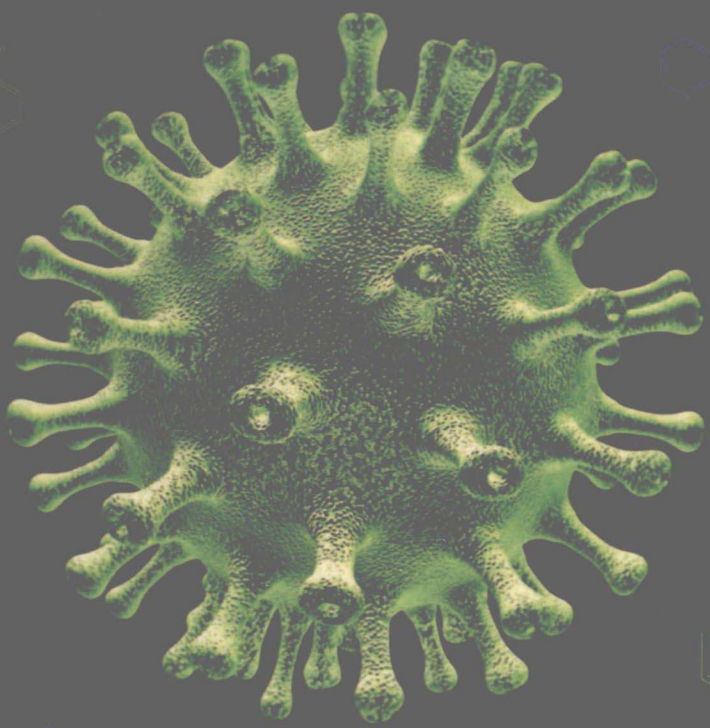
Edited by **Satya Prakash Gupta**

Cancer-Causing Viruses and Their Inhibitors



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Preface

Cancer-causing viruses are also called oncoviruses or tumor viruses. Their infection in the human body leads to cancer. According to the World Health Organization Cancer Report 2008, cancer-causing viruses are responsible for up to 20% of cancer deaths all over the world; approximately 20%–30% of all cancers worldwide can be linked to viral infections. Cancer develops when cells start to divide uncontrollably because the "cell cycle machinery" that regulates this process stops working properly. These cancer cells can then invade other tissues. Cancer development is a complex process involving a series of genetic changes that disrupt the cell cycle machinery, interfering with cellular functions such as cell growth. Cancer-causing viruses play a key role in the development of certain cancers by contributing to these genetic changes. Although cancer itself is not an infectious disease, a significant number of human viruses have been linked to specific cancers, such as adult T-cell leukemia (ATL), hepatocellular carcinoma (HCC), Burkitt's lymphoma (BL), nasopharyngeal carcinoma (NPC), posttransplant lymphomas, Hodgkin's disease, cervical cancer, skin cancer in patients with epidermodysplasia verruciformis (EV), head and neck cancers, primary effusion lymphoma, and Castleman's disease. The involvement of these viruses in human cancer development means that the frequency of these cancers can be reduced either prophylactically by vaccinating against the viruses or therapeutically by treating the infections. Extensive studies of these viruses are currently taking place with respect to their life cycle, their mechanism of infection, the inhibition of their growth, and the development of vaccines to treat the cancer caused by them. This book will cover in detail all of these aspects of oncoviruses, and it may be of great interest to medicinal and pharmaceutical chemists as well as to those working in the area of biotechnology. Cancer researchers may also find it of immense value.

There are a total of fourteen chapters in this volume. In the first chapter, Gupta and Gautam discuss the cancer-causing viruses discovered to date and include a brief description of their structure, genotypes, replication, and mechanisms of infection leading to cancers. The second chapter, by Yasunaga, presents the pathogenesis of human T-cell leukemia virus type 1 (HTLV-1) as well as current and upcoming therapeutic strategies against HTLV-1-mediated diseases. Chapter 3, by Deval and Huber, discusses the hepatitis C virus (HCV)—which leads to hepatocellular carcinoma—and its inhibitors. The number of HCV infection cases has now reached more than 170 million worldwide; one of the main protein targets for the generation of HCV therapeutics is the viral RNA-dependent RNA polymerase (RdRp) NS5B. This chapter summarizes what is known to date about the structure and function(s) of NS5B, with a particular focus on its role in HCV replication, and it reviews the recent advances in the development of nucleoside and nucleotide analogs as inhibitors of NS5B. Combination therapy utilizing interferon-alpha (IFN-α), ribavirin (RBV), and a protease inhibitor is the current standard of care for HCV genotype 1 infection. In Chapter 4, Dash et al. discuss the hypothesis that a better understanding

of interferon's and ribavirin's HCV clearance mechanisms will lead to improvement in treatment response and will reduce the burden of liver cirrhosis and primary liver cancer. They present an overview of HCV infection clearance by treatment with type I and type III interferon (IFN), ribavirin, and other new emerging antivirals. Dash et al. also review novel antiviral strategies that aim to eradicate HCV infection and reduce the burden of liver cirrhosis and primary liver cancer. Like HCV, hepatitis B virus (HBV) is also a leading risk factor for hepatocellular carcinoma (HCC), with more than 80% of HCC cases occurring in regions that are also endemic for hepatitis B. In Chapter 5, Maiwall and Sharma discuss the factors associated with increased risk of developing HCC in chronic HBV-infected subjects and the preventive strategies for HBV-related HCC including the role of vaccination, nucleoside and nucleotide analogs, and interferon.

Epstein–Barr virus (EBV) is a ubiquitous pathogen that has adopted a unique and effective strategy for infection, persistence, and spread in its only biological host—human beings. It infects more than 90% of the human population worldwide and is associated with a diverse array of proliferative diseases in different parts of the world. It leads to BL, nasopharyngeal carcinoma (NPC), posttransplant lymphomas, and Hodgkin's disease. In Chapter 6, Jha et al. present the biology and pathophysiology of EBV and discuss currently available techniques for preventing EBV infection as well as for treating EBV-mediated malignancies.

More than four decades have elapsed since the initial hypothesis regarding the possible role of human papillomavirus (HPV) in the genesis of human cancers was postulated. It is now a matter of common knowledge that HPV infection accounts for almost 100% of cervical cancers and that HPV is responsible for 5.2% of all cancers including 25% of head and neck cancers. In Chapter 7, Chaudhury et al. present the structure and properties of HPV, its association with cervical and neck and head cancers, and the prevention and therapeutics of these cancers. Several recent studies have reported that high-risk HPVs are also present in human breast cancer tissues. Although several investigations did not confirm this fact, in Chapter 8, Al Moustafa presents an overview of the presence and role of high-risk HPVs in human breast carcinogenesis and focuses on the function of E5, E6, and E7 oncoproteins of high-risk HPVs in the progression of breast cancer.

Genital infection by HPV is the most common sexually transmitted disease in the world. Its global prevalence among women without cervical abnormalities is 12%. Chapter 9, by Cobucci et al., presents research data on promising prospective genital HPV infection therapies along with a brief description of current and future therapies.

Another of the viruses that infect humans, human herpesvirus 8 (HHV-8)/Kaposi's sarcoma-associated herpesvirus (KSHV), is described as a novel gamma-2 herpesvirus closely related to the human gamma-1 herpesvirus, Epstein–Barr virus (EBV). In Chapter 10, El Hajj et al. discuss the pathogenesis of HHV-8 and the treatment of the diseases associated with it, such as primary effusion lymphoma and Castleman's disease. Herpes simplex virus 1 and 2 (HSV-1 and HSV-2), also known as human herpesvirus 1 and 2 (HHV-1 and HHV-2), are two members of the Herpesviridae virus family that infects humans. Although HSV-1 and HSV-2 are closely related, they differ in several aspects of their pathology. HSV-1 is primarily

associated with throat and mouth diseases as well as ocular and genital infections, while HSV-2 is the leading cause of recurring genital herpes cases worldwide. HSVs currently have no cure, and some have developed drug resistance. However, in Chapter 11, Chu et al. discuss the importance of tea polyphenolic compounds, such as epigallocatechin gallate (a green tea polyphenol) and theaflavin (a black tea polyphenol), against these HSVs.

People with AIDS have a weak immune system and thus are at an increased risk of developing infections, lymphoma, and other types of cancer. Therefore, HIV is also considered a cancer-causing virus. The most common types of AIDS-related cancers are Kaposi sarcoma and non-Hodgkin lymphoma. Other AIDS-related cancers include Hodgkin's disease and cancers of the lung, mouth, cervix, and digestive system. Anti-HIV drugs target multiple pathways in the life cycle of HIV and provide a large source of potential anticancer drugs. HIV integrase (IN) is one of the major viral targets for the development of new anti-HIV drugs. In Chapter 12, Garg and Ko have presented a review of HIV-related cancers and repositioning efforts to target some HIV IN inhibitors as anticancer agents as well as quantitative structure–activity relationship (QSAR) studies on HIV IN inhibitors that might be of great help in the design of more effective HIV IN inhibitors relevant to cancer treatment.

Oncolytic (tumor-killing) viruses vis-à-vis oncoviruses represent a heterogeneous group of viruses that have been observed/engineered to preferentially replicate in and destroy tumor cells but not normal cells. In Chapter 13, Vähä-Koskela et al. present a brief history of oncolytic viruses and their mechanism of action and clinical development. The authors assess whether there is any rationale—either molecular or immunological—for deliberate targeting of oncovirus-associated disease by oncolytic viruses. In this regard, they discuss a limited but expanding number of studies that indicate that it may be feasible to deliberately infect oncovirus tumors with oncolytic viruses and that such "virus wars" may result in substantial therapeutic benefit and long-term tumor control. Whereas oncolytic viruses have shown significant promise in cancer therapy, histone deacetylase inhibitors have also shown great promise for inhibiting cell proliferation in various cancer cell lines. Therefore, current research is directed toward combined use of these approaches. A detailed description of this aspect is presented by Patil and Gupta in Chapter 14.

In this volume, an attempt has been made to present a detailed account of cancer-causing viruses—their structure, genotypes, and replication; the mechanisms of infection leading to human cancers; modes of infection prevention; and the treatment of the cancers produced by these viruses. This book will be of great value to those working on virology and cancers and in the area of biotechnology as well as to general readers interested in viral infections. As the editor of this book, I have greatly enjoyed reading all the chapters and hope the readers do as well. I gratefully acknowledge the interest and zeal of all the authors for contributing such important, timely, and useful material for this book.

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About the Editor

Dr. Satya P. Gupta, formerly a renowned professor of chemistry at Birla Institute of Technology and Science (BITS), Pilani, India, is presently a professor in the Department of Applied Science at the National Institute of Technical Teachers' Training and Research (NITTTR), Bhopal, India. Prior to this, he served as a distinguished professor in the Department of Pharmaceutical Technology at the Meerut Institute of Engineering and Technology (MIET), Meerut, India. Initially, he spent a few years at the Tata Institute of Fundamental Research (TIFR), Bombay, under Professor Girjesh Govil, where he worked on the structure and functions of biomembranes. He later moved to BITS, where he initiated work on the quantitative structure–activity relationship (QSAR), a very prominent area of medicinal chemistry. Dr. Gupta developed a deep understanding of QSAR, the modes of drug–receptor interactions, and the roles of physicochemical properties in drug–receptor interactions. Dr. Gupta earned an MSc in physical chemistry and PhD in quantum chemistry.

In 1985, Dr. Gupta was made a fellow of the National Academy of Sciences, India, and in 1989, he was awarded the coveted Ranbaxy Research Foundation Award. Dr. Gupta is one of the pioneers of QSAR. He has published approximately 200 papers in various journals of repute on the topic and has contributed dozens of authoritative reviews in prestigious journals such as *Chemical Reviews* (American Chemical Society), *Progress in Drug Research* (Birkhauser Verlag Basel), and *Current Medicinal Chemistry* (Bentham Science, the Netherlands and the United States). Dr. Gupta has also contributed several chapters in books produced by internationally reputed publishers such as J. R. Prous Science Spain, Elsevier Science BV (the Netherlands), Springer Heidelberg, and Springer Basel. He has edited several books published by Springer Heidelberg/Basel, namely, *Topics in Heterocyclic Chemistry,* Vol. 3 and 4 (2006); *Ion Channels and Their Inhibitors* (2011); *Matrix Metalloproteinase Inhibitors—Specificity of Binding and Structure–Activity Relationships* (2012); and *Hydroxamic Acids: A Unique Family of Chemicals with Multiple Biological Activities* (2013). In addition, Dr. Gupta has been the editor-in-chief of four international journals published by Bentham Science: *Cardiovascular and Hematological Agents in Medicinal Chemistry*, *Current Computer-Aided Drug Design*, *Current Enzyme Inhibition*, and *Current Bioinformatics*. Dr. Gupta also serves on the editorial boards of several journals.

In 1996, Dr. Gupta's book, *Quantum Biology* (New Age International Publishers, New Delhi), was highly acclaimed by theoretical chemists and biologists. His recent book, *QSAR and Molecular Modeling* (published in 2011 by Anamaya, New Delhi, in collaboration with Springer, the Netherlands), has become the most popular volume among those interested in QSAR and molecular modeling—the most fascinating area of drug design. This book is a result of his vast work experience in QSAR.

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