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INTERVIEW

"The Virus Man"

Prof Ramareddy V Guntaka

Interview

PROFESSOR
Ramareddy V Guntaka

Dr. Ramareddy V Guntaka is a Professor at the Department of Molecular Sciences, University of Tennessee Health Sciences Center, Memphis, USA and Chief Scientific Advisor and Board Director of Sudershan Biotech Pvt. Ltd.

Dr. Ramareddy's research background was strengthened in the field of Microbiology. He earned his Ph.D in Microbiology from Kansas State University, Manhattan in (1970). He was graduated with B.Sc in Chemistry and Biology, A.N.R. College, Gudivada, India. Dr. Ramareddy got his M.Sc in Microbiology from U.P. Agricultural University, Pantnagar, U.P., India (1965). He has received many honors and awards like Government of India Merit Scholarship, 1963-1965; American Cancer Society Senior Dernham Fellowship, 1973-1975; Research Career Development Award, National Institutes of Health 1979-1984.

He was appointed in various positions like Associate Professor, Department of Microbiology, School of Medicine, University of Missouri, Columbia; Assistant Professor, Department of Microbiology, College of Physicians and Surgeons, Columbia University; Assistant Research Microbiologist, University of California, San Francisco. In his research career he has published over 110 research papers in reputed journals including Nature and also holds a patent.

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MAJOR CONTRIBUTIONS TO SCIENCE:

a) One of the four-member team that discovered proto-oncogenes (precursors to the cancer causing oncogenes). The 1989 NOBEL PRIZE was given to the two American Scientists.

b) Identified many fundamental steps in the life cycle of Retroviruses, viruses that cause cancer, AIDS and many other diseases.

c) First one to molecularly clone the whole genome of a retrovirus – Rous Sarcoma Virus, which is being used all over the world. This infections clone, sequenced by the Nobel Laureate Walter Gilbert of Harvard University, became the proto-type virus clone in retrovirology.

Sir, what is your Personal background/ Upbringing/ Early education and Motivation to pursue research career.

I hail from a small village, Bollapadu, in Krishna District, Andhra Pradesh. My parents were farmers and had no education. I attended a local elementary school and then a High School in a neighbouring village Mudunuru. I graduated from Akkineni Nageswara Rao (a famous Telugu Film Actor) College, Gudivada, which was affiliated to the Andhra University. I proceeded to do M.Sc in Pantnagar, U.P, following which I went to USA, where I did my Ph.D.

There was no guidance for me and things happened one after other. One of my biggest plus point was that my brother, who had some education at elementary level, encouraged me and provided support, freeing me from going to fields.

Since I was the youngest in my family, my whole family, inspite of their lack of education, was always behind me in my pursuit. I came to complete High School at a very early age, much before I reached maturity and mostly wandering in the village. My teacher thought I was smart and encouraged my family to send to school and further higher education.

In my first attempt I failed S.S.L.C (High School) because I got low marks in my own native language, Telugu. I took remedial courses and passed High School. After completing High School, I had a couple of years break wondering what to do, especially because I was not wealthy to go to College. In the interim I learned Typing and Shorthand with an aim to get a clerical position. Then suddenly I experienced a spark of enlightenment (God's grace), motivating or guiding me to go to college. I was so determined to excel that in College, I even got an award for Telugu subject (earlier I failed in High School). I also stood first in College majoring in Chemistry, Botany and Zoology.

BT people

THE HINDU • FRIDAY, FEBRUARY 10, 2006

Biotechnology parks in 6 states by 2010: official

Geetha Reddy opens BioAsia-2006, foresees upswing in BT

BEFITTING HONOUR: *Minister for Industries J. Geetha Reddy presenting Genome Valley Excellence Award to Rama Reddy V. Guntaka of the US at BioAsia conference in Hyderabad on Thursday.* – PHOTO: SATISH H.

After pondering what to do next, with some input from my relative, I joined the M.Sc program in Microbiology at the GB Pant University, Pantnagar, UP, which was the first University in India to adopt American type of education system.

After completion of MSc, I had a short stint of Instructorship in the Chemistry Department at the Sri Venkateswara Agricultural College in Tirupati, affiliated to Andhra Pradesh Agricultural University. From there on September 4, 1966 I landed in the USA for my Ph.D. on a Scholarship given by the Kansas State University and remained in USA ever since. Nowadays I spend 2 to 3 months in Memphis, TN and one month in Hyderabad, promoting activities at the Sudershan Biotech Pvt Ltd.

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Sir, where do you work now and How long have you been working here? Please share some memorable previous positions.

Currently I am a Professor at the University of Tennessee, Memphis, TN, USA for the past 15 years. Before that I was an Associate Professor for 3 years and a Professor at the University of Missouri, Columbia for almost 14 years.

My faculty career started at the College of Physicians and Surgeons, Columbia University, New York where I was an Assistant Professor for 7 years. Prior to joining Columbia University, I was a Research Microbiologist at the University of California, San Francisco and a Postdoctoral fellow at the University of California, San Diego. I did my Ph.D. in Microbiology at Kansas State University, Manhattan, KS, USA.

Sir, what is your research title and why you chose only this? How did you become interested in this subject? What questions are you trying to answer in your work? What process do you follow to find answers? What is the role of technology in your job?

I have had many research titles over the years – DNA replication and polymerases; Retroviruses and their life cycle; Transcription factors and their role in carcinogenesis, restenosis and wound repair; Triplex-forming oligonucleotides as therapeutic agents for Organ Fibrosis; Environmental carcinogens and cancer; Hepatitis Viruses and Cancer; Vaccines for Hepatits B Virus and Hepatitis C Virus. In all these I published more than 115 papers in major journals.

In each one of these areas I wanted to address specific issues related to human health. For example, in retrovirus research we wanted to know how these viruses cause cancer and alter cellular metabolism. Why Rous sarcoma virus replicates only in fibroblasts (just like AIDS virus or HIV replicates in CD4 positive cells). What causes this tissue tropism? To address these questions, we devised various experiments which led us to clone new host cell factors (like Y-box binding protein-1) that help virus to propagate in those fibroblasts. Then we found that when Rous sarcoma virus infects fibroblasts it suppresses collagen gene transcription and activates matrix metalloproteinases; this scenario facilitates cancer cells to metastasize.

These studies led us to discover Triple Helix Forming sequences in the collagen gene promoter. So we synthesized these Triplex-forming oligonucleotides (TFOs) and showed that they form efficient and stable triplexes and suppress collagen gene transcription. This discovery paved the way to control fibrosis. We applied this triplex strategy to prevent liver fibrosis and improve liver function in rats. Liver fibrosis leading to cirrhosis and liver cancer is the major outcome of HBV and HCV infections in humans. I have a patent on these TFOs. Now our goal is to take these to preclinical and clinical trials with an ultimate aim of curing fibrotic disorders in humans (liver cirrhosis, lung fibrosis, renal fibrosis etc).

Since HBV and HCV are the major culprits implicated in liver cirrhosis and liver cancer, our plan is to control these infections. I cloned HBV vaccine gene in Pichia pastoris and directed the preventive vaccine project at Shantha Biotech. This vaccine, Shan-

vac, is now in the market in all the developing countries at an affordable price. My immediate goal is to bring a similar vaccine for HCV for which I have cloned and expressed in Pichia pastoris an epitope-derived antigen. Now we are going to intensely work on this and hopefully in the next 3 to 4 years, we can bring this vaccine into market. This way we can prevent the blood-borne liver diseases.

My other and most important motive is to bring into Indian and world market several high value therapeutic molecules, such as human serum albumin, interferons, vaccines for viruses such as Dengue and Zika, at an affordable price, in a similar way we accomplished with vaccine for HBV.

Nobel controversy hits home

UMC scientist caught in international quarrel.

By JENNY THELEN
of the Tribune's staff

Just after the winners of this year's Nobel Prize in medicine were named yesterday, international news services carried stories about a French researcher who said he should have at least shared the award.

But UMC microbiologist Ramareddy Guntaka said the Frenchman, Dominique Stehelin, is making an exaggerated claim. In the early-1970s, the two worked together as post-doctoral fellows in the laboratory run by the California researchers who yesterday became Nobel laureates.

J. Michael Bishop and Harold Varmus were credited with discovering a family of genes that have helped scientists understand how malignant tumors develop.

"When you have something bad, nobody takes credit," Guntaka said this morning. "When you have something good, everybody wants a share."

Guntaka and Stehelin worked under the Nobel winners along with a half-dozen other fellows at the University of California School of Medicine in San Francisco. The laboratory's work centered on the cancer-causing retrovirus that is present in animals' normal genetic makeup but sometimes mutates to other cells and triggers uncontrolled growth typical of malignant tumors.

Bishop and Varmus came up with the research idea, Guntaka said, adding that he and Stehelin "were only the post-doctoral research fellows. We were working in their lab." Guntaka said he did the first six months' work on the project that eventually yielded the Nobel. After that, he said, supervisors transferred the project to Stehelin, whose own project wasn't going anywhere. Stehelin continued as the principal investigator for two years and was listed as the primary author of the first two published reports of research findings, Guntaka said.

Although the Nobel winners were only listed as co-authors, Guntaka said, they initiated and pursued the project. Research findings, he said, are "the propriety of the people in whose lab we were working."

"I find all that very unfair and rotten," Stehelin yesterday told the French news agency Agence France-Presse. Now a director of research for the National Center for Scientific Research at the Pasteur Institute in Lille, France, Stehelin said: "I did the work all by myself, from A to Z. I spent three years in their San Francisco lab, from 1972 to 1975, at a time when nobody other than me was working on the subject."

UMC's Guntaka, however, said he sees no reason to include Stehelin among Nobel recipients. "Many times there are many people who contribute to that work. The evolution of research goes like that. It is a general pattern.

"Anybody can claim anything later."

Bishop and Varmus will share the $469,000 prize. Their studies demonstrated that all normal animal cells carry the seeds of cancer in the form of specialized genes, known as oncogenes. Left alone, these genes apparently play an important role in normal growth and development; but if damaged, they can trigger cancer.

UMC School of Medicine researcher Ramareddy Guntaka, foreground, discusses a research project with assistant research professor Jagannadha Kandala this morning in the school's microbiology department. (Steve Levin photo)

During this process of getting answers to all the projects outlined above, we have to develop our own ingenious methods. I believe that science and technology is the most important indicator of a country's growth and development. We are witnessing phenomenal advancements in countries which heavily invested and are continuously investing in science and technology. Unfortunately, India is lagging behind many countries although we have a rich resource of intelligent and highly talented people. Other countries are tapping our talent but in India they are unable to excel for several reasons.

BT people

Sir, can you tell us Milestones of your research in particular its societal impact.

Every invention we made has an impact on society. I started my major career when reverse transcriptase of retroviruses was discovered. First I began to study how Rous sarcoma virus, retrovirus containing a RNA genome and causes solid tumors in birds, replicates in the cell. We showed that reverse transcription first occurs in the cytoplasm which translocate into nucleus where it integrates into the host chromosomal DNA. In addition, we found that at the ends of the genome Long Terminal Repeats are generated that aid in the integration process. Several drugs for AIDS and other retrovirus infections were developed targeting reverse transcriptase and integrase.

The second seminal discovery was proto-oncogenes, precursors for oncogenes that cause cancer. Using Rous sarcoma virus and deletion mutant as prototype viruses, we isolated the src sequence and found that it is present in all the metazoans. This was the basis for discovering more than 60 proto-oncogenes, for which the 1989 Nobel Prize was awarded to my colleagues Mike Bishop and Harold E Varmus. I was the one who started the work leading to this discovery.

Subsequently I cloned the first infectious Rous sarcoma virus DNA which was sequenced by Walter Gilbert (Nobel Laureate) and his colleagues at Harvard University. This was the prototype viral DNA that was being used all over the world in studies on the role and mechanism of src oncogene in cancer.

As discussed in other sections of this interview, my other contributions in science that is more pertinent to India include development of vaccine for Hepatitis B, cloning and sequencing for the first time in India of the Indian strains of Hepatitis C Virus.

Sir, how the expenses incurred during research work are fulfilled like different biggest granting agencies funding your research?

My research was largely funded by the National Institutes of Health, USA and some private organizations including Sudershan Biotech Pvt Ltd, Hyderabad. My sabbatical year in India during 1999-2000 was funded by a Research Development fellowship from the University of Missouri, Columbia, where I was a Tenured Professor. No funds came to me from Indian sources.

Sir, what aspects of your work do you think could be described as Indian science?

I was the Principal Scientist behind the successful cloning and development of the recombinant hepatitis B vaccine (Shanvac) in India, made by Shantha Biotech. Without my involvement and guidance this would have never seen the light in India. In addition, I also cloned and guided the scientists at Shantha Biotech to successfully launch Interferon-α (Shanferon), the first therapeutic to be made in India. In year 1999-2000, I came as a Visiting Scientist, with my own funds, to Hyderabad and cloned and sequenced the Hepatitis C Virus genome, the first ever achieved in India. Dr. Murli Manohar Joshi, the then Human Resources Minister, gave a press release in Delhi and later I was invited by the President of India, Sri Abdul Kalam.

Now I am intimately involved with operations at Sudershan Biotech where we cloned several en-

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MILESTONES IN BIOLOGICAL RESEARCH

The Discovery of Proto-oncogenes

J. Michael Bishop

I had given little thought to research on cancer when, as a newly minted assistant professor, I arrived at the University of California, San Francisco, in February of 1968. Instead, I was preoccupied with the replication of poliovirus RNA. But to fill spare time, my mentor and alter ego Leon Levintow suggested that I join Warren Levinson to mount a molecular study of RNA tumor viruses (later rechristened "retroviruses"). After all, the replicative mechanism of these viruses ranked among the great unsolved problems of virology. Pilfering resources from my poliovirus grant to get a start, we flailed away with meager success until David Baltimore and Howard Temin reported their discovery of reverse transcriptase in the late spring of 1970 (1, 2). That lightning bolt immediately provided us with tactics that would permit the molecular detection of both viral particles and viral nucleic acids within cells. We quickly prospered.

Then lightning struck again, in the form of Harold Varmus, who joined our laboratory in the fall of 1970 as a postdoctoral fellow, already accomplished as a scientist and not much disposed to being supervised. Harold and I began our work together with a study of retroviral DNA in infected cells. But we were also acutely aware of recent findings from Steven Martin, which showed that cellular transformation by Rous sarcoma virus is both initiated and sustained by a viral gene (eventually designated as SRC for the sarcomas that it elicits)(3). As our understanding of retroviruses deepened, Harold and I were led to what at first seemed an arcane question: Whence SRC?

The question had two origins. First, there was an evolutionary puzzle. The presence of SRC in the genome of Rous sarcoma virus apparently makes no contribution to the welfare of the virus (3). Why, then, is the gene there? Might SRC have originated as a cellular gene and later found its way into the viral genome by a molecular accident? Second, there was the "oncogene hypothesis" of Robert Huebner and George Todaro, according to which all cancer might arise from the activation of retroviral oncogenes that had been implanted into vertebrate germ lines by infection eons ago (4). Perhaps SRC embodied one of these "enemies within." Both the evolutionary puzzle and the oncogene hypothesis suggested that it might be profitable to perform a search for SRC in the DNA of normal cells. I for one failed to foresee the eventual outcome in any way, shape, or form.

The search would require a cDNA specific for SRC. That was not a simple order in those days before recombinant DNA. Peter Vogt got us started by supplying deletion mutants of Rous sarcoma virus that removed SRC from the viral genome with canny accuracy (5). The RNA fr these mutants provided a means which to separate cDNA for SRC fr cDNA representing other portions the viral genome. Initiated by Ra Guntaka and carried to fruition Dominique Stehelin, the preparati and authentication of the DNA pro required a technical tour de force elaborate that it had to be doc mented in a separate publication (Now days, the enterprise would vastly simpler and could be buried a paragraph in a section on materi and methods. Should we have wait a few years to spare ourselves mu difficulty? Heaven forfend!

It was Dominique who then pe formed the crucial experiments wi

J. Michael Bishop (left) and Harold E. Varmus in the courtyard of the University of California, S Francisco, shortly after they received the Nobel Prize for Physiology or Medicine in 1989.

Address correspondence to Dr. Bishop, at: T G. W. Hooper, Research Foundation, Univers of California, San Francisco, San Francisco, 94143-0552, USA.

zymes and more than 15 therapeutic molecules, the most noteworthy of which is the Human Serum Albumin. We have expressed this in Pichia pastoris. This will be the first ever made in India and probably the second or third in the world. In addition, for the first time we have cloned and expressed a **six-epitope antigen** for Hepatits C Virus, which we are now purifying to test for its potential as a vaccine. If succeeded, this will be the first recombinant HCV vaccine in the world. What is more gratifying being that this vaccine is for the Indian strains of HCV and could be the first to come into market in the world?

To my knowledge I am the first Indian in recent years to bring recombinant DNA technology to India. I was the key person behind the successful production of Shanvac and also clone the HCV genome of Indian strains. I look forward to develop many more therapeutic proteins including monoclonal antibodies in India for an affordable cost in near future.

Sir, what do you think are the challenges of using traditional ways of knowing with Indian science?

I venture to say that India has a long way to advance in Science. As of now, not even a single discovery was made in India, especially in Life Sciences. Cutting-edge is not done in India but Indians on other soil, especially USA, are excelling in all branches of science. I ask why? Although funds are available, the working environment is not conducive for doing ground-breaking work. Encouragement to talented youngsters is lacking. There is a tremendous paucity in communication and exchange of scientific thought, encouraging team work and collaborations, deep dedication to tackle the problems facing India. In America they recognize and encourage merit, give them freedom to think and come up with ideas and compete and most importantly reward them for their discoveries. They tap the talent and promote them. Unfortunately, we don't see that in India. Here politicians care very little for science and technology development; it is beyond their grasping power and hence no appreciation for it.

Sir, how do you think scientific research, which contains a lot of technical language and data, can be more accessible to the general public, specially of India?

In USA and other countries excellent journalists with scientific background are doing an outstanding job in writing scientific articles in such a way that a common man can understand. In India also we are seeing the same in recent years and this has to be accelerated. Newspapers in local languages can transliterate these scientific articles in a simple and understandable language highlighting the importance of these discoveries. This way they can create enthusiasm in readers about the importance of scientific discoveries.

Sir, what do you enjoy most about being a scientist?

I love to work at the bench and still do my own experiments including cloning, expression and purification of proteins. I would like to do basic research that has vast potential in applications to human health. I am always curious to find solutions for complex biological issues. I also enjoy teaching and in my University I give about 20 to 25 lectures every year to graduate students in various courses – Cancer Biology, Virology, Biochemistry, Molecular Biology and Techniques.

BT people

THE PERFECT 'GENE'TLEMAN

Professor Ramareddy V Guntaka's pioneering work led to the isolation of the Indian Hepatitis C virus and the discovery of the proto-oncogene.

SRABANA LAHIRI *meets the scientist who believes human clones are worth a try*

THE DECCAN CHRONICLE, Hyderabad 2nd September, 200?

GENE MAN: *Prof Guntaka is now involved in research on the Y-box protein, which has a key role in cell proliferation*

What he worked on in the late 70s later led scientists to discover the AIDS virus. His research with fellow scientists D Stehelin, H E Varmus and J M Bishop resulted in the discovery of proto-oncogenes, for which the 1989 Nobel Prize was awarded to Bishop and Varmus. And his recent characterisation of the Indian strain of the Hepatitis C virus will actually lessen the incidence of liver cirrhosis and cancer in the land of his birth. He is Professor Ramareddy V Guntaka, and a Professor in the Department of Molecular Sciences, University of Tennessee Health Sciences Centre, Memphis, at least a size like Telugu. Having rubbed shoulders with the greats of the scientific community the world over, what made him carry out research on the Hepatitis C virus in India? "An estimated 20 million Indians are infected by the Hepatitis C virus, mostly through blood transfusion, posing a major health hazard. About 20-30 per cent of them end up with liver cirrhosis or liver cancer. Developing a vaccine had been a problem, since the virus could not be grown in a laboratory. The American and Japanese strains had been cloned, but the Indian strain could not be characterised. Even 'interferon', the only drug approved for treatment of Hepatitis C, was proving ineffective in about half of the cases the world over. Curing it became vital," says Prof Guntaka.

So a couple of years back, he came to Hyderabad to work on the elusive Indian isolate of the Hepatitis C virus. His work began at the Deccan College of Medical Sciences, where he collected blood samples, isolated the serum, and subjected it to reverse transcription. At a later stage, he worked in the laboratories of two leading city-based biotechnology companies — Shanta Biotech and Sudarshan Biotech — cloning the product in different vectors. Finally, he took his work to his Tennessee lab. He succeeded in cloning the whole molecule and sequenced the genome of the virus, mapping its 9,500 nucleotides. The result was a stunning discovery — the Indian virus was totally different from its Japanese counterpart, and could be dangerous indeed. Thanks to Prof Guntaka, anybody can now make use of his finding to make diagnostic kits to study how the virus propagates and grows in the liver cells. "If every blood centre is screened, the chances of liver cancer can actually be lessened," says Prof Guntaka.

I sold land to fulfil my desire to study. I secured high marks, but didn't get into medicine, because I did not come from an influential family

Prof Guntaka was born in the village of Bollapadu in Krishna district, to a family of farmers. His early years did not show the promise of genius, and he went through school without much effort. As he was the youngest in the family, his brothers decided to exempt him from the family profession of farming. For a time, he cycled all the way to the nearest town of Vuyyuru to learn typing and shorthand. Then came the realisation that it was not something he could do all his life. He needed to study. "I sold land to go to college to fulfil my desire to study," says Prof Guntaka. "I secured high marks, but did not get into medicine, because I did not come from an influential family."

After pre-graduation in Microbiology from U P Agricultural University, Pantnagar, he left for the USA for higher studies. In 1970, at the end of four gruelling years of research at the Kansas State University, he was awarded the doctorate degree. After that, there was no stopping him — he worked with the best names in his field, carried on pioneering research work, won awards and fellowships in the dozens, and was invited by almost every prestigious scientific institution worth its name to speak on his research topics and work.

"After my PhD, I wanted to come back to India. But I realised that with my salary in India, I couldn't help my family much. So I stayed back," says Prof Guntaka, a committed family man. He makes it a point to spend a lot of time with his wife, who also works at the University of Tennessee, and calls his married daughter and son frequently during the week.

In Hyderabad, the big gap in infrastructural facilities hampered Prof Guntaka's work a lot. For simple reagents and primers, he had to wait for days on end. These would be available on demand in the US. "Even getting high quality water is a problem here," he laments. "Our scientists are talented, but have no facilities for adequate training. Teachers don't have the proper background to teach. Exposure level is low. But of course, things are getting better."

He is hopeful about the performance of the biotechnology sector, and rates the immunogenicity of Indian products such as vaccines higher than that of their counterparts produced by MNCs such as SmithKline. All that is needed, he feels, is stringent quality control.

"Regulators have to check every batch of every product. There is no easy way out," he says. "And the biotechnology industry will have to forget all about rivalry in the greater interest of the country."

Shift focus to a modern day scientific dilemma. What are his views on human cloning? "As a scientific experiment, they can try it to see how the clone behaves," he chuckles, "For childless couples, it might be a way out. But if an evil person is cloned, we don't want 10 of them!"

Prof Guntaka holds the worldwide patent for a drug that inhibits excess collagen formation in tissues. His current work involves a particular gene called the Y-box protein, which appears to have a key role in cell proliferation and replication. "I'm very excited," says Prof Guntaka. "If we find out how it works and develop an inhibitor that stops cell proliferation, well, we could have the cure for cancer." Here's hoping he succeeds.

If we find out how the Y-box protein works, and develop an inhibitor that stops cell proliferation, well, we could have the cure for cancer

Sir, any comment on GMOs like you support it or abort it or any other suggestions?

GMOs are widely used all over the world. In the healthcare sector, recombinant proteins made are used everywhere and cannot be replaced by any other way. In agriculture, there is a lot of debate on the merits and demerits of these which has to be weighed on an individual basis.

CORRESPONDENCE

Antecedents of a Nobel prize

SIR—The award of the 1989 Nobel Prize in Medicine and Physiology to Drs J. Michael Bishop and Harold E. Varmus has ended up in a controversy raised by Dr Dominique Stéhelin. As an author of one of the two papers and one who worked for the first six months on this project, I am well placed to describe the events leading to that masterpiece work. I record here the relevant chronology as I know it so that the scientific community can judge that the prize was properly awarded.

I joined Bishop's laboratory on 4 January 1973 as an assistant research microbiologist. Stéhelin had preceded me by a few months and was working on characterizing polysome-associated virus-specific mRNA. Very soon, Stéhelin and I became close friends and began to exchange views on a variety of issues, ranging from science to politics. He was somewhat frustrated because his project was not going well and because of personal problems.

Before joining the laboratory, I had set my mind on working on the various DNA intermediates in retrovirus-infected virus cells because of the spectacular discovery of reverse transcriptase by Mizutani and Temin, and by Baltimore, in 1970 (Mizutani did not get the prize, Temin did). When I arrived in the laboratory, Bishop suggested that I should talk to all the postdoctoral fellows and technicians to familiarize myself with various projects. After several discussions, I made up my mind to work on DNA intermediates, as nobody else was actively pursuing that topic. Varmus himself was working on integration by network formation followed by reassociation kinetics. He advised me on various tissue culture and molecular biology techniques, and Nancy Quintrell, a research assistant, provided me with valuable information on preparing probes and so on.

After a week, I had a meeting with Bishop and Varmus, at which Varmus suggested that I should first start by preparing the *src* probe. He outlined the rationale, which was based on the original observation by Peter Duesberg and Peter Vogt that transformation-defective variants lack a sequence of about 1,000 to 1,500 nucleotides. It sounded to me very interesting and I therefore set out to do the experiments.

I prepared radiolabelled cDNA probes from wild-type virus and hybridized them to the 70S RNA from transformation-defective (td) virus. I began to notice differences in the extent of hybridization between them and therefore pursued this observation vigorously for three or four months. As my heart was set on doing experiments with viral DNA intermediates, I began those experiments simultaneously. In about two or three months, I obtained evidence that the first steps of reverse transcription occur in the cytoplasm. We were all excited by what seemed to be a seminal observation, but I had to prove that the DNA we detected in the cytoplasm was not due to leakage from nucleii. After these initial observations, Varmus started enucleating the cells to show conclusively that DNA synthesis occurs in the cytoplasm.

In the next few months, we concentrated on this project, which resulted by the end of 1973 in the discovery of supercoiled DNA. As a result of this diversion, I had to slow down the work on *src*, and was only occasionally able to work on that project. One day in July 1973, Bishop came to me and said, "Ram, since your project on DNA synthesis is going so well, do you mind if Dominique continues this project; but I want to assure you that you are part of this project as well".

I readily accepted the proposal, since Stéhelin was (and is) a good friend, and his original project was not going well. I handed over my notebook to Stéhelin. He started working on this project at the end of July or August 1973, while I pursued the studies on DNA intermediates. By the end of 1973, we found supercoiled DNA, and the work on this was presented in 1974 at a symposium held at Rutgers University and at the Cold Spring Harbor meeting and later published in *Nature* in 1975.

I continued to attend the weekly meetings with Bishop, Varmus and Stéhelin until the middle of 1974, but discontinued later because of my own projects and also because of my intensive effort at job hunting. Stéhelin worked hard, and successfully prepared the *src* probe. Once the probe was defined, it was logical to evaluate it on all the DNAs available.

In my view, Bishop and Varmus deserve the Nobel prize. Several others such as Peter Duesberg, Peter Vogt, H. Hanafusa, Jeff Cooper and R. A. Weinberg could have been included, because the first three laid down fundamental work which made possible the oncogene work on retroviruses and the last two contributed to identifying cellular oncogenes not present in retroviruses.

In retrospect, it seems to me that if I had not obtained positive results, there would have been no oncogene project. In many laboratories, many students and research fellows begin work on new projects, but not many succeed. Initial failure of any project results, in general, in its abandonment. Very few continue on a project when several experiments fail. That was what happened to Stéhelin's first project and therefore, to my mind, fortuitous circumstances paved the way for his involvement in the oncogene project.

Therefore, as the first participant in the early work, in the 1970s, which led to the award of the 1989 prize, I believe that the Nobel committee acted prudently in the selection of Bishop and Varmus. I hope that the Nobel committees will continue to base their decisions on scientific merit, ingenuity and the impact of discoveries and ignore the publicity and politics which develop following some discoveries, such as that of the AIDS virus, which is but one among many such discoveries and controversies of the past decade.

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SIR—Under the heading "Conduct unbecoming", *Nature*[1] says that "As all agree, Stéhelin was the main pair of hands behind the experiments that first showed that the oncogenes of tumour viruses are stolen and corrupted versions of genes from the cells. . .". The latter half of this statement is incorrect for the following reasons.

The first demonstration of the cellular origin of viral oncogenes was published from entirely different laboratories three years before the paper by Stéhelin *et al.*[2] appeared in 1976. Scolnick *et al.*[10], cited in Stéhelin *et al.*'s 1976 paper, and Tsuchida, Gilden and Hatanaka[4] observed in 1973 and 1974 respectively that the *ras* sequences, then called *src*, of Harvey and Kirsten sarcoma viruses were from cellular genes. The title of a paper by Scolnick and Parks in 1974 is "A second murine Type C virus with rat genetic information"[3] and that of a paper by Tsuchida, Gilden and Hatanaka is "Sarcoma virus related RNA sequences in normal rat cells"[4]. The protocol of these experiments was exactly the same as that used later by Stéhelin *et al.* and so was the conceptual basis, namely to test Huebner's and Todaro's oncogene hypothesis of 1969[5] with the then newly discovered viral oncogenes. The oncogene hypothesis postulated the existence of switched-off cancer genes in normal cells. The only technical distinction between the original experiments with the Harvey and Kirsten viruses and the later ones by Stéhelin *et al.* with the Rous sarcoma virus was that, in addition to sequences from the cell, the Harvey and Kirsten viruses had also 'stolen' sequences from an endogenous rat retrovirus. This was painstakingly and convincingly sorted out by the Scolnick group in subsequent years.

Further, there is no mention in Stéhelin *et al*'s paper[2] that the sequences transduced had been 'corrupted' cellular sequences. Instead, these sequences were called viral homologs of cellular genes in this[2] and subsequent studies[6]. Indeed, on the basis of this homology, the cellular progenitors of viral *onc* genes were proposed to be switched-off cellular

BT people

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India maps Hepatitis C

Our New Delhi Bureau
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FOR THE first time in the world, the complete sequencing of a microbe of Indian origin — Hepatitis C — has been successfully done by Indian scientists. The achievement opens up enormous opportunities for development of diagnostics, vaccines and new drug targets.

Minister for science and technology Dr Murli Manohar Joshi today announced the successful sequencing of the genome of the Indian isolate(strain) of Hepatitis C virus (HCV).

HCV causes serious human liver diseases like hepatitis, liver cirrhosis and hepatocellular carcinoma. An estimated 170 million people worldwide are infected by HCV, which is four times as many as HIV-infected. In the next few years, the number of deaths from HCV is expected to overtake deaths caused by AIDS, annually.

Credit goes to a department of biotechnology (DBT)-supported project carried out over the past two years by the Centre for Liver Research and Diagnostics (CLRD) of the Deccan College of Medical Sciences in Hyderabad, with the help of NRI scientist Ramareddy V Guntaka, who is a professor of University of Tennessee, the US.

Financial support came in from Shantha Biotech and Sudershan Biotech Ltd where Prof Guntaka is the chief scientific advisor. The genome data has been submitted to the Gene Bank.

Speaking to ET, Dr V K Vinayak, advisor (medical), DBT, said the most frightening aspect of HCV was that it was a 'silent epidemic' and those affected were often in the dark as the virus had an ability to be dormant for long periods of time.

The HCV is heterogeneous — there are 11 genotypes and several subtypes — and it has so far been difficult to pinpinpoint which variation causes the affliction. The variations now revealed in the Indian isolate would provide some clues.

Dr C M Habibullah of CLRD said that blood samples would now be collected from 100-500 HCV positive patients in India and studied to detect the variations. This is expected to provide a clue as to why some patients respond to treatment, while others do not.

Dr Guntaka said that anti-HCV treatment drugs now available are Interferon Alpha and Ribavirin. But both anti-virals were prohibitively expensive and beyond the reach of common man in countries like India, Bangladesh and Pakistan.

However, only about 40 per cent of the patients respond to Interferon, and in some cases, also develop resistance to the treatment after a while.

"If we could develop a tissue culture to study HCV replication, it can be used to screen various anti-viral compounds. Using the Indian HCV sequence, we would like to construct replicons and establish virus producing human cell lines.

"These will be used for identification of critical regions in the genome which cause the disease and which block the body's response to treatment as well," he explained.

Dr Manju Sharma, secretary, DBT, expressed confidence that the new tools would soon be available to doctors for better management of Hepatitis C.

With the prevalence of HCV in the world ranging between 0.2 per cent and 2 per cent, the highest being in Egypt (14 per cent -26 per cent), the findings by the department of biotechnology would have a global impact.

Sir, any message to Life sciences community.

There is a vast potential for biotechnology and in order to tap these resources the Government has to come forward with generous funding for goal-oriented projects. This is the only field where Indian scientists can compete with advanced countries. If properly directed and funded, this is an unlimited source for producing biologicals important for human and animal health as well as agriculture. Indian life science community should focus on applied research pertinent to India. It is shameful to see that India is still the number one country where infectious diseases and deaths from these are alarmingly high. We should concentrate on research to eradicate these maladies, which can not only improve health of individuals but also save billions of rupees. It is unfortunate to see that very little support for research by industries especially the pharma sector. Because of this and lack of jobs very few talented youngsters are opting Life Sciences.

Sir, can you tell us about future goals of your lab?

In my laboratory at the University of Tennessee, Memphis and at Sudershan Biotech in Hyderabad, we want to produce high value recombinant protein therapeutics including several peptides using our own novel vector-host expression systems. Another major goal is to bring a vaccine for Hepatitis C Virus, a silent killer.

By
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