these stones are erected," explains Sundara Adiga, a former archaeology professor from Karnatak University in Dharwad.

The children's excitement was justified – this was no ordinary stone. It was a veeragallu

According to Adiga, most hero stones found in the Karnataka region were made between the 8th and 17th centuries. These stones. which show a great deal of regional variation, also differ in style depending on the period. "For instance, a veeragallu made during the Ganga period is likely to be very plain," says KR Narasimhan, a Kannada scholar and epigraphist. But veeragallus made during the more prosperous Hoysala period can be more intricate. "[During] the Hoysala period, we have stones that have beautiful narrations with elaborate panels and inscriptions," adds Lathashree Kolla, a public archaeologist. The presence of inscriptions in particular are useful to historians since they may contain additional information, such as the name of the martyr, the place and date of the incident, and the reason for the encounter.

The stone at IISc, which Balasubrahmanyam's children chanced upon, is a hulibete veeragallu. Though part of the stone is missing – it has been cut down the middle – it clearly shows the left hand of the martyr holding a bow, while the missing right hand is about to launch an arrow at what looks to be a pouncing tiger.

The IISc veeragallu is only one of three hulibete veeragallus that are known from Bangalore – the others are in the western (Bangalore University campus) and the southeastern (near BTM bus stand in Madivala) parts of the city. But it lacks an inscription. "It's difficult without epigraphy, [but] in the absence of inscriptions, we work with styles, jewelry, weaponry," says Lathashree. The photographs of the IISc hulibete veeragallu were studied by R Sesha Sastry, a former professor from the Sri Krishnadevaraya University in Anantapur, Andhra Pradesh, and one of Karnataka's foremost veeragallu experts. He assesses it to be from the 10th century, when Bangalore was under the rule of

the (Western) Gangas. According to him, the hulibete veeragallu in Bangalore University is likely to be either from the 7th or 8th century, also during the reign of the Gangas, and the third one in Madivala is from the 14th century, when the Bangalore region was part of the Vijayanagara empire.

The wildcats depicted in these stones are almost certainly tigers, as the noted tiger conservationist Ullas Karanth points out, since the word "huli", which means tiger in Kannada, is used in similar veeragallus where inscriptions are available. This is not surprising – tigers roamed all across the Deccan Plateau and the Western Ghats until not too long ago. Moreover, it is unlikely that killing a leopard, which weighs less than 60 kg, would be commemorated. But if one kills or gets killed by a 200 kg tiger, it is a story worth immortalising in stone.

Medaraningahalli

It is entirely possible that the area around the hulibete veeragallu at IISc might have other hidden archaeological artefacts that will shed more light about the place from this period. But we do know more about its recent history, thanks to a Kannada inscription from 14 November 1669 carved on a boulder in the Kaadu Malleshwara temple (referred to in the inscription as the Mallapura Mallikarjuna temple) on 15th Cross, just off Sampige Road, in Malleswaram. It records the gifting of a village called Medaraningahalli to the temple by the then ruler of Bangalore, Ekoji Rao (the step brother of Shivaji Bhosala I, the famous Maratha king). The term "gifting" as used here essentially meant that tax revenues from the village would be diverted to the temple instead of being collected by the king's revenue officers. This method of using tax revenues to meet the expenses of important temples was then a prevalent practice. And the "authorisation permit", a royal edict, would be inscribed on stones in the vicinity of the temple or the village.

The proclamation inscribed in the temple reads (with the English transliteration):

೧ ಸೌಮ್ಯ ಸಂವತ್ಸರದ ಮಾರ್ಗಶಿರ ಶುದ್ಧ (೧/೨ ?) ಲೂ
(1. saumya sa vatsarada mārgaśira śuddha (1/2 ?) lū)
೨. ಶ್ರೀಮತು ಮಲ್ಲಪುರದ ಮಲ್ಲಿಕಾರ್ಜುನ ದೇವರ ದೇವ ಮಾನ್ಯಕ್ಕೆ ಯಕೋಜಿ ರಾಯನ ಬೆಂಗುಳುರ
(2. śrīmatu mallapurada mallikārjuna devara deva mānyakke yakoji rāyana be guḷura)
೩. ಮಹನಾಡು ಕೇಳಲಿಕಾಗಿ ಮೇದರನಿಂಗಹಳಿಯ ಧರ್ಮಕ್ಕೆ ಕೊಟ್ಟನು ಕೋಟಿ ಚಂದ್ರ ಸೂರ್ಯರು
(3. mahanā u keḷalikāgi medarani gahaḷiya dharmakke ko anu ko i ca dra sūr-yaru)
೪. ಉಳ ಕಾಲಲು ಧರ್ಮಕ್ಕೆ ಕೊಟನು ಯಿ ಧರ್ಮಕ್ಕೆ ವಕ್ರ ಮಾಡಿದವರು ಕತ್ತಿಯ ಕಾಗಿಯ ಚಂಡಾಲರ ಜಲ್ಮ
(4. uḷa kāla:u dharmakke ko anu yi dharmakke vakra mā idavaru kattiya kāgiya ca ālara jalma)
೫. ದಲಿ ಹುಟುವರು
(5. dali hu uvaru)
೬. ಮುಸಾಲಮಾನರಾದವರು ಮಕೆಯಲಿ ಹಂದಿತಿಂದ ಬ್ರಾಹ್ಮಣ ಚೆತ್ರಿ ವೈಶ್ಯ ಸೂದ್ರ ಕಾಸಿಯಲಿ ಗೋವ
(6. musālamānarādavaru makeyali ha diti da brāhma a cetri vaiśya sūdra kāsiyali gova)
೭. ಕೊಂದ ಪಪಕೆ ಹೋಗುವ
(7. ko da papake hoguva)

The text of this inscription is as provided in Volume 9, Bangalore Supplement, of *Epigraphia Carnatica* by B Lewis Rice (line numbers are not part of the original inscription, but adding them is a default practice). This edict, whose spellings and terms may vary from what would be considered correct today, roughly translates into English as:

"Heeding to the request of the people of Bengaluru, for as long as the Sun and Moon exist, Ekoji'raya gifts rent free Medarlingahalli to the Mallikarjuna temple in Mallapura. One who violates this grant will be born a donkey, crow, chandala. A Musalman [violator] will attract the equivalent [sin] of eating a pig in Mecca. A Brahmana, Chaitri, Vysya and Shudra will attract the equivalent [sin] of eating a cow in Varanasi."

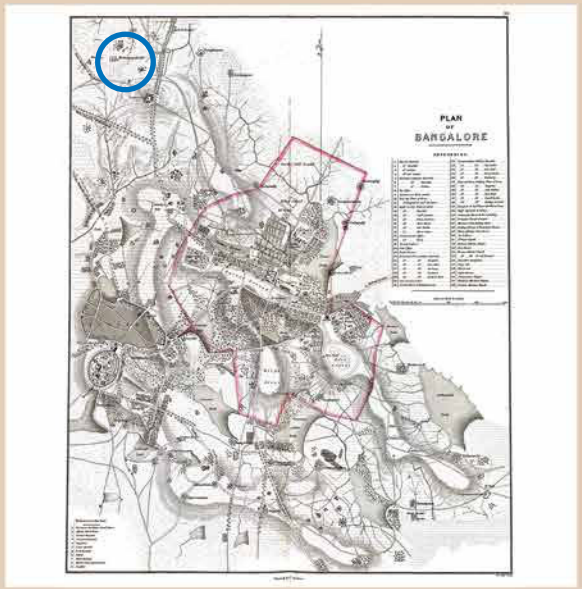


Image courtesy: Pharoah & Co, Madras; J & C Walker//Creative Commons Licence/Wikimedia Commons

An 1854 map of Bangalore showing Medaraningahalli indicated by the blue circle

This inscription is significant for two reasons. One, it tells us that Malleswaram (or Mallapura as it was then called) existed at least 230 years before it was supposedly established by the British though they did develop the locality in the late 1890s following the plague epidemic.

And two, it refers to the village of Medaraningahalli. An 1854 Bangalore map and other older maps show this to be a village of reasonable size in North Bangalore.

When these old maps are digitally superimposed on today's maps, it clearly shows that Medaraningahalli would have spanned the eastern part of IISc campus in and around the swimming pool, the Staff Colony of CPRI (Central Power Research Institute) and the area beyond New BEL Road into CPRI.

Medaraningahalli is named after Medaras, an old tribe found in parts of Karnataka, Tamil Nadu and Telangana. Traditionally, the Medaras worked with bamboo – they would gather fresh green bamboo from nearby forests and fashion them into baskets, mats, and other items. Interestingly, even today, we find bamboo thickets near the swimming pool and Jubilee Gardens in IISc though it is not clear whether they are remnants of old bamboo vegetation or were planted more recently.

Photos: Udaya Kumar PL

Bamboo is found in IISc to this day

It was not uncommon in those days for a village to be named after the predominant tribe or a caste from the village. We have numerous examples of this practice in Bangalore: Kumbarapete (town of potters), Byadarahalli (village of hunters), Agrahara (Brahmin settlement), Ganigarahalli (village of oil extractors), Gollahalli (village of cowherds), Kurubarahalli (village of shepherds). Bangalore, in fact, has at least two other places named after the Medaras: Medarahalli near Chikkabanavara and a Medarapete in the old pete area of the city.

So what happened to Medarningahalli? One possibility is that the village was evacuated sometime in the 1890s, when the devastating bubonic plague struck Bangalore and its surroundings. We know that several other villages and parts of the city were abandoned to escape the dreaded epidemic, including perhaps Devasandra.

Devasandra

The northeastern parts of the IISc campus originally belonged to Devasandra, a village that has existed for at least 650 years. About 100 m from the Centenary Visitors House (CVH) gate at IISc is an inscription stone from 1376 inside the Balanjaneya temple. This inscription in Tamil records the gifting of land in Devasamudra (the old name of Devasandra) to a few Brahmins.

The word "samudra" in Devasamudra refers to a lake in the vicinity of the village. Over time, "samudra" changed to "sandra". We have several other examples of names of places in Bangalore with "sandra" in them: Allalasandra, Jakkasandra, Bommasandra, Channasandra and so on. The Devasandra lake (also known as Geddalahalli lake) is now filled over, and on it stands the upmarket RMV 2nd stage.

The 1376 Devasandra inscription uses the royal epithet Hinduraya Suratrana ("Hindu Sultan" in Sanskrit) for King Bukkaraya, one of the founders of the Vijayanagar kingdom. The Vijayanagar kingdom emerged from the collapse of the Hoysalas following a series of invasions by the Delhi-Bahmani Sultanates down south. The founders of the Vijayanagar kingdom, who successfully stopped such invasions from the north, assumed the title of *Sultan of the Hindus*.

The Devasandra inscription is not the only one in the city that is in a language other than Kannada. Inscriptions in Tamil and Telugu were quite common after the 10th century, a testimony to the cosmopolitan nature of the region for over a thousand years.

Like Medaraningahalli, Devasandra also seems to have been affected by the 1890s plague and the village was relocated about a kilometre north of where it originally existed. When people left their villages and established new ones, they often named the new settlement after their native village.

Hebbal

About 3.5 km northeast of IISc in Hebbal village is an ooralivu veeragallu with inscription in Kannada. Discovered only in June 2018, it is from around 750 CE, and is now considered to be Bangalore's oldest stone inscription. The inscription mentions the name of the place where it is installed as Perbolalnaadu Muvatu (muvatu in Kannada is 30). PV Krishnamurthy, an eminent historian and epigraphist, who deciphered the inscription, has derived the etymology of modern day Hebbal from Perbolalnaadu as: Periya + Polal (Periya = big, Polal = town) -> Perbolal -> Pebbolal -> Pebbol -> Pebbala -> Hebbala. Adding a numeral to the name of an important town was a common practice. It indicates the number of smaller towns and villages under its jurisdiction. In fact, other inscriptions from this period show that Hebbal was then part of a larger country called Gangavadi 96000 and was ruled by the Ganga king Sripurusha residing at Manne near Nelamangala. Ganagavadi covered the areas of modern day Kolar, Bangalore, Krishangiri, Salem, Erode, Mandya, Mysore, Coorg, Chikamagalur, Shimoga and Tumkur districts.

Photos: Udaya Kumar PL

A recently constructed Ganga-style mantapa for the 750 CE Hebbal-Kittayya veeragallu (left) and a close-up showing the carving and the inscription, made conspicuous with rice flour (right)

The 750 CE ooralivu veeragallu is dedicated to Hebbal native Kittayya who saved his town from being destroyed by the Rashtrakutas. Because the Hebbal-Kittayya inscription is Bangalore's oldest inscription, Kittaya is the earliest known resident of the city. Had he failed to defend the important town of Hebbal, this part of Bangalore may have taken a very different historical course.

It is also worth mentioning that in close proximity to the Hebbal veeragallu in Bhoopasandra, in the vicinity of the Hebbal lake, lies an 8th century Durga idol with a fragmented Kannada inscription. The idol was discovered and rescued from destruction when the Outer Ring Road was being built in the late 1990s. Durga idols are commonly installed and worshipped alongside water bodies. The inscription refers to wetland farmers, suggesting that the Hebbal Lake may have existed at least 1,200 years ago.

Yeshwantpur

But the neighbourhood of IISc has a history that goes back even further in time. People who lived in these parts some 2,000 years ago seemed to have had trade relations with Rome during its heady days. On 17 April 1891, when building the railway line about 1.5 km west of IISc (close to Yeshwantpur Railway Station), workers discovered an earthen pot with 163 denarii (plural of denarius, an ancient Roman silver coin) from 23 BCE to 51 CE, a period when Rome was ruled by Augustus, Tiberius and Caligula. The existence of trade ties between people in the Bangalore region and Rome is supported by the discovery of Roman coins in other parts of the city as well. For instance, in 1965, when the runway for the HAL airport was being built, a pot with 256 denarii from the same period was unearthed. A similar discovery of Roman coins was made by the historian DR Gordan in 1945 in Bellandur.

Jalahalli

The earliest evidence of human habitation in the IISc neighbourhood has been discovered in Jalahalli, about 4 km northwest of IISc campus. In 1946, a British archaeologist and commander in the Royal Indian Navy KRU Todd, while convalescing in the Indo-British hospital at Jalahalli, was intrigued by the granite quarries adjoining the hospital. As soon as he recovered, he visited the site, where he discovered several hundred microlithic (small-stone) prehistoric tools made from quartz, rock crystal and red jasper. These tools were so numerous that he thought that the site was a factory for making stone tools. The artefacts are now housed in the British Museum in London. Subsequently, in 1948, he published an article about the discovery titled "A Microlithic Industry in Eastern Mysore" in *Man*, now called *the Journal of the Royal Anthropological Institute*. A few years later, M Seshadri, the Director of the Mysore Archaeological Department, after studying the implements in the British Museum, concluded that these tools were from the pre-iron age era, 1000 BCE or earlier, making Jalahalli the site of the earliest known human settlement in the region.

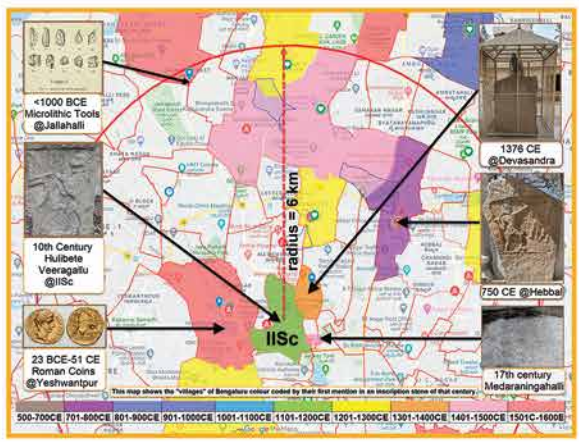


Image: Google Maps and Udaya Kumar PL

A map showing summarising the 3000-year history of IISc's neighborhood

The stories about the different villages and towns that make up this part of Bangalore are disparate. As we discover more, we will someday be able to weave together these diverse strands into a more comprehensive historical narrative of the region. But we already know that IISc's neighbourhood has a long history – there were well-established villages 500 to 1,500 years ago, a thriving international trade centre 2,000 years ago, and a settlement where artisans made sophisticated stone tools 3,000 years ago. Not many university campuses in the world can boast of a history as rich as this.

Note: Even when not mentioned, all dates provided in the article are in CE (Common Era)

Udaya Kumar PL, a passionate Bangalorean, works in the technology sector and is the founder of a citizens group, Inscription Stones of Bangalore. *This group is focussed on securing Bangalore's endangered inscriptions and strives to educate people about the pre-16th century history of Bangalore and its localities.*

ABSTRACTS

IISc Photography Club