

## Ashok Venkitaraman



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Ashok Venkitaraman is a cancer biologist well-known for his contributions in understanding the genetics and biology of cancer, particularly in elucidating the impact of genome instability in carcinogenesis and cancer therapy. His research has not only illuminated some of the fundamental mechanisms governing genome repair, replication and segregation during cell division, but has also provided insight into their connections with the pathogenesis and treatment of cancer. At present, he is the Director of the Medical Research Council's Cancer Cell Unit in Cambridge and is also the Ursula Zoellner Professor of Cancer Research at the University of Cambridge. Recently, he was conferred the Jubilee Professorship by the Indian Academy of Sciences, Bangalore. As the first Jubilee Professor, Venkitaraman delivered a talk entitled 'Cancer suppressor mechanisms that guard the human genome', on 2 August 2012 at the Indian Institute of Science (IISc), Bangalore. He later visited other Indian institutes interacting with students, researchers and faculty in other cities. During his stay at Bangalore, he spoke to *Current Science* on his research, the Indian medical education system and the translation of biomedical research to clinical practice.

*Transition from being a doctor to a researcher*

My first experience of research began while I was posted to the medical wards of the Christian Medical College Hospi-

tal (CMCH) in Vellore, where I was a medical student. I noticed an unusually high number of adult staff and students who were admitted to the isolation unit with chickenpox, typically described in the Western medical textbooks I was reading as a disease of children, not adults. My curiosity led me to talk to T. Jacob John, Head of the Department of Virology at CMCH, who was internationally known for his work on polio immunization. He was good enough not only to encourage me to try to investigate the problem, but also to let me work in Virology laboratory. So began my first attempts at formulating and answering by experiment a scientific question. Working whenever I had spare time over a period of about two years, I was able to demonstrate with much help from Jacob John and other colleagues, that not only were a surprisingly high number of adult hospital staff and students at CMCH seronegative for antibodies to the varicella zoster (chickenpox) virus, but also that there were seasonal peaks and troughs in the incidence and transmission of the disease amongst the hospital population. This work resulted in the publication of a few papers in international journals – and I was bitten! I am afraid that I spent more time during my last few years at medical school pursuing my spare-time research hobby than focusing on preparation for my medical exams; thanks to Jacob John, who allowed me to work in Virology Department laboratories in the evenings and at night when I was free from my classes and clinical postings. The work I was doing suggested that the sero-epidemiology of infections due to the human herpes viruses in the Indian population might be quite different to what had been noted elsewhere. I was fortunate enough to find a fellowship jointly funded by the World Health Organization (WHO) and the Lady Tata Memorial Trust to investigate this at Gilbert Lenoir's laboratory in France. Again, with the help of my colleagues there and in Vellore, I was able to complete experiments demonstrating that there were indeed differences in exposure to human herpes viruses amongst Indians that might possibly explain variant patterns of infectious disease. From these beginnings, it was logical to seek to extend my research training in the field

of immunology and infectious diseases after the completion of my medical degree.

*When did you choose to work on cancer?*

That's a long story (laughs). My training in immunology was first with Marc Feldmann at University College, London where I did my Ph D, followed by post-doctoral work with Michael Neuberger at the MRC Laboratory of Molecular Biology (LMB) in Cambridge. I was interested in understanding the steps involved in the development of B lymphocytes, at a time when it had become clear that these cells undergo quite profound genome rearrangements during their development, leading to the expression of the antibody genes. This was a very exciting time in the field with several Nobel Prizes having been awarded (for example to César Milstein in 1984, and Susumu Tonegawa in 1987). My interest in the control of genome rearrangements continued when I started my independent laboratory at LMB. A few years afterwards, the so-called breast cancer genes, *BRCA1* and *BRCA2*, were identified, mutations in which were found to predispose women to breast and ovarian cancer at very high risk. This was front-page news in science at the time, and although it was in not my field, the fact that Alan Bradley had implicated the *BRCA2* gene in radiation sensitivity caught my attention. It was natural to follow this train of thought and wonder if *BRCA2* might regulate genome rearrangements. This was the problem that I then followed, with K. J. Patel and Veronica Yu (a postdoc and a Ph D student in my laboratory respectively), helped by my Cambridge colleagues Bruce Ponder and Martin J. Evans. It was during this time that I began to think about cancer as a disease, and in particular, the role that genome instability might play in its pathogenesis and treatment.

*What forms of cancer are you looking at primarily in your laboratory?*

I should emphasize that my interests are in understanding the fundamental molecular mechanisms that drive cancer pathogenesis, and not just on any one cancer type. That said, what my laboratory

## IN CONVERSATION

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investigates is primarily relevant to epithelial tumours and in particular, we have studied tumours of the breast, ovary and the pancreas.

*How has your research contributed to the understanding of cancer?*

It is always difficult to talk about one's own research contribution, because advances in science typically come from the findings and work of many laboratories over many years. My laboratory has focused on understanding the mechanisms that maintain the integrity of chromosome structure and number during cell division, and on defining how defects in these mechanisms engender carcinogenesis. We have over the last few years discovered how several tumour suppressor genes, like *BRCA2* which I mentioned earlier, work to preserve chromosome stability, and how their inactivation leads to cancer. This has led to advances in our understanding of the fundamental mechanisms that control DNA replication, repair and segregation in dividing cells. Excitingly for me, several of these discoveries have provided a scientific basis for new approaches to cancer therapy. I described some of these developments in my lecture at IISc.

My focus now is on understanding the role of chromosomal instability from the perspective of cancer pathogenesis and treatment. Even laymen will know that there have been great advances recently in describing the genomes of advanced cancers in different tissues, and that what these studies show is that cancer genomes are hugely complex, unstable and keep on changing. The complexity and instability of cancer genomes give rise to several major challenges in understanding and treating cancer. For example, which of the myriad genomic changes are functionally important in particular cancer types? Which of these alterations should be targeted for cancer treatment? Will continuing genomic instability lead inevitably to treatment resistance? And so on.

A better understanding of the role played by chromosomal instability in cancer evolution is indispensable to answering these and other questions. Not only is chromosomal instability one of the earliest events to occur during epithelial carcinogenesis, but the defects that cause it are directly relevant to understanding how cancer cells respond to dif-

ferent forms of treatment, including for example, radiation or anti-mitotic drugs.

*How does your work help in overcoming this problem?*

In two ways, I think – first by telling us how to use existing cancer drugs more effectively, and second by helping to develop new drugs.

An example of the first comes from my lecture. I described how alterations in certain genes that regulate mitosis can not only create genome instability in cancers, but can also trigger resistance to anti-cancer drugs like taxanes. What this will help us do quite soon is to identify the patients who are most likely to respond to taxanes. In the example I gave in my lecture, we could test the patient's tumour for alterations in particular mitotic genes before treatment with taxanes to check if they are likely to respond.

Our work will also help us to develop new drugs. We have already identified new mechanisms and molecules relevant to cancer treatment through our research on chromosome instability, and we are working to convert this knowledge into the development of new drugs, that work differently from existing treatments. But this will take longer to reach fruition.

*On oncology research in India and abroad*

I have only recently begun to engage with oncology researchers in India, and hope to increase my exposure during the tenure of the Jubilee Professorship and subsequently. I believe that there are important new opportunities in this field for several reasons.

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**'Cancer is a relatively common disease and the number of sufferers in India is likely to increase as life expectancy increases hand-in-hand with general socio-economic development.'**

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Moreover, oncology has elsewhere been at the forefront of efforts to translate fundamental biological knowledge to clinical application for the benefit of patients. For example, close connections have been established between basic cancer research, the development of new medicines and new approaches to performing clinical trials. It is common to

find academic researchers and clinicians working with – not just working for – biotech and pharma companies to achieve common goals. These features make oncology a good field in which to begin to develop platforms and models for translational research that connect the laboratory to the clinic. These connections in my experience are as yet somewhat underdeveloped in India.

*On recent collaborations with the The Institute for Stem Cell Biology and Regenerative Medicine (inStem) and National Centre for Biological Sciences (NCBS)*

Despite the recent explosion in our understanding of the genetics and mechanisms underlying human diseases like cancer, our ability to translate this knowledge for the benefit of patients is still limited. There is an increasing focus worldwide on encouraging new approaches to address this problem. The collaboration with inStem and NCBS is envisioned to establish one model for this, through a multidisciplinary centre for chemical biology and therapeutics. This is still very much in a nascent phase, although I hope that the pace of progress will accelerate in the coming months. It is already clear to me, however, that I could not ask for a better environment in which to establish such a collaboration. The inStem/NCBS campus has many exciting researchers, supported by excellent facilities and an administration with a 'can do' attitude. So it is a terrific place to be working in. I have taken up an adjunct faculty position at inStem, and expect to spend several weeks each year working in Bangalore.

*On interdisciplinary research and need for communication among scientists*

Attempting to translate fundamental understanding of a disease like cancer to clinical application is one example of the type of problem in biomedical research that demands what I termed in my lecture a new type of research effort. It is pretty clear, to use this example, that to convert exciting new mechanistic insight concerning how a disease pathway works to the development of a new drug requires a multidisciplinary team effort on a large scale, and cannot be accomplished in the traditional structure of academic biomedical laboratories or institutes. I envi-

sion that my collaborative research at inStem/NCBS will develop along this route.

However, I should add that there is an increasing focus worldwide on multidisciplinary research on a smaller and more focused scale to solve specific biological problems. For example, there are increasingly sophisticated applications of statistics and mathematical modelling to not just interpret complex 'omic' datasets, but to make predictions about the way that biological systems work. There have been several fruitful examples of collaborations between biophysicists, engineers and biologists to solve problems connected with the mechanism of molecular motors, the control and consequence of mechanical stress on cell behaviour, and on new methods to image biological structures and dynamic processes using light microscopy. These are just a few examples chosen at random from the top of my head, but they serve to emphasize that elegant and definitive experimental solutions to important biological problems increasingly demand communication, collaboration and interdisciplinarity.

This is not always easy to initiate, for several reasons.

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**'To exchange ideas and potentially collaborate with colleagues working in very different disciplines, you first need to transcend the barriers of scientific language and culture. This requires effort, as well as a willingness to move outside one's own 'comfort zone' and learn about radically different methods and concepts. Moreover, it takes two to tango, and so interdisciplinary collaborations are crucially dependent on finding collaborators who are also willing to make the effort.'**

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*Why is a need being felt to expose medical students to biomedical research?*

I think that medical training should ideally equip students not only to practice medicine, but also to change the practice of medicine.

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**'In other words, doctors should be trained to continuously evaluate and improve their practice through evidence-based methods. I believe that the exposure of medical students to re-**

**search will help enormously in achieving this, whether they eventually end up practising privately, or become hospital doctors or clinical academics after their training.'**

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Exposure to research teaches students how to search and evaluate the medical literature, which will be essential for them to keep up with ever-advancing medical knowledge. It also teaches them how to analyse observational data in a rigorous way, which will be essential if they are to constantly improve their practice from their own clinical experience. In short, research exposure helps to teach medical students how to think, and not just how to do.

*What could be the possible reason of trained medical professionals not opting for a career in research?*

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**'It takes a great deal of motivation for somebody who has graduated in medicine to turn towards research anywhere in the world, but particularly in countries like India.'**

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Clinicians in India who are attached to major hospitals or medical colleges carry a very large clinical load, leaving little time or motivation for research. Careers in research are less structured and therefore more uncertain than in clinical medicine, because of the uncertainty inherent in making the major scientific advances necessary for promotion up the academic ladder. The financial rewards of research are not likely to be as good, particularly in the surgical specialities where private practice is common.

*How does the medical education system in UK differ from that in India? Do you see a disparity?*

I see a few differences, although it must be emphasized that my knowledge of Indian medical education is limited. My first observation is that the medical curriculum in India seems to be rigidly set by the Medical Council of India, leaving little freedom for the evolution of the curriculum or the methods of teaching it. My second observation concerns the dearth of opportunities for research, which I have discussed already. Research exposure is 'built in' to the undergradu-

ate medical curriculum at many UK universities.

*On being the first Jubilee Professor of the Indian Academy of Sciences*

I am honoured to have received the award, and have already enjoyed the first week of my tenure as the Jubilee Professor. I will try to remain true to the spirit behind the award, which is to interact with and influence researchers and students all over India, and not just in the major centres. With this in mind, I expect to visit five institutions in different cities over the next 3 weeks. I have arranged to travel back to India later in the year to visit more institutes.

*How will the Jubilee Professorship shape up your scientific career?*

I have already visited major research centres for example, in Delhi, Hyderabad and Bangalore, over the past year or two. Now that I am more familiar with some of these institutes, I would like through the Jubilee Professorship to broaden my experience to other places and other institutions.

*An overview of biomedical research in India*

Again, any remarks I make must be moderated by my relative unfamiliarity with biomedical research institutes in India. My first observation is that there are outstanding scientists doing outstanding research at many institutions all over India, and that some institutions in the major metros have a relatively higher proportion of internationally competitive research programmes. However, it is also clear that the number of internationally competitive researchers and research institutions in the biomedical field is relatively low when considered in light of the sheer size of India and its research enterprise.

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**'The major challenge for India over the next 10 years will be to greatly increase the overall number of outstanding researchers and research institutions throughout the country, and not simply to remain content with making the good ones better.'**

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