

Marshall Nirenberg (1927–2010)

Marshall Nirenberg – ‘one of sciences’ great titans’ – passed away on 15 January 2010 after fighting a brief battle with cancer. In the last few months several noted molecular biologists have written about his achievements in cracking the genetic code and their associations with him. These events were of the calm and tranquil but highly competitive days at NIH and the deciphering of the genetic code was a galvanizing event.

What I wish to write about here is the post-genetic code era of Marshall’s achievements. In the late 1960s, Nirenberg’s interest shifted from genetics to neurobiology. At this time, neuroblastomas were typically studied to fight the cancerous cell growth which most often afflict infants and young children. He made an innovative move by using the neuroblastoma tumour cells towards a different end. In the laboratory of biochemical genetics, neuroblastoma cells were cloned and cell lines with desired characteristics were created. Many papers published from his laboratory showed that these tumour cells could be differentiated and exhibited the phenotypes of mature neurons and formed functional synapses with muscle cells in culture. A ‘cell bank’ created in his laboratory continues to be the source of samples from all over the world. In the 1970s, Nirenberg used this model system as a platform for explorations into the morphine receptors. It was at this time I joined Marshall’s lab as a Fogarty International Fellow (on leave from AIIMS faculty). There were about 15 young scientists in his laboratory including William A. Catterall (who discovered sodium and calcium channel proteins), Zvi Vogel, Urie Littauer and many others. A. G. Gilman (awarded Nobel Prize in 1994) had left. We started searching for neuroblastoma cell lines which had high density of morphine receptors. In our studies on opiate addiction, we developed a cellular model which made it possible to study the development of tolerance and dependence on opiates in a well-defined *in vitro* system. This model continues to provide guidance to the scientists working in the opiate research field.

By the late 1980s, a set of genes known as homeobox genes had become central to Marshall’s studies. At that time, there were

17 homeobox genes that were known and found in *Drosophila*; and Nirenberg found it a burgeoning field of study. His group discovered four new homeobox genes expressed in the nervous system which he named *Nk1* to *Nk4*. *Nk2* gene discovered by him performs a crucial function in early *Drosophila* neurogenesis. The expression profile of *Nk2* was studied in detail by Nirenberg in the mid-1990s. Later he initiated experiments on transcriptional regulation of the *Nk2* gene, which led to the discovery of each separate regulatory sequence for almost every *Nk2* positive neuroblast. Just after this he shifted his efforts toward downstream regulation of the *Nk2* gene. Nirenberg’s experiments concerning homeobox genes and the assembly of the nervous system in *Drosophila* were crucial in the advancement of the field of neurobiology.



In early 2000, Marshall was totally engrossed in identifying genes required for *Drosophila* nervous system development. His group screened a library of dsRNAs corresponding to about 25% of the *Drosophila* genome for their effects on the development of the embryonic nervous system. Nirenberg continued to make significant discoveries in neurobiology and genetics, from pioneering work in culturing neural cells to studying gene expression, stem cell differentiation and nervous system development. He and his associates discovered a *Drosophila* gene that is essential for normal heart function.

My association with Marshall spans over a period of 35 years. I was greatly influenced by his enthusiasm for plunging into new and exciting fields in science. Marshall always welcomed people desirous of inventing new things. He was a wonderful and modest person and always listened patiently to colleagues. One of the incidents I remember is the invitation from

him to join his lab after he learnt that my stint at AIIMS was over.

Marshall’s quest for new and exciting problems continued. In early 2009, he invited me to join his lab reviving his and my continued interest in opiate addiction. Marshall emphasized that with the use of cellular pathway assays, we can easily identify small molecule modulators of important physiological functions including memory formation and addiction. He wanted me to miniaturize and optimize the 1975 model of opiate addiction in a quantitative high throughput screening format. I knew of Marshall’s illness and was hesitant to go there but he insisted and informed me of the success of his ongoing chemotherapy. Marshall’s interest in research continued until the last few days of his life. Barely a week before his death, he phoned me from New York to enquire if the new instrument he had ordered was installed, enquiring into every little detail of demonstration and if I had good results using it.

Marshall made significant contributions to society outside the laboratory. He was a humanitarian and he joined efforts warning of the madness of the arms race, consequences of human cloning, exchange of ideas and political freedom and encouraged public understanding of science.

As I left his funeral, I thought how privileged many of us are to meet extraordinary individuals. In Marshall’s case not only because of the science he developed but, because of the personal qualities of empathy, deeply interested in the world around him and in the people to whom he was speaking. Once I asked him if he believed in life after death, he answered after a pause, ‘No, we don’t exist after death only in the memory of people who have known us’. Marshall was predeceased by his wife of 41 years, Perola Zaltzman a chemist from Brazil, and is survived by Myrna Weissman, Professor of Epidemiology and Psychiatry at Columbia University, College of physicians and Surgeons.

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