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Intervention on viral diseases by targeting host cellular factors: A novel approach

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Viruses are intracellular parasites which carry a limited set of genetic information and therefore are completely dependent on the host cells they infect to propagate and survive.

While antivirals have traditionally been designed to directly target viral proteins in search for specificity and good therapeutic indices, some virus-targeted drugs have been plagued with issues of toxicity that have severely limited their ability to be developed and utilized as therapeutics. Moreover, a common drawback for all such direct-acting antivirals is the emergence of resistance, resulting from rapid mutations of viral proteins.

An alternative approach to the direct-acting antivirals is to target the key cellular proteins that are essential for viral replication and survival. This approach helps to address the issue of resistance since cellular proteins are less prone to mutate than virally encoded ones. The perception that toxicity is an issue when targeting cellular factors is a misconception. In reality, the majority of drugs used in the past and in current medical treatments target cellular mechanisms. Significantly, these drugs have been used safely and efficaciously on millions of individuals, and many drugs targeting cellular factors can be safely used chronically, often for decades (e.g. anti-hypertensive, anti-cholesterol, etc.), a distinct advantage for the treatment of chronic viral infections.

Given the above, at ViroStatics we have focused our efforts on developing a new class of drugs that target viruses through the inhibition of host cellular factors. In this regard, we are pursuing the novel approach of targeting the cellular kinase CDK9 (Cyclin-Dependent Kinase 9), which is known to play an essential role for viral replication and survival in a number of infections, including HIV, EBV, HSV and HPV.

While there is a broad applicability to this approach, our initial focus has been on the indication for HIV/AIDS. We are developing first-in-class Transcription Inhibitors designed to attack the unexploited, post-integration phases of HIV replication through CDK9 inhibition. HIV/AIDS offers a natural proof of concept in support to this notion: Elite Controllers, a low percentage of untreated HIV infected individuals with an undetectable HIV RNA load, exhibit an intrinsic inhibition of CDK9 activity which occurs without any apparent safety issues or the induction of viral resistance. ViroStatics' compounds are designed to mimic this Elite Controllers' phenotype, in essence, to pharmacologically induce "elite control" that rarely occurs naturally.

Some ViroStatics' CDK9 inhibitors suppress HPV replication in vitro with an antiviral potency up to a thousand-fold higher than the reference control drug Cidofovir. Initial screening has shown good druggability and safety profiles of CDK9 inhibitors both in vitro and in vivo.

The absolute dependence of any virus on the host cellular machinery for propagation and survival represents the Achilles' heel for all viruses. Developing cell-targeted drugs as an alternative to virus-targeted drugs would provide a new generation of antivirals that addresses the continued unmet need of drug resistance and offers the potential for new medicines for infections that cannot be presently treated.

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