Chronic Hepatitis C: From Bench to Practice

Keng-Hsin Lan, M.D., Ph.D.

Division of Gastroenterology, Department of Medicine, Taipei Veterans General Hospital,

Hepatitis C virus (HCV) infects nearly 3% of the population worldwide and has emerged as a major causative agent of liver disease, resulting in acute and chronic infections that can lead to fibrosis, cirrhosis and hepatocellular carcinoma. HCV, a positive-stranded RNA virus of the Hepacivirus genus within the Flaviviridae family, contains a single-stranded RNA genome of approximately 9600 nucleotides and encodes a large polyprotein precursor of about 3,000 amino acids (aa) that is processed by a combination of host and viral proteases into at least 10 individual proteins: core, E1, E2, p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B. The genome RNA serves as both mRNA for translation of viral proteins and the template for RNA replication. HCV enters host cells through receptor-mediated endocytosis, and the process requires the co-ordination of multiple cellular receptors and co-receptors. HCV RNA replication takes place at specialized intracellular membrane structures called ‘membranous webs’, whereas viral assembly probably occurs on lipid droplets and endoplasmic reticulum. Previously, hepatitis C was treated with a combination of pegylated interferon and ribavirin, a treatment which was only partially effective and was plagued with significant adverse effects. Since the discovery of HCV in 1989, a plethora of experimental tools have been developed which enabled detailed analysis of various aspects of the viral life cycle and the interaction of HCV with its human host. In 1999, a breakthrough was achieved with the development of a robust in vitro replication model named 'replicon'. This system allowed intensive research into replication mechanisms and drug discovery. In 2003, pseudotyped retroviruses harboring envelop proteins of HCV were produced to specifically investigate the viral entry process. It was only in 2005 that infectious viruses were produced in vitro, enabling intensive investigations into the entire life cycle of the HCV. Advances in our understanding of the HCV life cycle have enabled the development of numerous clinically advanced direct-acting antivirals (DAA) and a growing list of targets for therapeutic intervention. Among potential targets are viral entry factors, including scavenger receptor type B1 (SR-B1) and CD81, as well as neutralizing antibodies against the viral glycoproteins. Popular targets related to translation and replication are the NS3/4A protease (inhibited by simeprevir and boceprevir) and the NS5B polymerase (inhibited by sofosbuvir), as well as the nonenzymatic targets such as NS4B and NS5A proteins. Host targets are also available, including microRNAs and cyclophilins. In this meeting, the development of different in vitro models to study HCV life cycle, their contribution to current knowledge of the virus biology and their future research applications, up-to-date knowledge of the preclinical and clinical development targets and pathways being explored in the translational and clinical settings, and aspects of the mechanisms of action of approved and investigational drugs for HCV, will be briefly reviewed.