Flex-nucleosides – a strategic approach to broad-spectrum antiviral therapeutics

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Replication is intrinsic to the lifecycle of all viruses, thus their survival relies on DNA or RNA polymerases. As a result, the polymerase is considered one of the most important targets for antiviral drug design. A highly effective strategy to target polymerases is through the use of nucleos(t)ide analogues. In an effort to explore flexibility as a design approach to increase polymerase recognition, as well as to develop a possible strategy against resistance mechanisms, a novel flexible nucleoside scaffold was designed in our laboratories.

The *"fleximers"* as we named them, featured a "split" heterocyclic purine base that retained the requisite hydrogen bonding elements necessary for recognition, but allowed free rotation around a single carbon-carbon bond. This endows the nucleoside scaffold with the ability to adjust and adapt when encountering point mutations in enzyme binding sites. Various types of fleximer nucleosides have been designed, synthesized and investigated in our laboratories over the years. Many of the fleximers have shown promise as antiviral, anticancer and antiparasitic therapeutics.

Most recently a new series of "doubly" flexible analogues was pursued, by combining our fleximer base modification with various modified sugars found in several FDA-approved antiviral nucleoside drugs, including the acyclic sugar found in Acyclovir. This has led to potent biological activity against a number of viral targets, including MERS, SARS, Zika, Dengue, Yellow Fever, Ebola, Sudan and other neglected viruses. The history and progress of some of these projects will be discussed.