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Anti Hepatitis C virus drugs show potential drug repositioning for SARS CoV-2 main protease: an in silico study

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Opinion

VIEWPOINT

Hepatitis C Virus—From Discovery to Cure
The 2016 Lasker-DeBakey Clinical Medical Research Award

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Viewpoint
pages 1252 and 1256

Supplemental content

The 2016 Lasker-DeBakey Clinical Medical Research Award has been presented to Ralf F. W. Bartenschlager, Charles M. Rice, and Michael J. Sofia for the development of a system to study the replication of the virus that causes hepatitis C virus and for use of this system to revolutionize the treatment of this chronic, often lethal disease.

The liver is the largest organ in the human body and is central for metabolism and many other functions. Several viruses specialize in infecting the liver and are called hepatitis viruses. Five such viruses are known, including *hepatitis C virus* (HCV), which was originally recognized as an agent of posttransfusion non-A, non-B hepatitis. Given that about 6% of patients receiving blood transfusions developed non-A, non-B hepatitis, tremendous efforts were mounted to isolate and molecularly clone this filterable agent, likely a virus.

In a landmark paper in 1989, Houghton and his team isolated the first molecular clone of HCV and provided a glimpse of the HCV genome: a positive-strand RNA virus with a genome length of around 9500 nucleotides encoding a long polyprotein that was likely cleaved cotranslationally and posttranslationally into 8 to 10 products.[1] Work in many laboratories, subsequently identified 10 HCV proteins generated by the action of host cell and viral proteases, including 2 viral enzymes, the nonstructural proteins (NS) 3-4A serine protease and the NS5B RNA-dependent RNA polymerase, highly attractive HCV drug targets. Subsequent research by Drs Bartenschlager, Rice, and Sofia led to the development of new and effective treatments for HCV.[2-7]

The bottleneck in drug development was the lack of cell culture systems for HCV, but the availability of molecular HCV clones raised hope because the RNA genome of positive-strand RNA viruses is infectious. Introducing genome RNA or a genome RNA equivalent transcribed from a plasmid into permissive cells can initiate an entire viral life cycle. The genome RNA is recognized by cellular ribosomes, translated to produce the viral proteins, and, in concert with additional factors from the host cell, amplified and used to make infectious virus. However, this approach, which had succeeded for many other viruses, failed for HCV. One reason was a missing piece at the 3′ end of viral genome finally discovered by the laboratories of Kunitada Shimotohno and Charles M. Rice. With the HCV genome now likely complete, making a functional complementary DNA (cDNA) clone should be easy, but how would this be tested without a cell culture system? In 1997, clones reflecting a "consensus" sequence were used to filter out possible lethal mutations present in the patient-derived HCV population or acquired during cDNA cloning in the laboratory. Injection of this synthetic, naked genome RNA into the liver of chimpanzees gave rise to a productive HCV infection and provided the first genetic system for proving that possible HCV-specific drug targets were essential for the virus.

With virtually unlimited quantities of HCV genome RNA, validated as infectious in vivo, it might be expected that finding a suitable cell culture system would quickly follow, but that was not the case. The solution came from work in the laboratory of Ralf Bartenschlager that used another HCV consensus genome cloned from the liver of a chronically infected patient. With the aim to isolate rare cells supporting robust HCV replication, "selectable minigenomes," called *replicons*, were engineered. These replicons encode the minimal set of viral proteins assumed to be required for autonomous replication and, in addition, a gene conferring resistance against the cytotoxic drug G418. By using drug selection, cells supporting efficient and long-term HCV replication could be isolated. This first robust HCV cell culture model recapitulated all the intracellular steps of the HCV replication cycle and because replication of these HCV RNAs relied on the viral enzymes, most notably the NS3 protease and the NS5B polymerase, the replicon system was suitable for drug development.

Subsequent studies conducted in the Rice and Bartenschlager laboratories unveiled the reasons for such high replication efficiency. First, the most HCV-permissive individual cells in a given cell pool had been selected; second, the replicons present in selected cell clones harbored mutations that enhanced HCV RNA replication by orders of magnitude. Insertion of these mutations into the parental replicon allowed direct measurement of HCV replication. Thus, the first widely useful genetic systems for studying HCV biology were created. Subsequent work by Bartenschlager, Rice, and others refined this approach.

With the robust HCV replicon whole-cell system available for screening of small molecules, the search for inhibitors of HCV became a major focus of pharmaceutical and biotech companies. This was propelled by the desire to identify direct-acting antivirals with the ultimate goal of replacing the then current standard of care for treating HCV infection, the combination of injectable interferon plus ribavirin, which was limited by severe adverse effects, modest cure rates, and limited genotype coverage.

In 2005 efforts in HCV drug discovery were focused on several key viral targets, including the NS5B RNA-dependent RNA polymerase (NS5B RdRp). The

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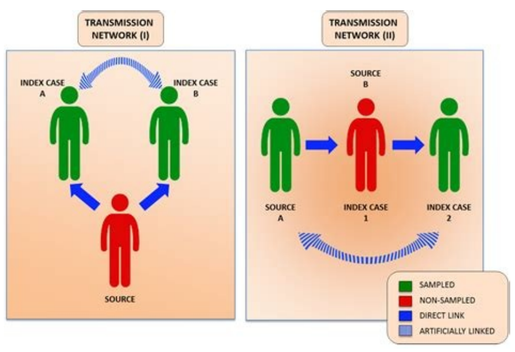

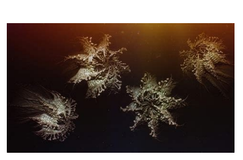

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A vaccine against hepatitis C virus (HCV) that includes GPE1/GPE2 wrapping glucoproteins derived from a single insulation causes wide cross-neutralization antibodies. More one. 2013; 8: E59776. [PubMed's free article] [Google Scholar] Page 2 The hepatitis C virus poly-protein is processed in a co-and later manner by host and viral proteases in at least 10 different proteins, which are organized in the order of NH2-C-E1 -E2-P7-NS2-NS3-NS4A-NS4B-NS5 The host signal peptide is required for divisions in the C-E1, E1-E2, E2-P7 and P7-NS2. NS2 operates the site between NS2 and NS3; The NS3/4A protein senrine releases the sites in the NS3-NS4A, NS4A-NS4B, NS4B-NS5A and NS5A-NS5B unions. Several new DAAs (e.g., Boceprevir, Simeprevir and Telaprevir) designed specifically to inhibit the NS3/4A protease are now available. The undulating lines mark the untranslated regions (UTR) of the genome RNA of the hepatitis C virus, while the rectangle represents the poly-protein derived from the long open reading framework. Click on the image to see a new version .n³Âisrev .n³Âisrev