The Good That Viruses Do

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It is astonishing that with our more than thirty-five combined years of working in the field of virology, we continue to read on a regular basis about novel emerging viruses infecting species from all three domains of life. The focus of our research is on single-stranded DNA viruses. Even for this apparently small group of viruses, many new members are identified each year that need to be characterized, providing seemingly endless opportunities for new research directions. Indeed, studying these new viruses does not end with characterization of their physical properties or disease-causing phenotypes, because many have the potential to be developed into useful biologics with therapeutic benefits to humans. Our experience as virologists suggests that the use of "good" viruses is common practice. If a survey were to ask nonvirologists for their opinions about viruses, the word "good" would be unlikely to arise. Instead, words such as "disease," "infection," "suffering," or "life-threatening" would likely dominate, as people primarily think of viruses such as HIV, Ebola virus, Zika virus, influenza virus, or whatever new outbreak is in the news. However, as we are now finding out, not all viruses are detrimental to human health. In fact, some viruses have beneficial properties for their hosts in a symbiotic relationship (1), while other natural and laboratory-modified viruses can be used to target and kill cancer cells, to treat a variety of genetic diseases as gene and cell therapy tools, or to serve as vaccines or vaccine delivery agents. The ability to treat diseases using viruses, often referred to as virotherapy, has become the subject of intensive research in recent years.

Cancer is one of the leading causes of death worldwide. According to the World Health Organization, about 8.8 million people died from cancer in 2015. Conventional treatment of cancer is based primarily on chemotherapy, radiation therapy, and surgery. Although these therapies have increased patient survival rates, their efficacy is often limited depending on the type of cancer being treated. In addition, significant side effects occur because noncancerous cells are also targeted by these treatment modalities. Recurrence after successful treatment is also of concern. An emerging field in cancer therapy comprises alternative therapies that use viruses to kill cancer cells selectively. The idea for this approach came through early observations of cancer regression in patients suffering from unrelated viral infections (2). In the past two decades, viruses from a variety of different families (e.g., *Adenoviridae*, *Herpesviridae*, *Rhabdoviridae*, *Parvoviridae*, *Picornaviridae*, *Reoviridae*, and *Poxviridae*) have been studied for their potential use as anticancer agents (3). Due to their tropism for tumors and their ability to replicate selectively in and eventually lyse cancer cells

https://doi.org/10.1146/annurev-vi-04-071217-100011

without harming noncancerous cells, they are referred to as oncolytic viruses. Currently, multiple phase I to phase III clinical trials are ongoing for the treatment of various cancer types, including hepatocellular carcinoma, glioblastoma multiforme, colorectal cancer, and cancers of the lung, breast, prostate, pancreas, bladder, and ovaries (4). In 2015, the first oncolytic virus therapy based on a herpesvirus was approved by the US Food and Drug Administration and European Medicines Agency for the treatment of melanoma lesions in the skin and lymph nodes (5). In the near future we expect to see that the successful completion of several clinical trials will lead to the approval of additional oncolytic virus therapies.

In contrast to oncolytic virus therapies, where the treatment is based on virus replication and cell death, nonreplicating viruses are being utilized as vectors for corrective gene delivery. The goal of virus-mediated gene therapy is the delivery and expression of therapeutic genes to desired target cells to restore the function of a defective gene for the treatment of monogenetic disorders. Viral gene therapy uses the natural capacity of virus particles to protect the encapsidated nucleic acid from degradation and to deliver the DNA to the nucleus. For the ideal gene therapy vector the viral wild-type genome is almost entirely substituted with a recombinant transgene expression cassette. This aspect is a major difference compared with the oncolytic viruses used in anticancer therapies, which encode many viral genes. In hundreds of ongoing clinical trials, the most commonly used vectors for gene therapy are adenoviruses, retroviruses/lentiviruses, and adeno-associated viruses (AAVs) (6). Each system has its pros and cons that must be considered prior to use to ensure efficient gene delivery and expression for clinical success. Recent successes in various clinical trials have been achieved especially using lentiviral and AAV vectors (6). Lentiviral vectors are primarily used for ex vivo hematopoietic gene delivery, where patient cells are removed and transduced with the viral vector, resulting in modified cells that can be transplanted back to the patient after thorough screening of the transplant. The pre-administration screening allows the identification of mutagenic integration sites of proviral genomes in the cellular genome of the transplant. These screenings were incorporated into clinical trial design after the discovery of insertional oncogenesis leading to T cell leukemia in patients undergoing retroviral gene therapy. In contrast, AAV vectors are used mainly for in vivo gene therapy applications, where viral vector particles are injected intravenously, intramuscularly, intracranially, intravitreally, or subretinally, depending on the desired target cells. Notably, an AAV1 vector for the treatment of lipoprotein lipase deficiency was approved as the first viral gene therapy medical product in the Western world by the European Medicines Agency in 2012 (7). This approval led to a massive surge of industry interest and the growth of the AAV biotechnology field, including the raising of $2 billion by just ten companies in 2015 for the development of AAV gene therapies. Another example of a successfully completed AAV vector clinical trial involves an AAV8 vector expressing human factor IX for the treatment of hemophilia B. A single injection of these AAV particles resulted in a more than 90% reduction in the number of bleeding episodes in study participants over a period of more than three years, with no toxic effects (8). One downside is that AAV gene therapy is currently the most expensive therapeutic, at ~$1 million per treatment. Certainly, continued effort is required to make it affordable. Another problem with AAV gene therapy is the potential for immune responses against the virus capsid as well as the therapeutic gene products that are produced. Ten to fifteen years ago, it was believed that AAVs did not elicit an immune response. However, applications in large animals, nonhuman primates, and humans have since proved that this is untrue. Thus, in order to maintain the expression of the therapeutic protein, different strategies have been developed to avoid or suppress these immune responses (9).

In gene therapy scenarios, it is important to avoid immune responses to the virus capsid and transgene product. In contrast, for viral vaccines, elicitation of immune responses, including the generation of neutralizing antibodies, is the goal. To induce a protective immune response, patients

are injected with an attenuated or inactivated virus or with specific viral antigens. For patients with an immune deficiency disorder, passive immunization by direct administration of antibodies can be done. However, this immunity is temporary, lasting only for a few weeks or months. Therefore, gene therapy vectors have been developed that express broadly neutralizing antibodies that can be used for the long-term treatment of HIV and influenza as well as for cancer therapy (10).

Some of the viruses infecting humans are indeed capable of causing severe and often lethal diseases, but other viruses can be manipulated to be beneficial to human health. These viruses offer the potential to cure cancer, correct genetic disorders, or fight pathogenic viral infections. In addition, viruses are used in many genetic studies to determine molecular mechanisms, are used as insecticides, and have been reported to increase drought tolerance in some plants. Virologists must strive to downplay the "bad" reputation of viruses and promote dialogue on the many "good" things that they can do.

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