BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

Repurposing Catalytic Inhibitors Of Topoisomerase Cancer Drugs As Broad-spectrum Countermeasures Against Viral And Bacterial Threats

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The ideal countermeasure would be an effective, fast acting, therapeutic against an unknown variety of viral and bacterial threats. We propose that a line of cancer drugs targeting the catalytic domain of topoisomerases could be effective against a mechanistic requirement of a broad range of pathogens as they overtake human host cells. The need to alter the topology of the viral and host, nucleic acids, is common to all viruses (and even many bacteria). The topology needs to be correct for the virus to replicate and express its genes. Polymerases scanning along DNA creates supercoiling, that unless resolved, creates knots that inactivate the invading DNA, requiring topoisomerase to resolve. In other cases, transcription factors needed for the expression of genes will not bind to the invading DNA unless the viral template is supercoiled, requiring helicase. In my past research, we found that even in the tiny SV40 virus, part of its multifunctional T-antigen sharing antigenic determinates with a host protein, shown to be an RNA helicase. In my work on the larger ds-DNA virus Adenovirus, the E1A protein revealed its ability to increase transcription of viral genes by increasing access of the DNA binding transcription factor, TFIIIC. PC4 and topoisomerase I are a part of the TFIIIC complex that increases in activity during infection. My data had shown an increase in topoisomerase activity during a time-course of viral infection (thesis) using kinetoplast DNA as an assay template, which suggests that viral gene expression triggered by E1A may work by modifying PC4. Given our experience with this assay, which readily detects a time-course-dependent increase in topoisomerase due to viral infection, it could be used as a drug screen for previously developed topoisomerase inhibitors currently in use, or under development by pharmaceutical companies as cancer treatments. The assay would confirm for each drug tested if its mechanism of action affects overall telomerase activity in an infected cell. This data can be supplemented with other screening data where cells infected with a variety of agents are evaluated in a pharmacological study, where inhibition of infection is scored. Therapeutics targeting topoisomerases (ex., decreasing super-helicity)/helicases (ex., increasing super-helicity) have been used as cancer treatments (well-funded) but explored less on viral disease (not well funded). All viruses code for topology modulators, unique from the cells' own, which make them ideal drug targets. For example, COVID is a (+) strand RNA virus coding for its own 5'-to 3' helicase at nsp3. There are many types of viruses that could be used as bioweapons, especially as further genetically modified, and various isotypes of these can cause serious disease. Even adenovirus has types 40 and 41 which cause gastroenteritis, and are the main candidates for the current outbreak of acute liver failure in children with hepatitis. Other adenovirus types cause colds and conjunctivitis. Epstein Barr virus (mononucleosis and multiple sclerosis), has similarities to adenovirus and may regulate its early and late genes similarly. Inhibitors interfering with the ATPase site on telomerase, such as substituted 4,5'-bithiazoles are ideal candidates.

The ideas presented were developed at HOF Therapeutics, where future work will be conducted. Reference to earlier research results occurred while employed at Cold Spring Harbor Laboratory in New York, and during graduate work in Dr. Robert G. Roeder's laboratory first at Washington University in St. Louis and then Rockefeller University in New York City.