

## Drug Discovery in Combating Viral Diseases

Ann Sanoji Samarakkody

*Division of Hematology/Oncology, Harvard Medical School, USA*

Continued efforts toward discovery of novel therapeutic strategies is pivotal in combating viral diseases. Lack of proper therapies for a virus will inevitably cause a localized health crisis to move from an epidemic to a pandemic in a short period of time.

### Attacking a host cell

Virus are obligate intracellular pathogenic agents that are vastly different than bacteria parasites or any other pathogens. A virus requires a host cell to multiply. The packaging proteins and the enclosing genomic material are synthesized using the small molecules and the machinery of the host. Viral particles have their genetic material in the form of DNA and RNA enclosed in a protein capsid. In certain viral strains the protein envelop is enclosed in an additional lipid bilayer. Viral particles require hosts for its multiplication. The initial interaction with the host cell is the first key step of the viral infection. Such interactions are largely mediated by viral surface components such as membrane glycoproteins and viral surface proteins. These initial interactions are often less specific and tend to be electrostatic in nature. Once attached, a virus can employ various strategies in entering the host cell include and not limited to; involvement of specific cell surface receptor proteins for specific receptor-mediated entry, activation of intracellular signaling cascades to promote cell entry, direct penetration of the cell membrane, etc.

Once inside the host cell, undergoing intracellular trafficking, some viruses penetrate the cytoplasm or in the case of others migrate to the nucleus to replicate their genetic information. Replication of the genetic material depend on the nature of the genomic material of the virus. Viruses containing DNA often induce a DNA damage response facilitating the integration of the viral genome into the host chromatin. The double stranded or single stranded DNA lesions will allow the integration of the viral DNA molecule. In contrast, RNA containing viruses require different biochemical mechanisms for the replication of the RNA. Viruses containing the plus strand RNA, or the sense strand are able to use the translation

machinery on the RNA for the protein synthesis. However, negative and double stranded RNA viruses are packaged with a virus RNA polymerase to synthesize its own RNA prior to translation. It is noteworthy that viruses hold the highest rate of mutations in their nucleic acid sequences. Among all viruses, RNA viruses hold the highest mutation rates followed by single stranded-DNA and double stranded DNA viruses. Viral polymerases are error prone in comparison to cellular polymerases. However, these mutations are not only mere polymerase errors but caused by the ability of the virus to proofread and repair, spontaneous nucleic acid damage and genetic elements in virus that functions to generate mutations.

### History of Pandemics

Outbreaks of infections have led to pandemics multiple times through the history. From smallpox in the 16th century to Spanish flu in 1918, SARS in 2002 and Ebola outbreak in 2014 to ongoing viral diseases such as HIV/AIDS, MERS, and COVID-19 are few examples of the pandemics. In earlier days the interventions have largely focused on developing vaccinations. Development of a vaccination even during current times may take up to a year. Hence, drug discovery has taken an equal interest during current sudden outbreaks. Historically, drug discovery has been largely dependent on deducing potential molecules that may bind and hinder activity of a protein based on the information on known docking or binding compounds. However, a considerable effort has been made in development of drugs against widespread viral infections. (i) viral hydrolase inhibitors such as (S)-9-(2,3-dihydroxypropyl) adenine (DHPA), (ii) viral replication inhibitors (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU) and its derivatives, (iii) viral nucleoside transferase inhibitors 2',3'-dideoxynucleosides (ddNs), (iv) non-nucleoside transferase inhibitors such as HEPT, TIBO and their derivatives, (v) acyclic nucleoside phosphonates, (vi) bicyclams such as AMD3100, (vii) acyclic nucleoside phosphonates such as (S)-9-(3-hydroxy-2-phosphonylmethoxy-propyl)adenine (HPMPA), etc.

### Current Approaches

New drugs have transformed the treatment strategies for viral infections. One of the best examples thus far is the discovery of HIV protease inhibitors in the 1990s. The inhibitor binds to the active site of the protease to inhibit the activity of the enzyme to prevent protein cleavage. As a result, the viral particles produced are immature and are non-infectious. A second drug against HIV, raltegravir acts by inhibits HIV integrase to halt the integration of the viral genome into the host DNA.

During current times the virus particles get isolated from patients and grown in large scale using standard cell culture method. A large component of the experimental work focusses on sequencing the viral genome. However, it is also true that a large number of virus circulating today are either uncharacterized or poorly characterized. The vast diversity of the viruses also arises from their increased mutation rates. Hence, proper characterization can be achieved by using the complete information of the viral genome and the proteome. Secondly, whole genome characterization of novel viruses that lead to epidemic or pandemic situations is beneficial from a drug discovery perspective. Identification of receptors, kinases or polymerases are crucial repurposing drugs that are already being used. Once the proteome of the virus is known, other known viruses can be used to query for shared structures among the receptors or any other important viral enzyme. Simulation software can be used to study docking of available drugs and small molecules for docking to viral proteins. High throughput small molecule screens are often used to finding probable drug targets in parallel to simulations. Small molecule libraries are available through multiple vendors that also include a large fraction of FDA approved drugs. A successful FDA approved drugs will markedly reduce the amount of time for the drug discovery.

### Therapeutic strategies in recent outbreak of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

Traditional vaccines still remain the preferred and popular choice of therapy. However, during the H1N1 influenza outbreak in 2009 the vaccine became available after the peak of the infection had passed. There are three strategies that are being suggested. (i)

Use of broad-spectrum antivirals such as Interferons, ribavirin, and cyclophilin inhibitors. (ii) Use of the information on the viral genome to design a novel drug that is specific to SARS-CoV-2. Although this may be the ideal strategy, the time that would take to develop a new drug, validation through clinical trial and bring it up to a large-scale production may take a extended time. (iii) Following sequencing of the viral genome, several proteins have become candidates for the potential to be druggable. Current high throughput screening methods are very efficient and reliable and can be performed at a high reproducibility rate. One such candidate peptide is the sequence KRSFIEDLLFNKV of the glycoprotein proteolytic cleavage site on one of the spike proteins of the virus. Therefore, a potential drug candidate is emodin that binds the angiotensin converting enzyme type 2 (ACE2) receptor to inhibit the entry of SARS virus into the host cell. The proteolytic cleavage to activate the spike glycoprotein is predicted to occur thorough Type II transmembrane serine protease (TMPRSS2) where the later ins known to have several variants. In addition, carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1), and various dipeptidyl peptidases have also been proposed as potential candidates.

Various research groups have been successful in preliminary work with some of the potential compounds. Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown in vitro activity against SARS-CoV-2. Ivermectin, an FDA-approved antiparasitic drug with broad-range anti-viral activity is shown to inhibit replication of SARS-CoV-2 in-vitro. This drug has shown activity against RNA viruses such as DENV 1-4, West Nile virus and influenza. Patients suffering from advanced pneumonia may be benefited by the regiments used during the SARS outbreak such as protease inhibitors Lopinavir and ritonavir together with the nucleoside analog ribavirin. Results with Favipiravir, also known as T-705 or Avigan, a pyrazine derivative that inhibits viral RNA-dependent RNA polymerase, but is yet to be verified in SARS-CoV-2.

Given this rapid pace in data generation and discovery scientists together with clinicians will use the current evidence to determine the ideal therapeutic interventions to combat SARS-CoV-2

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