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Chemistry of Antiviral Drugs

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Introduction

A virus is a portion of genetic material, protected and transported by complex organic molecules, that can hijack the biochemical processes of a host organism to reproduce itself. Technically they are not alive, but are completely dependent on their host organism to exist and multiply.

Viruses are frequently categorized by the form of the genetic material they carry. Some viruses store their genome in DNA, while others store them in RNA. They are also categorized by the type of proteins that protect them, the shape they adopt, and mechanism of entering cells. COVID-19, for example, is a single-strand RNA virus protected by a phospholipid capsule.

Viral Propagation and Antiviral Therapeutic Strategies

There are two general approaches to treating viral infections: vaccines and drug therapies. Vaccines stimulate the immune system to create antibodies against the virus. Drug therapies are molecules designed to interrupt or block the viral propagation cycle.

It is important to understand the individual steps of viral propagation in order to develop therapeutics to prevent it. Therapeutics have been designed to block different steps of the viral infection pathway.

Although different classes of viruses use different molecular targets in the host cell, they tend to follow the same general series of steps:

- Fusion: attachment to the host cell
- Entry: Penetration of cell membranes
- Replication: hijack genetic machinery of host cell
- Packaging and assembly: creating new virus
- Release: emptying of virus into the environment or host

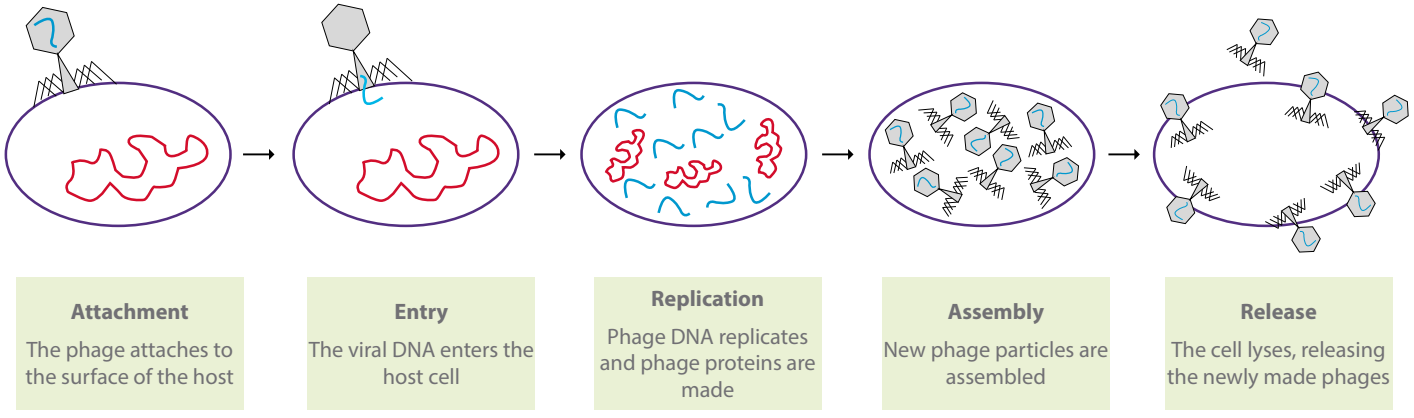

Figure 1. Host cell infection by virus

In general, viruses first contact the cell by interacting with a trans-membrane surface protein on the outside of the cell. There is clearly a great deal of interest in blocking COVID-19 infections. The spike proteins that cover the surface of this virus is known to bind to the ACE-2 receptor in human cells. ACE-2 blockers are, therefore, an important drug.

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Once the virus binds to the surface of the host cell, it has to penetrate the cell, and this usually includes partial decomposition of the viral structure. This is called the "uncoating" process, and some drugs in this category inhibit various forms of this uncoating. In the case of COVID-19, there are a number of human and viral proteins that are used to expose its RNA. This includes the proteases Furin and TMPRSS2, which are both active targets being evaluated as potential therapeutics.

There are quite a number of antiviral drugs that interfere with the replication of their RNA. One common target is RNA-dependent RNA polymerase (RdRP). This blueprint for making this protein is actually provided by the virus. Once it is prepared, it makes copies of the virus by combining the standard nucleotides to produce the copy.

Repurposing Established Antiviral Drugs

Given the current COVID-19 pandemic, researchers are frantically looking for effective drugs that can prevent and cure viral infections. Starting with a FDA-approved drug can greatly reduce the amount of clinical trials that need to be carried out before approval can be achieved. An approved drug can be fast-tracked through the system. However, efficacy, as well as a side-effect profile has to be demonstrated, particularly if a larger dose is required.

One class of drugs that has received a great deal of attention is RD-RDP inhibitors: Favipiravir, Lopinavir, Ritonavir, and Remdesivir. Favipiravir is an antiviral used in the treatment of influenza and some other viral infections. It is a RNA polymerase that induces lethal RNA mutations that lead to non-viable virus particles. Lopinavir is a protease inhibitor used against HIV infections. Ritonavir is also a protease inhibitor against HIV that is most often paired with Lopinavir. Finally, Remdesivir is a broad spectrum antiviral that is an adenosine nucleoside triphosphate analog that interferes with RNA polymerase (See Table 1).

Table 1. Common Antivirals and Mode of Action

Compound	CAS #	Action	Target
Amantadine	665-66-7	Blocks Penetration, Uncoating and Fusion	Influenza
Docosanol	30303-65-2	Blocks Penetration, Uncoating and Fusion	HSV
Enfuvirtide	159519-65-0	Blocks Penetration, Uncoating and Fusion	HIV
Maraviroc	376348-65-1	Blocks Penetration, Uncoating and Fusion	HIV
Oseltamivir (Tamiflu)	196618-13-0, 204255-11-8	Blocks Release	Influenza
Foscarnet	34156-56-4	DNA and RNA Polymerase Inhibitor	Broad Spectrum
Acyclovir	59277-89-3	DNA Polymerase Inhibitor	Broad Spectrum
Famciclovir	104227-87-4	DNA Polymerase Inhibitor	Broad Spectrum
Ganciclovir (Cytovene)	82410-32-0	DNA Polymerase Inhibitor	Broad Spectrum
Delavirdine	136817-59-9	Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	HIV
Nevirapine	129618-40-2	Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	HIV
Abacavir	188062-50-2	Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	HIV
Lamivudine	134678-17-4	Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	HIV
Tenofovir	201341-05-1	Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	HIV
Atazanavir	198904-31-3	Protease Inhibitor	HIV
Fosamprenavir	226700-81-8	Protease Inhibitor	HIV
Lopinavir	192725-17-0	Protease Inhibitor	HIV and COVID*
Ritonavir	155213-67-5	Protease Inhibitor	HIV and COVID*
Remdesivir	1809249-37-3	RNA Polymerase Inhibitor	Broad Spectrum
Ribavirin	36791-04-5	RNA Polymerase Inhibitor	Broad Spectrum
Favipiravir	259793-96-9	RNA Polymerase Inhibitor	Influenza and COVID*

** Being investigated for use with COVID-19*

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