

Recent Developments in Cancer Research

**Dr Harold Varmus
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National Institute of Immunology, New Delhi
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Lecture Report

Nobel Laureate, Dr Harold Varmus, recognized for his research on retroviruses and the genetic basis of cancer gave a lecture on “Recent Developments in Cancer Research” at National Institute of Immunology (NII), New Delhi, an event co-organised by NII, Wellcome Trust/DBT India Alliance and Department of Biotechnology, Government of India. His lecture largely gave an overview of the recent developments, challenges and the future directions in the field of cancer research, which included the current research of his group in this area.

Dr Varmus, who had spent time in Bareilly as a young medical student, described cancer as a complex disease that requires innovative research and treatment strategies. At the outset, Dr Varmus introduced the key questions that drive the cancer research field- Is cancer one disease or many diseases? What makes the cancer cell grow so stably in such an inappropriate manner? How does a normal cell become a cancer cell? Providing answers to these questions formed the backdrop of Dr Varmus’s lecture which drew from his research work till date and other advances in the field.

Dr Varmus entered the field of cancer research in 1970s as a postdoctoral scientist in the laboratory of Dr John J. Michael Bishop at University of California San Francisco, USA, the same year National Cancer Act was signed in the country. Dr Bishop and Dr Varmus together received the Nobel Prize in Medicine and Physiology (1989) “for their discovery of the cellular origins of retroviral oncogenes”. During his lecture, Dr Varmus confessed standing on the shoulders of giants of retroviral and cancer research such as Dr Peyton Rous, Dr Harry Rubin and Dr Howard Temin, to ask the question of how retroviruses transformed cells and cause tumours. This question led him to look for genes that make a normal cell behave like a cancer cell which initially involved studying cancer-causing RNA viruses/retroviruses in animals. The retrovirus that played a lead role in Dr Varmus and his colleague’s work was the *Rous Sarcoma Virus* (RSV), discovered by Dr Peyton Rous in 1911, which he showed caused a type of cancer in chickens. Dr Varmus and colleagues set out to prove the hypothesis that retroviruses enter host cells and capture normal genes in that cell by inserting their DNA, converting them into cancer-causing genes or oncogenes. Dr Varmus and his group employed various cellular, chemical as well as genetic tools to establish that retroviruses can indeed act as mutagens by inserting their DNA in host cells and turning them into cancer cells. After this his group went on to identify the cancer-causing genes present in the virus and subsequently discovered many new oncogenes, *v-Src* (a gene of RSV) being the first one. Following these discoveries and subsequently many others, led to the belief that the genetic basis of cancer is highly heterogeneous. Dr Varmus told us that in order to catalogue these complexities, the Cancer Genome Atlas was established in 2005, which till today serves as a collection of the genetic mutations responsible for different cancers.

Apart from the complexity and vastness of the cancer genome, other challenges in the field according to Dr Varmus are genetic heterogeneity and evolution of tumours due to various environmental factors such as, exposure to UV, pollution, tobacco use and other environmental carcinogens that are on the rise. He used the example of renal tumor evolution which illustrates Darwin’s theory of “evolution of species” to show that this rapidly changing genetic repertoire can have significant impact on diagnosis, therapeutic interventions and prognosis. Another issue of concern highlighted by Dr Varmus was the absence of suitable drugs against many common targets for cancer, such as cancer-causing *RAS* genes and many transcription factors, which have been shown to contribute towards cancer formation. Dr Varmus opined that lack of understanding of the underlying complexity of resistance to cancer therapies is another roadblock in cancer treatment. He was also strongly of the opinion that there are not enough public health interventions to prevent cancer- this he felt, needs to go hand in hand with finding cure for cancer.

Dr Varmus also offered solutions to these problems. He suggested that research needs to “look beyond genes and focus on patterns and pathways” and physiological changes taking place in cancer cells. He shared his group’s current interest in studying “oncogene addiction” which is based on the premise that some oncogenes not only give rise to cancer but also maintain the cancerous state of the cells. Interpreting the downstream effects of these cancer genes on the pathways could be employed as a strategy to attack multiple targets by drugs in different cancers. Even though he hailed the successes of many commonly used and extremely efficacious anti-cancer drugs such as, Gleevec, Gefitinib, Erlotinib, but in light of growing complexity of the disease, proposed the need for adopting more innovative drug discovery and treatment approaches. Continuing on the topic of therapeutics, Dr Varmus mentioned the recent advances in immunotherapeutic approaches to treat cancer, which would require us to understand why the otherwise combative immune system does not kill cancer cells. He suggested that gaining understanding of these immune check points and accordingly targeting them by antibody inhibitors could serve as one more effective treatment strategy- another project his research group has undertaken. In addition to these therapeutic approaches, Dr Varmus very strongly asserted that “not everything we talk about cancer should be about cancer therapy but also about prevention” and that this disease ought to be on the global health agenda.

Dr Varmus very eloquently concluded his talk by stating that “confronting cancer needs a balance between grasping its complexity and seeking simple solutions”. As expected, he received many questions from the audience after his lecture on the genetics and biology of various cancers, potential use of vaccines in cancer treatment, crosstalk of cancer with other diseases and many others, to which he responded with prudence and an underlying sense of optimism.

Prior to his lecture, Dr Varmus, over an hour meeting with 10 young cancer researchers, discussed their work. This group included the following Wellcome Trust/DBT India Alliance Fellows - Dr Reety Arora (ECF; InStem, Bangalore), Dr Anjali Bajpai (ECF; IIT, Kanpur), Dr Bushra Ateeq (Int Fellow; IIT, Kanpur), Dr Kundan Sengupta (Int Fellow, IISER, Pune) and Dr Sandeep Singh (Int Fellow, NIBMG, Kalyani). Dr Varmus also sought information on the India Alliance Fellowships and was impressed by its funding model and reach.