Face to Face

This section features conversations with personalities related to science, highlighting the factors and circumstances that guided them in making the career choice to be a scientist.

Going Solo: Adventures in Organic Synthesis

A V Rama Rao talks to Sujata Varadarajan

The synthesis of natural compounds and biologically active molecules has always been a challenging problem, as they occur in specific geometric form that is often hard to reproduce in the laboratory. Taking up such challenging synthetic work is the very nature of Dr. A V Rama Rao. While working in the National Chemical Laboratory, Pune, he developed new methods of asymmetric synthesis and total synthesis of natural compounds[1]. He is one of the scientists of the country to develop industrially viable processes for the preparation of biologically active molecules – a commendable achievement for a chemist who was not directly working in industry.

His foresight, keen interest in natural products and desire to do socially relevant science (of which he remains a strong advocate) directed his career along unusual lines. His skill as an organic chemist was evident from the early years of his research career. His technical training and interest in industrial processes led to a long and constructive interaction between his laboratory and several top pharmaceutical companies within and outside the country.

Using the Indian patent laws to his advantage[2], he shot into the news at periodic intervals – notably in the eighties for developing a cheaper alternative to the anti-cancer drugs obtained from the *Vinca rosea* plant as compared to that offered by Eli Lilly, in the nineties for ending the Burroughs Wellcome Company's monopoly on the production of the AIDS drug Azidothymidine (AZT) (*Figure* 1), and recently for his novel total synthesis of the anti-cancer drug Irinotecan by a method which has replaced the original process (which involved modifying a natural

[1] The complete synthesis of a natural compound instead of isolating it from natural sources.

[2] Indian patent laws at that time recognized the patenting of only processes and not products in the pharmaceutical industry.

PRODUCTION OF AZT

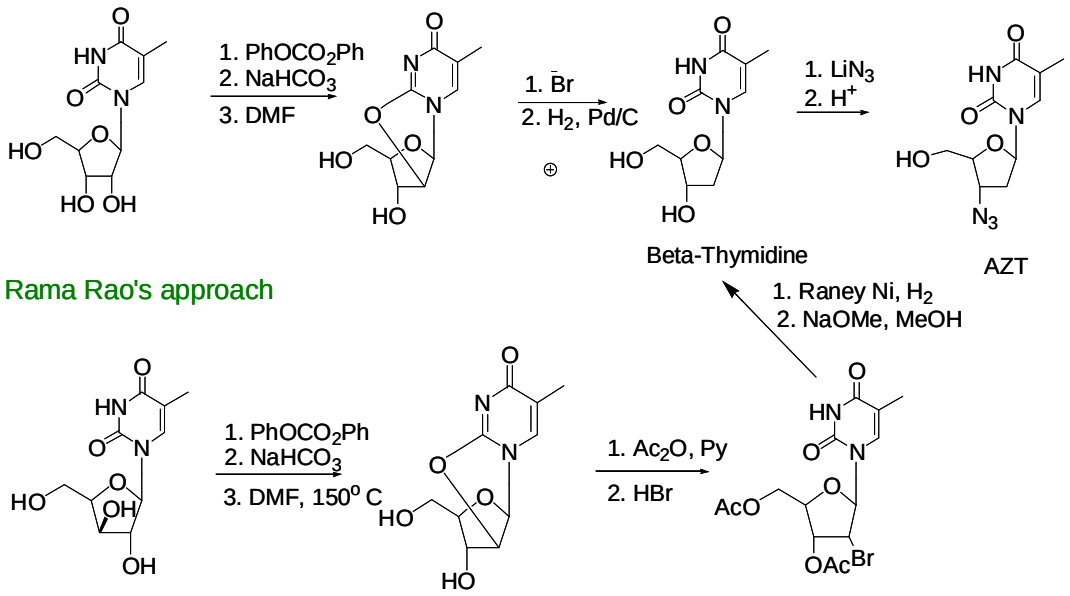
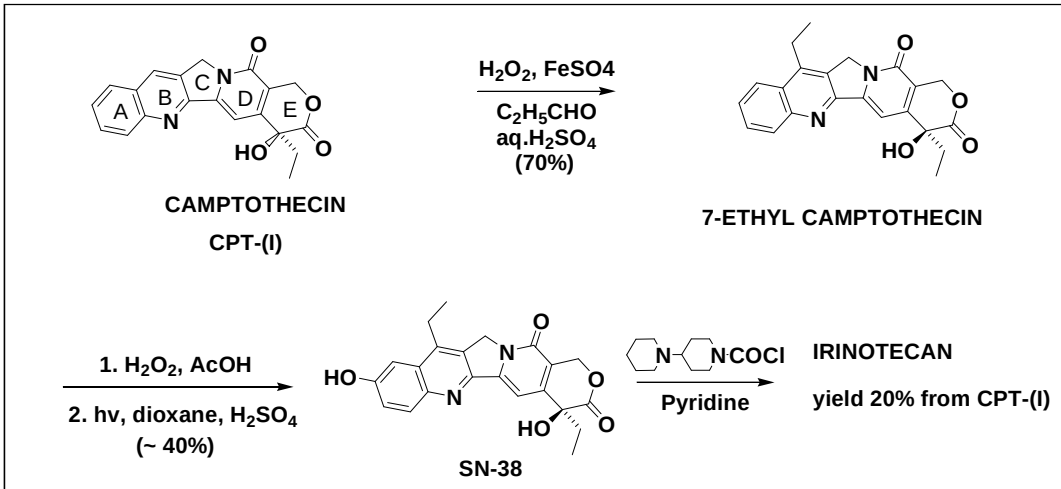


Figure 1. The synthesis of AZT using a ribose derivative (top panel) and A V Rama Rao's method, using a xylose derivative (bottom panel). More details can be found in Rama Rao et al, J.C.S. Chem. Commun., 1994, 1255

product, Camptothecin which was isolated from the Chinese tree *Camptothecin accuminata*) (*Figure* 2). A V R played the main role in turning around the Regional Research Laboratory (now called the Indian Institute of Chemical Technology) at Hyderabad [1]. After retiring as Director from IICT, his courage and entreprenuership impelled him to chart a complete new terrain. He set up a company for custom synthesis and process chemistry (development of chemical processes or products to order). In a span of a little over ten years, the company, AVRA, has grown from being a small lab in a godown to an impressive three-unit institution with state-of-the-art research labs, innovatively designed pilot plants and GMP (good manufacturing practice) production units conforming to FDA regulations, with production capacities of one tonne. They have expanded their range of activities as well, and are now producing their own chemicals in addition to synthesizing for companies (*Figure* 3). A fourth unit is being planned at Visakhapatnam.

AVR's list of synthesized compounds is impressive, which includes anti-bacterial, anti-inflammatory, anti-histamine, anti-hypertensive, anti-anxiety, anti-asthmatic, anthelminthic, anti-cancer and anti-HIV agents. His work on asymmetric synthesis of complex natural



AVRA'S TOTAL SYNTHESIS OF IRINOTECAN AND ITS KEY INTERMEDIATES

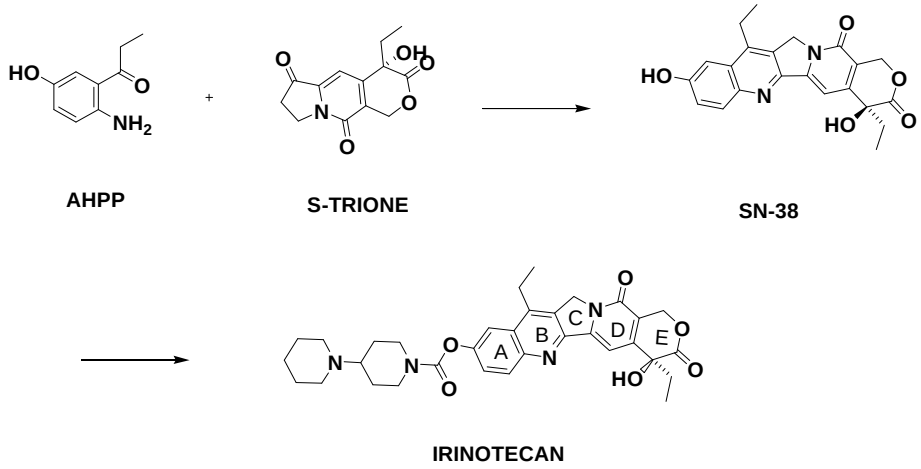


Figure 2. A. Irinotecan (trade name Campostar) is a safe analogue of Camptothecin and is used as a prodrug. Its synthesis from Camptothecin is shown here.
B. The total synthesis of Irinotecan, developed at A V Rama Rao's lab.

products is notable for intelligent planning and using easily available starting compounds. It includes the synthesis of macrolides[3], anti-HIV agents, immunosuppressants and anti-cancer cervinomycins[4]. He developed a novel method of the synthesis of Fredricamycin A [2] and provided asymmetric synthesis of FK-506 [3, 4] (which has 14 asymmetric carbons) and MeBmt (an unusual amino acid present in Cyclosporin-A) [5]. He has also initiated projects on

[3] A group of drugs (usually antibiotics) belonging to the polyketide class of natural products.

[4] A family of antibiotics classified on the basis of their structure.

Figure 3. (a) The pilot plant at AVRA. (b) AVRA- Unit II. (c) At the newly inaugurated Unit III (2nd April, 2008) - a display of samples of chemicals produced by AVRA. (d) Dr. A.V. Rama Rao, at IICT, Hyderabad, April 2008

the rational design of anti-HIV and anti-cancer molecules in collaboration with Abbott Laboratories and National Cancer Institute, USA.

Not surprisingly, AVR has won accolades and awards from a large number of institutions and societies, both within and outside the country. He was awarded a Padmashree in 1991. Over time, his blunt, no-nonsense approach has ruffled many a feather. Known to be a hard taskmaster, he is forthright and vocal about his views, especially regarding science and technology. At the same time, one also witnesses a spontaneous, cheery sociability, courtesy and an infectious enthusiasm in his interactions with people. He has started the A V Rama Rao Foundation, which promotes scientific talent in the country by organizing scientific lectures, felicitating eminent chemists and generously providing endowments in the form of awards to upcoming and established scientists.

His close, supportive family is one of his strengths. His sons, Ramakrishna and Chandrashekhar (Chandra) have now joined his venture, adding their considerable and diverse skills to it. His quiet and warm hearted wife, Hymavathy, remains, as always, the backbone of this accomplished family unit.

SV Could you tell us about your early education?

AVR I was the first child among the nine to my parents. My father was a clerk in the State Government and he was frequently transferred from one place to the other. For this reason my elementary education did not go well. But I went to high school at Guntur by staying with my grandparents.During this period I spent most of the time in playing and I scraped through exams till I reached SSC.

During my SSC days, I stayed with my aunt's family. My father was sending Rs.40 per month for my maintenance. They used to manage the entire home with this amount. That was the time I realized the importance of education and I never looked back in securing good marks in all my subsequent examinations.

I entered the Hindu College, Guntur, for my Intermediate, selecting Biology, Physics and Chemistry as optional subjects as I was scared of Mathematics. I did not realize that BPC was the choice of those who aim to take up medicine. Although I secured good marks in my final exams, I was (ranked) somewhere around 15 which was not enough to get admission to Guntur Medical College and did not opt to enter Vizag medical college. The next best choice was to join BSc with chemistry as main subject, which fascinated me from my high school days, so joined Andhra Christian College at Guntur, where I also served as a student leader. This did not affect my performance in examinations and I was one among the four who secured a first class.

SV What did you do after this?

AVR I was keen on pursuing my studies for an MSc degree but the family financial conditions did not permit me to go beyond Guntur. I decided to apply for the post of a demonstrator in the same college. As the principal had a good opinion about my academic abilities I was selected for this post.

At the same time I was selected for a postal Clerk's position, and my father was very keen that I join as a clerk rather than accept a temporary demonstrator's post because he firmly believed that a Government job offers more security and also pension after retirement. For the first time I did not accept my father's advice.

Before I completed the academic year (as a demonstrator), I was selected as technical assistant in State Agricultural College at Bapatla. I took up this position, thereby fulfilling my father's wish of my joining government service. However, in no time I realized that a BSc degree will not take me further in my career. Also, there was

always bickering between technical graduates and pure science graduates, as the former were rated better in the assessment for promotion, etc.

After convincing my parents, I applied for admission in the Department of Chemical Technology of Bombay University (BUDCT), a well-known Technical Institute, and secured a seat for BSc (Tech.) with Pharmaceuticals as the special subject. Here I studied engineering subjects (Chemical Engineering, Mechanical Engineering) and subjects relating to Pharmacy (Microbiology, Biochemistry, Medicinal Chemistry, manufacturing basic drugs and formulations). My interest was more in pure Chemistry rather than Pharmacy or Chemical Engineering.

In 1960, I joined NCL for my PhD (Tech.), under Prof. Venkataraman, the Director. After completing PhD, (in 1964) I wanted to go abroad for post-doctoral work. But since Prof. Venkataraman wanted me to work with him for some more time, I continued for one more year. During this period I worked on the colouring matter of lac. This is one of the dyes that comes from lac resin, found mostly in the eastern part of India – Orissa, Madhya Pradesh, Bihar, Bengal. This was the main dye used to colour silk and wool during the 19th century. After World War II, it was replaced by synthetic dyes. I found that it is not one compound, but a mixture of four compounds. I was able to determine the structures of all the four laccate acids, due to the availability of modern tools like NMR (nuclear magnetic resonance spectroscopy), separation techniques. As a result of this success, Prof. Venkataraman wanted me to continue for some more time. So I asked him for a job in 1965, as I was married and my daughter was born. I became the first Sc-B (Scientist, B position) in NCL without crossing the seas. As Sc-B, I worked on structure and reactivity of synthetic dyes.

After his retirement, Prof. Venkataraman was given a PL-480 project (from the US Forest Department). As he had crossed 70 years of age, they insisted that a younger scientist should head the project and Prof. Venkataraman should remain as advisor. Those days, the head of the department of a national laboratory was of the rank of scientist E, who was usually selected by advertisement. So, when they wanted person for a HOD rank, I got two jumps and directly got that position.

To review the progress of the PL-480 project, Prof. John from the US Forest Department at Wisconsin was visiting us every year. He was keen that I should spend work for two years in a good school in the US and recommended me to Prof. Hargobind Khorana at MIT. By then Khorana had won the Nobel Prize for his work in biological chemistry. Although, I received a fellowship offer from him, I preferred to work with an organic chemist and joined Prof. E J Corey at Harvard University. It

was in EJ's lab that I learnt the synthesis of complex, biologically active compounds. My two year stint with him changed my outlook on research and I was very confident in tackling the synthesis of complex molecules.

After my return in September 1977, I started working on the total synthesis of biologically active compounds. I was also very particular that the work should have some practical relevance. So I used to look for molecules which have definite physiological activity, and would make a dent in the market. I first chose the synthesis of Adriamycin. Even today, it is one of the widely used anti-cancer agents. It is called Doxorubicin. If we use cheaper reagents in the synthesis, then it becomes commercially viable. By this way I got recognition in the US Pharmaceutical industry because they were interested in these compounds.

SV What were some of the industrial projects that you undertook?

AVR In 1972, the Indian patent law was changed wherein product patents were not permitted and process patents were curtailed to five years. Mrs. Indira Gandhi, in her capacity as President of CSIR, sent a letter to all the Directors of National Laboratories to initiate industrial research for speedy industrial development of the country. I became interested in exploiting the new patent law to my advantage by selecting a project on a value-added drug. At that time diazepam (an anti-anxiety agent manufactured by Roche) was a best selling product worldwide. I found the Roche process a bit tedious. I succeeded in providing simpler and cheaper alternative route in three months. During that period, I met Dr. Y K Hamied, Chairman & Managing Director, CIPLA and he was very much impressed with our approach. He met Dr. B D Tilak, Director NCL, and finalized the deal to transfer the lab process for a one-time payment. To my knowledge, this was the first project (that was) sold to industry from NCL and commercialized in less than six months after the transfer.

My second project, after my return from Harvard University, was on the isolation of two anti-cancer agents from the leaves of *Vinca rosea*. This proposal was submitted to the Maharashtra State Science and Technology Cell. Maharashtra was one of the largest exporters of dry leaves from which Eli Lilly of US used to isolate Vinblastine and Vincristine by a tedious column chromatographic method. As this plant grows mostly in India, Eli Lilly used to import these leaves. Till the early '70's, mostly forest tribals collected the leaves and sold them to traders who exported the leaves. As the demand for the leaves grew by mid '70's, the traders started adulterating the dried leaves. Eli Lilly initiated their own plantation in Houston and we lost all our trade to

USA. This prompted the Maharastra Government to initiate the project and our proposal was timely and we got a liberal grant from them (Rs.4 lakhs in 1978). In a year's time we succeeded in isolating Vinblastine on 15 g scale from 40 kg of dried leaves (without chromatography) and converted it to Vincristine by simple selective oxidation. We also formulated these products with the help of HAL, Pimpri, and carried out clinical studies at Tata Cancer Institute Bombay with the help of Dr. Shetty, the head of Chemotherapy division.

I was keen to transfer the technology in 1982 and approached Dr. Hamied, to exploit the technology because nobody was making anti-cancer drugs in India. When he looked at it, he told me that I'm a good scientist but not a good businessman. The reason was: cancer drugs were very expensive. In India, only Rs. 25 lakhs worth of Vinblastine and Vincristine vials were imported. He asked me, "What type of investment is required?"

I calculated – the minimum amount required was Rs. 2 crores for collecting the leaves, storage, extraction, separation, purification, etc. In those days the bank interest was 20%- so he would have to pay Rs. 40 lakhs as interest per annum while the business would pay only Rs. 25 lakhs. He said, "What nonsense! It is not a wise decision." But he appreciated the method I had developed.

Then I went back thinking, "Where did I go wrong? I thought I had come up with a good technology. How is it that Eli Lilly is selling (the product)?" I went to the library and looked at the patent life of this product. The patent would expire in '85. The next morning, I called him and told: "Dr. Hamied, you have not looked into it carefully. Never look for any Indian business for this type of product. We should export it. The patent expires in 1985. You have three years more to commercialize it. You can obtain US FDA registration by then. We'll give a hard time to Eli Lilly, become a world leader."

For the first time he showed excitement and agreed to undertake the project. We went ahead and made our own sample vials, which we were not supposed to do. We had no idea of the regulations. I went to Tata Cancer Hospital where Dr. Hamied introduced me to Dr. Shetty, Head, Chemotherapy Division. He tested our vials on patients and found them to be as active as Eli Lilly's. The product went through clearances fast and was commercialized. For the first time CIPLA produced these compounds in a GMP plant to export to the United States. Thus CIPLA entered the anti-cancer field.

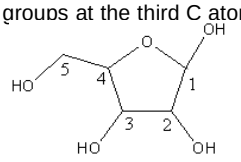
Another project, which I was keen to take a re-look, was on Vitamin B6. The project had been initiated as early as 1958 and continued till 1973, but without success. When I took over as head of Organic Chemistry Division in NCL in 1980, I felt that I should revive this project and succeed rather than (let it) remain as a black mark in our minds. I realized where my predictions had gone wrong earlier and finally succeeded in selecting a correct approach and transferred the technology to Lupin in 1983. My group from NCL and Lupin set up a pilot plant and worked for two years to optimize the process. Lupin started its regular production of 40 tonnes per annum by 1989.

SV What are the other areas you have worked in?

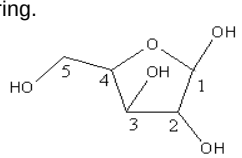
AVR Every five years I used to change my area of work. I worked on anti-tumour agents, then later we went to immunosuppressants, then we went to cyclic peptides (Vancomycin, etc.).

In 1989, I read about a young boy, who had undergone blood transfusion in the Gulf, returned (to India) and died due to AIDS. AIDS had just appeared in India and from 1985 onwards people became aware of it. Initially there was no drug for AIDS. The National Cancer Institute (USA) has a huge stock of potential anti-cancer drugs. They started screening the drugs which had shown anti-viral activity, and thus AZT (Azidothymidine) was discovered – purely by screening and not by design. In 1985, US FDA approved its use for HIV patients. I knew that was the only drug available at that time. So, I thought, "India has a huge population, and AIDS may become a major issue one day." That is how I chose this project. The synthesis of AZT involved the use of ribose, which was at the time $200 a kilo. The nearest product to that is xylose, which was $10 a kilo. The two differ in sterochemistry at only one centre i.e., C-3 with its OH on the opposite sides[5]. Luck favoured us – when we did the synthesis, we got a produce inverted on its own, beautifully – 100% inversion, giving the same optical activity (*Figure* 1). This was a new, beautiful chemistry and we came out with a better, cheaper way of making AZT. It was given to CIPLA once again and the doing was introduced in the Indian market in 1993. Now CIPLA is the largest manufacturer of all anti-AIDS drugs and supplies (them) world over.

[5] The structures of D-Ribose and D-Xylose are shown below. They differ only in the spatial orientation of the H and OH groups at the third C atom of the sugar ring.



D- Ribose



D- Xylose

SV What was your shift from NCL to RRL (Regional Research Lab, Hyderabad) like?

AVR The post of Director of RRL-Hyderabad fell vacant in 1985 and Prof. M M Sharma was appointed as Chairman of the Selection Committee. He used his prerogative and directed me to appear before the Selection Committee for that position. I went and appeared before the Selection Committee with an open mind. Finally, the selection came in my favour. Even then, as I always thought the RRL was not in good shape, I was reluctant to go to Hyderabad. However, Dr. Paul Ratnaswamy, head of the Catalysis division of NCL, impressed on me to move to Hyderabad. Hence I decided to move to Hyderabad.

I took over RRL as Director in July 1985 and by 1990, it became number one by the CSIR yardstick. In 1988, CSIR initiated a young scientist award, and each year an RRL scientist won that award in Chemical Sciences till I retired in 1995. The single exception was when it once went to NCL, that too to one of my former students. When CSIR introduced a Technology award, we won that too, not only in the very first year but most of the time. In 1993, CSIR instituted a Business Development cash award and I was the first to receive the award. I also changed the name of the institute from RRL to Indian Institute of Chemical Technology in 1988. Sir John Maddox, writing in *Nature* on Indian Science wrote about IICT thus: "The most improved laboratory in India must be the Indian Institute of Chemical Technology (IICT) at Hyderabad. Ten years ago, as the Hyderabad Regional Research Laboratory, it was one of the worst. The difference is not so much the change of name, but the arrival as Director of Dr. A V Rama Rao, a vigorous no-nonsense organic chemist of distinction." [6].

When you retire as director of a scientific institute you may become a distinguished scientist in that institute, but in our country you really become an "extinguished scientist" once you lose your chair or power. Hence I preferred to go on my own by becoming an entrepreneur at the age of 60. However, every one I knew discouraged me in taking this path. The only person who fully supported was Prof. M M Sharma, stating that he was confident that I would succeed in whatever I undertook because of my commitment.

SV Was the idea building up for some time or did it occur suddenly?

AVR No, I decided immediately. Nothing was thought about till the day I retired because I was so busy. I used to go for lecturing every year to the US. That year also I had several pending invitations, and I went. Before I went, we discussed in the family about the company. My younger son also liked the idea of my becoming an entrepreneur. He

gave me a good example, which I still remember. He said, "Suppose you start climbing Everest, and you have succeeded, then what will you do? Will you sit on it? No – you have to come down." Right? "So, you've gone on the peak in your field, now you come down and start climbing a second time. Now you don't have the same route, you're taking a different direction. So, start in that direction," he said.

We discussed what sort of name the company should have. My wife said, "You are the brand name, why do you want other names?" My initials are AVR, but my family said "You can't call it AVR Lab, it doesn't look nice.". When I told Dr. Hamied about the name he said, "You add one more letter 'A' from Rama. Then it becomes 'AVRA'– it is a word." And that's the way AVRA was started.

When I went to USA, for my lecture tour in 1995, G D Searle, a company which is now a part of Pfizer, wanted to sponsor a project with me. I said, "I've retired.

"Then what are you going to do?" they asked.

I said, "I want to go on my own."

"Why don't you take up this project?" they said.

It was a God-given gift you know, sometimes some sort of surprises happen. I agreed.

Thus AVRA was registered in July 1995 (I retired at the end of April). At that time we didn't have any place, but Chairman of Dai-ichi, Karkaria promised to provide their basement in Nacharam (Hyderabad), converted into a lab. It was literally a godown, where you store cement. An organic chemistry lab requires only fume cupboards. So we built some four cupboards with an exhaust fan – it was not a sophisticated lab. G D Searle gave me the project. They showed me a molecule for which they wanted me to work out a process (of synthesis), because their process was not suitable. It produces a nasty by-product. That's all they told me. "We don't want to tell you our route, you find your own. But see that it should be safe, scaleable." I said, "Yes".

Then they asked me, "How much will you charge?" I had never thought about this aspect. I said, "One crore rupees, which is two hundred thousand dollars" (in '95). They readily agreed. I said, "I need 50% of the money, as advance." They gave me a cheque the next morning. So I got the money, I got the place to work, and I've not invested even a paisa of my own. We made a success of that project which moved to phase II clinical trials. Then it went to phase III. I optimized the process well. They

were very happy with the project and asked me to scale up. So we built our own lab with pilot plant, what we call Unit I, in 2000, with all the profits ploughed back. In 2001, we bought a sick unit – what was initially called Uniloyds, where Dr. Anji Reddy started his career. We re-built it with production facility (this is Unit II), and formally inaugurated it in 2005.

Today, everybody is talking about CROs – Chemical Research Organizations. We were one of the first to demonstrate that we can do this. Now there are a large number of organizations outsourcing chemicals. But what we did was actually research, not making simple things for others. Recently we started realizing that we should have our own products, rather than work for others.

For the last four years we have identified molecules in the anti-cancer area. Why anti-cancer? I used to work in this area anyway. Also, cancer is affecting the world over. Anti-cancer drugs are complicated and difficult to manufacture. Most of them are natural products, derived either from plants or microbes.

Always, we think, "Synthesis of a natural compound can never beat in cost the natural product itself." I was always thinking about this (whether it is true). So I picked up Camptothecin. We did two years' work and came out with the total synthesis. For the first time we have introduced a synthetic compound without going into isolation. That is our real contribution. Its analog, Irinotecan, has become a generic drug and now everybody is buying from us because we are offering it cheaper than the one derived from the natural product. Qualitywise ours is 99.9% pure while semi-synthetic products never reach more than 98% purity. China is the largest source of (natural) Camptothecin. Today, we are exporting SN-38 (see *Figure* 2) to China.

SV What are your other interests?

AVR As hobbies I have nothing except going to movies. I go with my wife once a week for a movie. I am not serious about movies; I take them purely as entertainment. I also like spending time in chemical labs. I had a lot of interest in this and used to visit many factories, see the labs, and talk to people. Even when I was at NCL, I was working as a consultant and used to help entrepreneurs without charging. That's the way I got to know many things about industry. I also worked as a consultant to a US company and I used to get many projects from the US. Those days, nobody used to believe that we could attract sponsorship from US Pharma companies. Now things are different.

SV Do you have any suggestions for students who want to pursue research, and set up

companies?

AVR One thing I tell you – we are not creating leaders. The reason is that we don't work on projects that are relevant to the nation. We are followers of the US. Let me tell you, I am very blunt about this. We always publish in the best international journals because many read them, because it is useful. I agree to all that. But, is it relevant to our country? That nobody bothers. Or even, is it relevant to society? Young scientists should be more ambitious and work on important projects of national relevance rather than publishing mediocre papers and counting numbers. Science is always exciting and more and more should take up science education and research.

Nowadays, parents are influencing children to take up Computer Science as it fetches good jobs. But they are not realizing that computers are tools and it depends on us how we take advantage of them. On the contrary, biology and physical sciences offer several challenges and we should produce more scientists rather than computer engineers.

I would like to see many science graduates turn into entrepreneurs. Just a PhD degree will not help. They have to have at least a little exposure in working in production or industry so that they have a feel for what is to be done or how to go about it. If they start immediately, I don't think it is very easy. They should have somebody as a partner who has been exposed to industry. Jointly they can do it, but otherwise a fresh PhD can do at the most projects like making chemicals in a small way in a lab. But, to make it on a large scale, one has to undergo a certain amount of industrial exposure.

Acknowledgements

SK thanks Ashish Misra for help with ChemDraw.

Suggested Reading

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