

The Drug Development Process: The Case of Hepatitis C Virus

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HCV causes significant morbidity and mortality worldwide with nearly 3% of the world population infected by this virus. Fortunately, this virus does not establish latency and hence it is possible to eradicate it. HCV infections become chronic in about 50% of cases, and about 20% of these chronic patients develop liver cirrhosis that can lead to hepatocellular carcinoma. Because current therapies such as interferon-alpha (IFN- α) and ribavirin carry limited efficacy and are associated with significant side effects even when used with the newly approved HCV protease inhibitors Incivek and Victrelis, there is a need for more effective anti-HCV agents that can be used in IFN- α /ribavirin sparing regimens. The limited treatment options present with significant manifestation of detrimental clinical symptoms, and currently complete eradication of virus with combined drug modalities has not yet been achieved for the majority of chronically HCV-infected individuals. Restricted treatment options, lack of a universal cure for HCV, and the link among chronic infection, liver cirrhosis and hepatocellular carcinoma necessitate design of novel treatment options, especially in HIV co-infected individuals. Understanding the relationship between the immune response, viral clearance, and inhibition of viral replication with pharmacology-based design can ultimately allow for complete eradication of HCV. Traditional methods for general drug discovery typically include evaluating random compound libraries for activity in relevant cell-free or cell-based assays. Success in antiviral development has emerged from the discovery of more focused libraries that provide clues about structure activity relationships. Combining these with more recent approaches including structural biology and computational modeling can work efficiently to hasten discovery of active molecules, but that is not enough. There are issues related to biology, toxicology, pharmacology, and metabolism that have to be addressed before a hit compound becomes nominated for clinical development. The objective of gaining early preclinical knowledge is to reduce the risk of failure in Phases 1 to 3, leading to the goal of approved drugs that benefit the infected individual by providing new treatment options and innovative modalities. The need for multidisciplinary efforts to discover new antiviral drugs for the benefit of humanity is essential.

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