Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

journal homepage: www.elsevier.com/locate/bj


News and Perspectives

# The 2020 Nobel Prize in medicine for the discovery of hepatitis C virus: An epic saga of the fight against a troublesome virus


*Chun-Yen Lin* [a,b,*], *Rong-Nan Chien* [a,b], *I-Shyan Sheen* [a,b]

[a] *College of Medicine, Chang Gung University, Taoyuan, Taiwan*
[b] *Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital at Linkou, Taoyuan, Taiwan*

ARTICLE INFO

*Article history:*
Received 12 January 2021
Accepted 1 July 2021
Available online 7 July 2021

ABSTRACT

Chronic hepatitis C, which is caused by the hepatitis C virus, represents a substantial health threat to humans and causes approximately 700,000 deaths each year worldwide. However, 30 years after the discovery of this virus in 1989, nearly perfect antiviral drugs that can clear up to 95% of this virus have been developed due to numerous biomedical research studies and cooperation among members of the hepatitis C community. Because of these advances, the WHO announced a goal to eliminate the hepatitis C virus globally by 2030. Reviewing prior advances in detail, it is clear that all these achievements are based on initial seminal research conducted by the three 2020 Nobel laureates in medicine, namely, Harvey J. Alter, Michael Houghton and Charles M. Rice. In this short essay, we describe the seminal studies conducted by these authors. At the same time, the impacts of the contributions of these researchers on subsequent developments in research and in the treatment of chronic hepatitis C are honored.

On 5 October 2020, a press release by the Nobel Assembly at the Karolinska Institute marked an event organized to combat the troublesome hepatitis virus by awarding three pioneering researchers, Harvey J. Alter, Michael Houghton and Charles M. Rice, for the discovery of the hepatitis C virus (HCV). In this announcement, the assembly summarized the contributions of these researchers as follows: "This year's Nobel Prize is awarded to three scientists who have made a decisive contribution to the fight against blood-borne hepatitis, a major global health problem that causes cirrhosis and liver cancer in people around the world." [1] Actually, this prize recognizes not only the contributions made by these three pioneering researchers but also appreciates all the members of the hepatitis C community, including basic researchers, public health experts, pharmaceutical company workers and medical professionals who donated their time, resources and energy to the cause of fighting this troublesome virus.

HCV infection can cause acute hepatitis but rarely results in grave outcomes. The real threat of HCV infection is its chronic nature, which may eventually lead to the development of cirrhosis and hepatocellular carcinoma [2]. In addition, chronic HCV infection can also be considered a systemic disease with significant impacts on several chronic diseases, such as chronic renal failure, insulin resistance, diabetes,

* *Corresponding author*. Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital at Linkou, 259, Wenhua 1st Rd., Gueishan, Taoyuan 333, Taiwan.
E-mail address: chunyenlin@gmail.com (C.-Y. Lin).
Peer review under responsibility of Chang Gung University.
https://doi.org/10.1016/j.bj.2021.07.001

hyperlipidemia, coronary artery disease, autoimmune disease and lymphoproliferative disorder, either as a causative agent or as an aggravating factor [3]. It is estimated that the global prevalence of viremic HCV is approximately 1.0%, corresponding to 71.1 million viremic infections, and HCV infection causes approximately 700,000 deaths each year [4].

The history of the fight against HCV, waged through cooperation among different researchers/professionals in various fields, is also a notable achievement. After the identification of the causative agent for non-A and non-B hepatitis, known as HCV, in 1989, the FDA approved the first alpha interferon to treat hepatitis C in 1991, although the viral eradication rate exhibited by this therapy was only approximately 10% [5]. Seven years later, in 1998, a combination of ribavirin with alpha interferon was observed to significantly increase the viral eradiation rate to nearly 50% [6]. In the following 10 years, the introduction of pegylated interferon in combination with ribavirin replaced the original combination of drugs and achieved a slightly better viral eradication rate of up to 60–70% [7], but this treatment had substantial adverse effects that significantly reduced the tolerability and willingness of patients to accept this treatment regimen [8]. However, the research into HCV has not ceased and is not likely to stop. Because a better understanding of HCV structure, enzymes and lifecycle has been achieved, scientists from either academic institutes or pharmaceutical companies introduced new drug targets that led to the discovery of direct antiviral agents (DAAs) in 2011 [9]. After that advance, a new era of HCV treatment was developed. To date, the latest generation of DAAs has achieved a viral eradication rate greater than 95% with minimal adverse effects [10]. Based on this development, the WHO announced the goal of eliminating HCV globally by 2030 [11].

All the achievements made in the last 30 years that have led to possible near-future HCV elimination are based on three seminal papers [12–14] that were the foundation for subsequent full-scale HCV research. The fundamental breakthrough contributions were derived from different scientific approaches, including clinical and epidemiological studies, molecular biological studies and virological studies, reflected as different profiles of these three laureates as a physician, a molecular biologist and a virologist [1]. Initially, Dr. Harvey J. Alter from the Department of Blood Transfusion at the US National Institutes of Health in Bethesda, Maryland, worked on transfusion-related hepatitis that was not due to hepatitis A or hepatitis B virus after the discoveries of hepatitis A and B in the 1960s. The amazing achievements of Alter and his colleagues were to characterize this non-A non-B hepatitis to be a disease entity and to define a new, distinct form of chronic viral hepatitis by showing that blood from these patients could transmit the disease to chimpanzees, the only susceptible host aside from humans [12]. This important clinical and epidemiological breakthrough established the foundation for the subsequent discovery of the viral genome by Dr. Michael Houghton, although a decade required to reach this goal. This notable step that Dr. Houghton had taken was to use a different approach, not isolating the virus directly but instead using the traditional molecular biological method of gene cloning. Together with his Chiron colleagues, Qui-Lim Choo, PhD and George Kuo, PhD, Houghton generated cDNA libraries from nucleic acids isolated from livers and plasmas of infected chimpanzees and transferred them to a bacteriophage cloning system. After that step, these researchers screened the peptides translated by these cDNA fragments (that could possibly encode viral proteins) by a binding assay using patient-derived antibodies and characterized the viral genome, naming it “hepatitis C virus” [13]. Furthermore, this specific assay used a polypeptide synthesized in recombinant yeast clones of HCV that could also detect the presence of anti-HCV antibodies that not only implicated this virus as the missing agent but could also screen which patients might be infected by HCV [15].

There was still a “missing link” in the research at that time. Did this virus truly cause chronic inflammation of the liver, or was it only an innocent bystander? Next, Dr. Charles M. Rice, a virologist, and his team, working at Washington University in St. Louis, Missouri, at the time, attempted to solve this puzzle. After a tedious and painstaking genetic engineering approach, these researchers finally generated whole HCV RNAs and identified a full-length clone that resulted in a productive viral infection and liver disease in chimpanzees [14]. These results finally filled this gap and confirmed that HCV alone is the real culprit for non-A, non-B chronic hepatitis. After that step, an increase in HCV research from every scientific aspect led to the development of DAAs with nearly 100% viral eradication ability in 30 years.

Even in light of all the history regarding the discovery of HCV and respecting these three laureates, we still need to face the current unmet needs in the battle against chronic hepatitis C. First, only a minority of the infected patients worldwide are aware of this disease [16]. Without knowledge of the disease, the patients will not seek medical help until the infection is too advanced to be treated effectively. In addition, on a global level, many patients might not easily reach medical facilities. Scaling up the prevention and treatment towards the global elimination of hepatitis C is a challenging task [17]. Furthermore, reinfection remains a substantial public health challenge, especially in intravenous drug users [18]. Moreover, continuing frustration of HCV vaccination programs made reinfection challenge a real concern [18]. Finally, while DAAs could successfully clear the virus, the risk of hepatoma remains a life-threatening complication for patients who are already in advanced liver disease [19]. Therefore, although the story of the battle against hepatitis C virus has largely been written, the final chapter is still waiting to be completed.

To review the history of this disease, this 2020 Nobel Prize in medicine was awarded not only to memorialize and appreciate all the seminal studies conducted by these three laureates but is also to appreciate all the members of the hepatitis C community who made the dream of HCV global elimination an achievable goal. Moreover, to adopt a broad perspective, this prize also values the tremendous cooperation among humans from different sectors of human society, including biomedical researchers, medical professionals, public health experts, government officials, pharmaceutical company workers and the patients themselves, who work together to fight against any human disease.

Therefore, the story of the fight against the hepatitis C virus, which began in earnest with seminal studies conducted by these three laureates, is truly an epic saga worthy of the Nobel Prize.

## REFERENCES


[1] NobelPrize.org [internet]. MLA style: Press release: The Nobel prize in physiology or medicine 2020. Available from: https://www.nobelprize.org/prizes/medicine/2020/press-release/.

[2] Thrift AP, El-Serag HB, Kanwal F. Global epidemiology and burden of HCV infection and HCV-related disease. Nat Rev Gastroenterol Hepatol 2017;14:122–32.

[3] Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015;149:1345–60.

[4] Blach S, Zeuzem S, Manns M, Altraif I, Duberg A-S, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161–76.

[5] Shindo M, Di Bisceglie AM, Cheung L, Shih JW, Cristiano K, Feinstone SM, et al. Decrease in serum hepatitis C viral RNA during alpha-interferon therapy for chronic hepatitis C. Ann Intern Med 1991;115:700–4.

[6] Davis GL, Esteban-Mur R, Rustgi V, Hoefs J, Gordon SC, Trepo C, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. N Engl J Med 1998;339:1493–9.

[7] Lindsay KL, Trepo C, Heintges T, Shiffman ML, Gordon SC, Hoefs JC, et al. A randomized, double-blind trial comparing pegylated interferon alfa-2b to interferon alfa-2b as initial treatment for chronic hepatitis C. Hepatology 2001;34:395–403.

[8] European Association for Study of Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. J Hepatol 2014;60:392–420.

[9] Götte M, Feld JJ. Direct-acting antiviral agents for hepatitis C: structural and mechanistic insights. Nat Rev Gastroenterol Hepatol 2016;13:338–51.

[10] Ghany MG, Morgan TR, AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C guidance 2019 update: American association for the study of liver diseases–infectious diseases society of America recommendations for testing, managing, and treating hepatitis C virus infection. Hepatology 2020;71:686–721.

[11] World Health Org [Internet]. Combating hepatitis B and C to reach elimination by 2030: advocacy brief. Geneva: World Health Organization; 2016. Available from: https://apps.who.int/iris/bitstream/handle/10665/206453/WHO_HIV_2016.04_eng.pdf?sequence=1&isAllowed=y/.

[12] Alter HJ, Holland PV, Morrow AG, Purcell RH, Feinstone SM, Moritsugu Y. Clinical and serological analysis of transfusion-associated hepatitis. Lancet 1975;2:838–41.

[13] Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989;244:359–62.

[14] Kolykhalov AA, Agapov EV, Blight KJ, Mihalik K, Feinstone SM, Rice CM. Transmission of hepatitis C by intrahepatic inoculation with transcribed RNA. Science 1997;277:570–4.

[15] Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. Science 1989;244:362–4.

[16] Chung RT, Baumert TF. Curing chronic hepatitis C–the arc of a medical triumph. N Engl J Med 2014;370:1576–8.

[17] Heffernan A, Cooke GS, Nayagam S, Thursz M, Hallett TB. Scaling up prevention and treatment towards the elimination of hepatitis C: a global mathematical model. Lancet 2019;393:1319–29.

[18] Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, Lauer G, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine. Lancet Infect Dis 2012;12:408–14.

[19] Setiawan VW, Rosen HR. Stratification of residual risk of hepatocellular carcinoma following HCV clearance with DAA in patients with advanced fibrosis and cirrhosis. Hepatology 2020;72:1897–9.