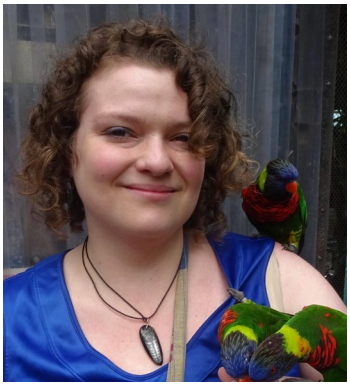
The Role of RNA Research in Community Health



Nucleoside Analog Inhibitors: Timeless & Timely Beacons of Hope

By Sydney Simpson

RNA research is a vital pillar of community health with contributions to the prevention and treatment of diseases ranging from cancers to viral infections. These contributions include the development of therapies against viral infections causing previously untreatable diseases. Through these breakthroughs, RNA research has pioneered several of the first FDA-approved antiviral medications that have saved countless lives.

One of the most notable examples is the discovery of AZT, a nucleoside analog that was the first medication to effectively treat Human Immunodeficiency Virus (HIV). HIV is a retrovirus with a positive-sense RNA genome and the causative agent of Acquired Immunodeficiency Syndrome (AIDS). AZT was originally synthesized in the 1960's as a potential anti-cancer agent but failed to stop cancer cell growth. AZT was shelved following its conception until the 1980s when it was included in a drug screen against HIV[1]. In 1987 the FDA approved AZT for the treatment of HIV[1,2]. AZT is a nucleoside analog reverse transcriptase inhibitor (NRTI) that targets the viral protein reverse transcriptase (RT). RT is an RNA-dependent DNA polymerase that transcribes viral genomic RNA into pro-viral DNA, which is then inserted into the host-cell genome. Nucleoside analogs function as competitive inhibitors, mimicking cellular nucleosides and being modified by host enzymes into nucleoside triphosphates – the building blocks of RNA. However, NRTIs differ from traditional nucleosides in that they contain a different 3' group than the customary 3'-OH group found on cellular nucleosides[3]. AZT, an analog of thymidine, contains a 3'-amino group, which prohibits it from forming 3'-5' phosphodiester bonds between the newly incorporated NRTI and an incoming 5'-nucleoside triphosphate, resulting in premature chain termination[1]. NRTIs are preferentially selected over normal nucleoside triphosphates by the viral RT while human DNA polymerases contain proofreading mechanisms to excise NRTIs if they are accidentally inserted[4].

Today, there are 24 HIV medications available, five of which are NRTIs[5]. NRTIs remain a vital component in the HIV treatment regimen, in part because they are less likely to target host cell proteins compared to other anti-viral medications. RNA viruses are prone to high rates of mutation which can result in drug resistance, and HIV is no exception. Due to mechanistic studies of RT with respect to interactions between RT and NRTIs, novel NRTIs have been developed. Present-day treatments employ a combination of drugs as a cocktail to prevent selection for drug resistant viruses. NRTIs remain the backbone for combinatorial treatments, with many treatments often utilizing two NRTIs alongside another class of medication[3,5]. Notably, NRTIs are more than just an effective treatment – they are also prescribed as a preventative measure. When used in combination, two NRTIs are highly effective at preventing HIV infection in high-risk individuals. The same combination is also used, alongside another class of medication, to prevent infection *following* a known exposure. Since 1987 NRTIs have efficiently transformed from becoming the first treatment for HIV to preventing infection entirely[5].

Importantly, nucleoside analogs have since been utilized as treatments against viruses other than HIV. Up until a few years ago, individuals with chronic Hepatitis C Virus (HCV) infection and advanced liver disease had a poor prognosis with limited treatment options[6]. Liver failure and hepatocellular carcinoma related to HCV infection were the most common indication for liver transplant in North America[7]. Patients fortunate enough to receive a transplant had increased rates of graft rejection and mortality following the transplant[8]. However, the recent development of HCV RNA-dependent RNA-polymerase (RdRp) nucleoside analog inhibitors, such as Sofosbuvir, can cure what was once a chronic infection[8,9]. Sofosbuvir is also used in conjunction with inhibitors that target the viral NS5A protein, which plays a critical role in replication of the HCV RNA genome.

The discovery of drugs that block viral RNA replication has done far more than improve the quality of life for people with HCV – they have also ushered in a new era of organ donation. Prior to the advent of these medications, people infected with HCV were rarely permitted to donate or receive organs[9-11]. With the ability to cure HCV infection, more organs have become available for persons in need, representing hope for many people on waitlists. The unfortunate rise of opioid abuse in recent history and the resulting opioid epidemic

have resulted in increased overdose rates in young individuals. Intravenous drug users are at high risk for HCV infection, and thus were often shunned from becoming organ donors. However, with highly efficacious HCV treatments available, organs from otherwise healthy overdose victims are now able to be transplanted into individuals in need[12,13].

More recently, another nucleoside analog inhibitor called Remdesivir has been tested and shown to be efficacious against current epidemics caused by the positive-strand RNA viruses Ebola and SARS-CoV-2[14,15]. Remdesivir is an adenosine nucleoside triphosphate analog that targets viral RdRp in a similar manner as the previously mentioned medications, with the difference being that Remdesivir results in a delayed chain termination as opposed to an immediate one[16]. As of this article, Remdesivir is the only medication authorized by the FDA for emergency use in treating COVID-19 patients with severe symptoms[17]. However, several other nucleoside analog drugs have been shown to be able to impair SARS-CoV-2 replication *in vitro*[18,19]. One promising drug, NHC, was recently shown to be even more potent than Remdesivir in inhibiting viral replication[18]. This is believed to be due to two extra hydrogen bonds, one being formed by the N4 hydroxyl group on the cytidine ring with the side chain of K545 in the active site of the RdRp, the other occurring between the cytidine base and the guanine base on the template strand[16,18]. The structures of RdRp both bound and unbound to these drugs serve as a prime example of where RNA research has shed critical insight into the mechanisms by which these drugs work. By understanding drug mechanisms and using molecular structures, future research will be able to develop new and efficient treatments based upon pre-existing compounds. Additionally, such research will be vital in developing novel therapies against drug-resistance in these viruses.

In essence, RNA research has led to many of the first treatments for previously untreatable diseases as well as a cure for what was once a debilitating life-long infection. Moreover, RNA research has been utilized to understand the structures of viral RNA polymerases and to perform mechanistic studies on how antiviral compounds function. Such mechanistic studies are vital for continuing to develop novel therapies, creating compounds that will work against ever evolving drug-resistance in these viruses. All of the therapies discussed here target RNA-dependent polymerases of positive-strand RNA viruses, and likewise all of these treatments have had major impacts on human health and quality of life.

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