DESTINATION: CURE

by Jeannie Wraight

Cure Research with a Heart

TRANSLATION INHIBITORS MAY BE PART OF A THERAPEUTIC STRATEGY

To date there are over 100 documented cases of HIV remission and one occurrence of HIV eradication. Researchers are currently investigating numerous HIV cure and remission strategies including monoclonal antibodies; gene therapies; stem cell transplants (such as the procedure that cured Timothy Ray Brown); and post-treatment control and therapeutic vaccines/other immune-boosting agents that would allow the immune system to more effectively control HIV. Also being studied is a new approach currently known as "block and lock" where researchers attempt to essentially 'lock down" the HIV reservoir to prevent dormant HIV from becoming active.

The most widely recognized and studied approach is the kick and kill strategy, which aims to reactivate the latent HIV in viral reservoirs and then kill these infected cells with a combination of antiretrovirals and immune-boosting agents. Although a recent kick and kill study failed to achieve its goals, as reported in last month's Destination: Cure column, several other kick and kill studies are planned with varying components.

When investigating these strategies, it's essential to keep in mind that in addition to efficacy, an effective HIV cure strategy must be one that is not only safe and efficacious but also is affordable to the entirety of the world. As such, strategies such as stem cell transplants and costly gene therapies, if they were to work, would likely have a limited reach excluding much of the developing world, where the majority of people living with HIV reside. Although some strategies will only be applicable to certain people or populations, a viable overall cure must be accessible to everyone.

At AIDS 2018, a new class of drug called RNA helicase translation inhibitors was unveiled. Translation inhibitors (TI) are being researched and developed as an HIV therapeutic that could also be applicable in a kick and kill strategy. Numerous aspects of this class of drug, as well as the company that is developing TIs, check all the boxes of an intervention worthy of attention.

Unlike current antiretrovirals that work against HIV itself, TIs target a human host factor, DDX3. Although DDX3 is involved in several cellular functions of RNA metabolism, preclinical and mice assays have shown no toxicities related to inhibiting DDX3. Strong activity against HIV replication, including numerous drug- resistant strains, has been observed in preclinical research and drug resistance is expected to be minimal or unlikely. A DDX3 TI approach could also be used as salvage therapy to treat those with multi- drug resistant HIV, or in addition to ARVs, to limit the occurrence of drug resistance.

By inhibiting the DDX3-mediated viral protein translation apoptosis (cell death) can be induced. If this is shown in vivo in the presence of HIV, it could disrupt the establishment of viral reservoirs, thus making DDX3 translation inhibitors a good candidate to be studied as part of a cure strategy.

In addition, DDX3 is involved the replication of various viruses, tumor proliferation and the above-mentioned inflammation. Thus, as well as activity against HIV replication, it may also show benefit against several HIV-related comorbidities and co-infections such as hepatitis C, Kaposi sarcoma, and immunesuppressive-related tumors. TIs are expected to reduce the inflammatory state associated with HIV, directly acting on the production of inflammatory mediators as observed in cellular assays. HIV-related inflammation has been associated with numerous HIV co-morbidities that can greatly impair health, quality of life and survival.

"Translation inhibitors are promising compounds to treat HIV infections and in particular to attack resistance. If you target host factors crucial for the viral replication [such as DDX3] it makes it much more difficult for the virus to escape because the protein cannot mutate to escape the inhibition. A combination of both inhibitors against host factors as well as antiviral compounds will be one of the best combinations of drugs you can have," stated Prof. Dr. T.B.H. Geijtenbeek, Head of the Department Experimental Immunology at the University Medical Center of Amsterdam.

The makers of translation inhibitors, First Health Pharmaceuticals BV, have therapeutics in development for numerous viral infectious diseases such as HIV, HCV, Zika, Ebola and Dengue fever, as well as anti-tumor agents for several forms of cancer. Typically, when I write about notable research, my focus is solely on the drug and the research that makes it credible. However, in the case of translation inhibitors, the company behind the drug and their mission play a vital role, in addition to the research, in why we should focus on TIs and what makes them viable as an HIV therapeutic/potential component of a kick and kill strategy that could be used across the globe.

First Health Pharmaceuticals BV has created a non-profit organization founded with the purpose of promoting life science R&D for the benefit of humanity in general. First Health Pharmaceuticals BV has pledged to donate a portion of the proceeds from their therapeutics and the largest part of its antivirus pipeline to its non-profit First Health United foundation, to provide their medications free or at cost to low-income countries, especially in the sub Saharan region. Thus, drugs created and approved for any of the indications targeted, including an HIV therapeutic or cure, will be made accessible to all who need them. It's extremely heartwarming and rare to see a pharmaceutical company that values lives over profits. I will be closely following the development of this new class of drug and reporting my findings in future columns.

Jeannie Wraight is the former editor-in-chief and co-founder of HIV and HCV Haven (www.hivhaven.com) and a blogger and writer for TheBody.com. She is a member of the Board of Directors of Health People, a community-based organization in the South Bronx and an advisor to TRW (Teach me to Read and Write), a community-based organization in Kampala, Uganda. She lives with her husband in New York City.

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