Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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LEARNING FROM PAST PANDEMICS

Life Beyond COVID: Pay Attention to Viruses

Paul M. Harari, MD,* and Paul F. Lambert, PhD†

*Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; and †Department of Oncology, McArdle Laboratory for Cancer Research, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

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Oncologists know plenty about cancer. More than ever before, there is also great value in oncologists knowing about viruses. After all, 1 in every 6 patients with cancer owes his or her cancer to a prior viral infection. Indeed, scientists have identified that trillions upon trillions of viruses fall from the sky each day with the capacity to modulate the function and evolution of all living things (Fig. 1).

The first author served as an internal medicine intern at the University of California Davis Medical Center in Sacramento, California, from 1984 to 1985. A handful of the medicine ward patients had a diagnosis of human T-cell lymphotropic virus (HTLV)-3, a viral infection that made them remarkably sick and unable to fight off infection. Most would go on to die of this mysterious new virus. This was HIV, which causes AIDS, in its early years of recognition by the medical community.[1] There was only modest understanding of how to help these patients beyond treatment of their opportunistic infections and best supportive care. We would often wear face masks (COVID-19-style but circa 1984) when in close contact with these patients, although there were no universal policies because clear-cut understanding about disease transmission was just beginning to emerge.

During the late 1980s and 1990s it was increasingly common to see patients with a variety of AIDS-related malignancies, including Kaposi sarcoma (KS), lymphoma, anal cancer, and cervical cancer. Medical students possess "lecture recall" of the Rous sarcoma virus discovered by Peyton Rous in 1911,[2] in which an infectious agent (later confirmed as a virus) was identified to cause cancer in chickens. This remarkable discovery effectively opened the burgeoning field of tumor virology. For a radiation oncologist in the early 1990s with a primary focus on head and neck cancer and skin cancer, it was common to design treatment strategies for patients with oral or skin KS lesions as well as AIDS-related lymphomas. The KS lesions often involved the oral mucosa or facial skin, for which low-dose radiation had a temporizing effect that rendered lesions less symptomatic and less visible to others. Yet it was quite clear that we were not affecting the underlying viral disease that was predisposing these patients to the development of new cancers.

Head and neck radiation oncologists become familiar with Epstein-Barr virus (EBV) as they treat patients with nasopharynx cancer and learn that this is among the most common malignancies in several regions of the world (South Asia, Middle East, and North Africa). EBV has long been known as a cause of nasopharynx cancer, and innovative international clinical trials are under way that measure serum EBV markers for nasopharynx cancer screening and monitoring of patients after curative-intent treatment with radiation to assess early patterns of recurrence.[3,4] EBV induces cancer initiation years prior, and now these viral footprints are becoming leading biomarkers of the disease and early indicators of recurrence.

Gynecologic cancer radiation oncologists become highly expert in the treatment of cervix cancer, a challenging

Corresponding author: Paul M. Harari, MD; E-mail: harari@humonc.wisc.edu

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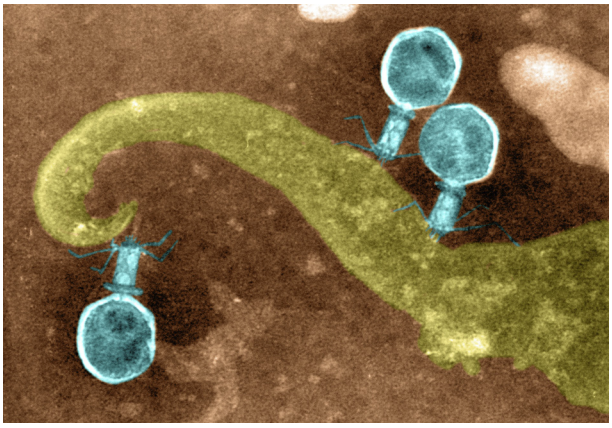

Fig. 1. Viruses attached to a fragment of a bacterial cell wall. Viruses modulate the function and evolution of all living things. Adapted from Robbins J. Trillions upon trillions of viruses fall from the sky each day. *New York Times.* April 13, 2018.

disease associated with another major player in viral oncology, the human papillomavirus (HPV). This virus is linked to 90% to 100% of cervical cancer cases, and sexual transmission of HPV has also become a dominant focus in head and neck cancer with the finding that approximately 75% of oropharynx cancers in the United States are associated with HPV. Indeed, HPV-positive oropharynx cancer is now recognized as a separate malignancy from HPV-negative cancer in the head and neck with distinct genetic constitution, treatment response profiles, and survival outcomes.[5]

Several regions of the world display high rates of hepatocellular carcinoma (HCC) associated with liver cirrhosis related to chronic hepatitis B virus or hepatitis C virus infection. It is estimated that approximately 5% of the world population (~400 million people) is chronically infected with hepatitis B virus, and we are seeing an increasing incidence of HCC in the United States. Highly conformal radiation techniques with intensity modulated radiation therapy and stereotactic body radiation therapy have enabled radiation oncologists to play an increasingly valuable role in the treatment of patients with HCC.[6]

HTLV-1 infects about 20 million people worldwide, with a high prevalence in southwestern Japan, the Caribbean Islands, and parts of Central Africa and South America. This RNA virus infects T-cells, B-lymphocytes, and monocytes and can trigger adult T-cell leukemia. The recent finding of Merkel cell polyomavirus,[7] which plays a pivotal role in the induction of Merkel cell carcinoma, has opened new doors to treatment (including radiation) for this challenging and frequently metastatic cancer that commonly affects the skin of the face and neck in older individuals.

As the COVID-19 pandemic spreads across the globe with documented infection of greater than 10 million people and 500,000 deaths at the time of this writing, many unknowns remain. Will the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), prove to be more lethal in patients with cancer? Early data[8] and common sense suggest that this will be the case; these patients often experience immunosuppression secondary to their underlying malignancy and cancer treatment regimen. Will those infected by SARS-CoV-2 be more susceptible to the development of cancer in the long-term future? This issue remains unknown at present.

The COVID-19 pandemic places a very powerful worldwide spotlight on viruses. The hundreds of millions of dollars invested in the development of new vaccines, viral therapeutics, and medical support for patients with viral infection will profoundly affect a generation of research scientists in virology. This can benefit oncology as we sharpen our understanding of viruses, including those associated with cancer.

The impact of the COVID-19 pandemic on the field of medicine may prove as far-reaching as the HIV-1 epidemic, and in ways that we cannot necessarily predict today. In the prophylactic arena, the extraordinary international efforts to rapidly develop and deploy SARS-CoV-2 vaccines has relied on using multiple new and as yet untried platforms for inducing immunity against viral infections, including the use of RNA, DNA, and viral vectors.[9] In many cases, these platforms were first designed in the context of developing therapeutic vaccines against cancer. If these platforms prove effective in preventing SARS-CoV-2 infection and consequent disease, their use for developing vaccines against other human pathogens, including viruses that cause human cancer for which we do not currently have vaccines (eg, Kaposi sarcoma herpesvirus, EBV, hepatitis C virus, HTLV-1, and Merkel cell polyomavirus) could dramatically alter the cancer landscape of the future. Importantly, these efforts also could hasten the development of long sought-after pan-influenza vaccines that rely on several of these same platforms. Indeed, vaccines against many other human and animal pathogens could be made more feasible if these vaccine platforms prove successful against the new SARS-CoV-2 coronavirus.

In the therapeutic arena, the absence of effective drugs to mitigate the acute respiratory complications and underlying chemokine storm has resulted in thousands of deaths due to COVID-19. Many more lives could likely have been saved if we had effective drugs in hand to mitigate disease caused by these potent respiratory viruses. Identifying and developing such drugs is a top priority to combat an equally, if not more, devastating viral pandemic than that currently faced with COVID-19. Unpredictably, the extraordinary efforts to develop antiretrovirals to affect AIDS may afford benefit to patients with cancer, as several antiretroviral drugs are now being investigated in clinical trials for cancer.[10] This illustrates the unpredictable nature by which scientific discoveries in one realm can affect another. What cancers might an anticoronavirus drug treat?

What anticancer drugs might be useful to treat coronavirus patients? Drugs such as tocilizumab, used to treat cytokine release syndrome after chimeric antigen receptor T-cell therapy in patients with cancer, are being used to dampen the cytokine storm implicated in severe COVID-19.[11] Other FDA-approved anticancer drugs could be identified through large-scale screening efforts now under way, to inhibit coronavirus replication in ways not necessarily predictable. These drugs could have immediate impact if repurposed to treat COVID-19 patients. Hopefully, the arsenal—both in terms of knowledge and clinical interventions—that we have built in the war against cancer will provide valuable new insights and tools to address the current viral pandemic, as well as future viral pandemics.

For medical students around the world and the greater than 20,000 new physicians who commenced their internships in the United States in July 2020, COVID-19 patients will become an integral part of their early training experience just as HTLV-3 patients were 36 years ago. Collaborating with scientists who study viruses, observant and inquisitive physician-scientists of today will help further illuminate the complex relationship between viruses and human cancers. Radiation oncologists can be significant contributors to this important new knowledge as we are strategically positioned at the forefront of cancer treatment for many of the most common viral-associated malignancies.

The take-home message: Pay close attention to viruses, as important and practice-changing scientific discoveries await.

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