Nobel Prize

Honouring the Winners of the Nobel Prize in Physiology or Medicine 2020 for Revolutionary Discovery to Eliminate Hepatitis C Virus

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Dr. Harvey J. Alter

He received his medical degree from the University of Rochester Medical School and trained in internal medicine initially at Strong Memorial Hospital and later at the University Hospital of Seattle. He joined NIH as a Clinical Associate in 1961. He then moved to Georgetown University and after spending several years at Georgetown University, came back to NIH in 1969 as a senior investigator at the Clinical Center's Department of Transfusion Medicine. He became Chief of the Clinical Studies soon after joining and later became Associate Director of Research in the Department of Transfusion Medicine at the NIH Clinical Center. Alter was awarded the prestigious Clinical Lasker Award in 2000 and in 2002, he became the first Clinical Center scientist elected to the National Academy of Science USA, and in the same year he was elected to the Institute of Medicine. In 2013, Alter was honoured with the prestigious Canada Gairdner International Award. Dr. Alter won the 2020 Nobel Prize in Physiology or Medicine.

Dr. Michael Houghton

He was born in UK and graduated with B.Sc. degree in biological sciences from the University of East Anglia in 1972. He completed his Ph.D. in biochemistry at King's College, University of London in the year 1977. After completing Ph.D. he moved to USA and joined pharmaceutical manufacturing company G.D. Searle & Company and later he joined the California-based biotechnology company Chiron Corporation. Houghton started investigation on NANBH with fellow Chiron scientists G. Ching-Hung Kuo and Qui-Lim Choo along with American Virologist D.W. Bradley. His group successfully identified a DNA clone derived from the HCV RNA genome. They also developed an assay to screen HCV in blood sample and contributed to the discovery of the hepatitis D virus genome. Houghton joined Epiphany Bioscience as the chief scientific officer in 2007 leaving Chiron. Finally after two years he moved to Canada to join as Li Ka Shing Professor of Virology at the University of Alberta where his research focussed on the development of an HCV vaccine. He received Robert Koch Prize in 1993, the Albert Lasker Clinical Medical Research Award in 2000 and received the Nobel Prize in 2020.

Dr. Charles M. Rice

He is an American Virologist. Rice graduated from University of California, Davis in 1974 with a bachelor's degree in zoology. Rice started to study biochemistry at California Institute of Technology and joined American virologist James Strauss to complete his graduate research on RNA viruses. Rice completed his Ph.D. in 1981 from Caltech and remained as postdoctoral fellow at Caltech. Rice joined Washington University School of Medicine in St. Louis as a faculty in 1986. In 1996 he successfully described the complete HCV genome and later in 1997 he demonstrated the infectious nature of the cultured virus. Rice moved to Rockefeller University in 2001. Rice was a recipient of the Robert Koch Prize (2015), the Lasker-DeBakey Clinical Medical Research Award (2016) and the Nobel Prize in 2020. He was an elected member of the American Association for the Advancement of Science (2004) and the National Academy of Science USA (2005).

Abstract

The Nobel Prize for physiology or medicine has been awarded jointly to Harvey Alter, Michael Houghton, and Charles Rice for the discovery of hepatitis C virus (HCV). This remarkable invention not only transformed the fields of virology or immunology but also saved millions of lives revolutionizing clinical care and management in terms of proper diagnosis using sensitive tests, effective treatment to cure HCV infection and for the prevention of liver cancer in a large number of populations. Through this review, Chettinad Health City Medical Journal honours Harvey Alter, Michael Houghton, and Charles Rice for their great effort and contribution.

Background

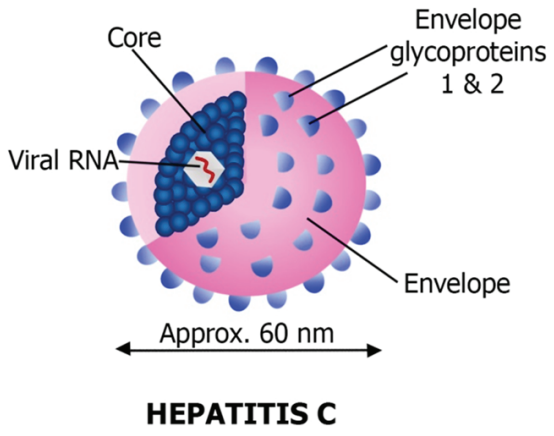
In the beginning of 1970s, the hepatitis B surface antigen blood test was introduced and that remarkably reduced the incidence of post-transfusion hepatitis. Meanwhile, Dr. Alter noticed an infection related to transfusion associated hepatitis in 22 patients which was different from hepatitis A and hepatitis B viruses.[1] The number of such transfusion associated infection from the unknown virus started to multiply and approximately 75% of the transfusion associated hepatitis became classified in the same category. Professor Alter postulated the plausible existence of the 'non-A, non-B' hepatitis (NANBH) virus.[2] In support of his hypothesis on NANBH, Alter demonstrated the transmissible nature of NANBH using a specific species of chimpanzees susceptible to both hepatitis A and hepatitis B viruses.[3]

There were several molecular approaches introduced for more than a decade of time to isolate the mysterious NANBH virus from the infected individuals. Most of the approaches ended up without any fruitful explanations. The research group of Professor Michael Houghton found out that the insufficient concentration of NANBH viral antigens was the main reason for the failure.[4] To resolve this issue Houghton followed the recommendation of Taiwan-born scientist Dr. George Kuo Ching-Hung and applied proteomics based blind complementary DNA immunoscreening. This novel method helped to generate a huge collection of random primed cDNA libraries utilizing NANBH chimpanzees. These complementary DNAs were introduced in bacteria for the production of cDNA encoded proteins that would match with NANBH antigens.[5] These proteins were then utilized for the screening of viral antibodies. A cDNA fragment was identified after giving continuous effort for more than two years from a novel RNA virus called HCV. At the same time Houghton developed recombinant technology based assay to generate HCV antibodies and successfully proved that HCV was the major cause of NANBH worldwide. He also introduced the idea for subsequent prevention of numerous cases of post-transfusion hepatitis.[6]

Charles Rice identified the 3' terminal region which was essential for the initiation of HCV replication. Initially, the viral replication was not functioning in animals even after the inclusion of the identified terminal region but Rice and his research group observed numerous inactivating mutations in the isolated clones which were responsible for preventing the viral replication process. Rice then determined a "consensus sequence" comparing those isolated clones to identify the potential mutations. Avoiding the possible mutations in the sequence and including the specific terminal region, Rice generated HCV RNA that caused hepatitis in chimpanzees. The finishing touch was given by Rice to this great discovery defining the structure of functional HCV RNA with replication capabilities that cause only hepatitis.[7]

Hepatitis C Virus

Hepatitis C virus is a positive single stranded RNA virus and it belongs to the Flaviviridae family. The viral genome contains nearly 9600 nucleotides with a single-open reading frame (ORF) encoding a large polyprotein of about 3008 amino acids. This polyprotein gets converted to the matured polypeptides. During this processing, three structural proteins – core, envelope 1 (E1) glycoprotein and envelope 2 (E2) glycoprotein and seven non-structural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A and NS5B) are generated. There are 7 major genotypes that differ from each other by approximately 25-35% and 67 subtypes that differ from each other by approximately 15-25% at the nucleotide level.[8] The glycoproteins E1 and E2 are very crucial in the clathrin-mediated endocytosis of the HCV. The virus enters into the cells by interacting with the membrane molecules existing on the basolateral hepatocyte membrane. CD18 surface receptors on hepatocytes and B lymphocytes play major role in binding to the membrane. After disruption of the viral capsid, the positive RNA strand gets released into the cytosol and is translated at the rough ER. The primary translated product contains approximately 3008 amino acids long polyprotein precursor that gets cleaved by the host and viral proteases into 3 structural and 7 non-structural proteins.[9] These function as the viral replication machinery along with a frameshift protein (F protein) and alternate reading frame protein (ARFP). NS2 is involved in virus assembly and release, whereas, NS3 and NS4A form the protease complex to cleave the polyprotein. NS4B plays a major role in virus-host interaction and NS5A is involved in replication. RNA dependent RNA polymerase NS5B is the key enzyme for HCV RNA replication. NS3 protein acts as helicase to synthe-



size a minus-stranded RNA that functions as template for a large number of plus stranded RNA.[10]

Interferon alpha was approved by the FDA in 1991 as first line drug initially for the treatment of hepatitis C patients but the success rate was just 10%. Later in 1998, a co-therapy with ribavirin was introduced that gained therapeutic efficacy nearing 30-50%. The pegylated interferon was introduced in the treatment in 2001 and showed long term therapeutic effects.[11] Therefore, the combination of pegylated interferon and ribavirin was the most widely used treatment against HCV with many side effects. From 2014 onwards, the interferon free DAA (direct acting antivirals) combinations of multiple antivirals of protease inhibitors (paritaprevir, grazoprevir, glecaprevir, and voxilaprevir), polymerase inhibitors (sofosbuvir and dasabuvir) and NS5A inhibitors (pibrentasvir, velpatasvir, ledipasvir, ombitasvir, elbasvir, and grazoprevir) have been used to cure almost all patients for a treatment period of 8-12 weeks without any considerable side effects.[11]

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