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Colloquium Paper

This paper serves as as introduction to the following papers, which were presented at a colloquium entitled "Genetic Engineering of Viruses and of Virus Vectors," organized by Bernard Roizman and Peter Palese (Co-chairs), held June 9–11, 1996, at the National Academy of Sciences in Irvine, CA.

Genetic engineering of viruses and of virus vectors: A preface

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> Give me a firm spot on which to stand, and I will move the earth.
> Archimedes

Nearly two centuries ago, Jenner used a live virus of another species to combat smallpox—one of the most lethal human pathogens known. In the intervening years, science has provided the tools to produce by design in the laboratory other live viruses capable of protecting against their more lethal siblings. We have learned to attenuate human pathogenic viruses by passage in nonhuman hosts, by cultivation at lower temperature, and by the genetic engineering of mutations in viral genomes. Science has not yet ablated the misery of human infectious disease. Indeed, as measured in terms of health costs, human diseases caused by human immunodeficiency virus, influenza, and the herpesviruses account for a very significant portion of the total costs. While efforts designed to eliminate other infectious diseases from human society continue, other uses for viruses emerged. They stem from four considerations.

First, viruses attack cells they recognize by specific receptors that are present on cell surfaces.

Second, viruses evolved by borrowing and modifying cellular genes. Yet, all viruses depend on specific cellular functions for their replication or survival in their hosts. Some of the functions required by viruses for their replication are expressed in most cells, some only in dividing cells, and some only in highly differentiated cells.

Third, viruses form two groups (those that infect organs at or near a portal of both entry and exit), multiply efficiently, and ultimately are eliminated by the immune response, and those that remain after infection are in a latent state for the life of the host.

Last and perhaps foremost, for the past two decades, molecular and genetic tools became available to construct novel viruses that never existed before and, in most instances, lack the evolutionary advantages that would permit them to survive in nature.

These considerations serve as the foundation of the idea that it should be possible to construct highly modified, attenuated, viruses that target specific cells and to introduce into the targeted cells desired functions deliberately incorporated into the viral genomes. These functions include the potential to selectively destroy cancer cells by "hit-and-run" viruses that in this instance would be eliminated by the immune system once their task is done, or to establish lifelong latency concomitant with the expression of a cellular gene necessary for the survival of the infected cell. As the accompanying reports indicate, the development of magic bullets is far along, but we are not there yet.

A decade ago, reports on genetic engineering of viruses would have focused on the development of better vaccines to prevent infections by our natural enemies—the viruses and microorganisms that prey on us. It is a reflection of the development of virology over the last decade that we are beginning to think of our ancient foes as our friends.