HHS Public Access

Author manuscript

Gastroenterology. Author manuscript; available in PMC 2017 September 05.

Published in final edited form as:

Gastroenterology. 2016 December ; 151(6): 1052–1053. doi:10.1053/j.gastro.2016.10.011.

Hepatitis C Virus: From Obscurity to the Lasker

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The 2016 Lasker-Debakey Clinical Research Award was given to Ralf Bartenschlager of the University of Heidelberg, Charles Rice of Rockefeller University, and Michael Sofia of Arbutus Biopharma for their seminal work on the hepatitis C virus (HCV) replicon system and drug development. The Lasker Award, often hailed as the pre-Nobel award, captures and epitomizes a Cinderella story in modern medicine. This story began with a vaguely described entity of non-A non-B hepatitis that remained in relative obscurity until accumulating epidemiologic and clinical evidence unveiled its importance as a global public health threat. The isolation and identity of the culprit, the HCV, had eluded the scientific community for decades and it was not until 1989 that Michael Houghton and his colleagues at Chiron successfully cloned a piece of the HCV genome after years of frustration and failures. Harvey Alter at the National Institutes of Health then unequivocally demonstrated that this virus was indeed the causative agent of hepatitis C. For their groundbreaking work, Houghton and Alter received the Lasker Award in 2000. Fast-forwarding to 2016, the story has continued its ascent to the pantheon of medical history with the recognition of Bartenschlager, Rice, and Sofia by the Albert and Mary Lasker Foundation.

Only 25 years after the discovery of HCV, the medical community was at the cusp of a major breakthrough in treatment of this pathogen. The development of the direct-acting antivirals (DAAs) heralded an unparalleled success of this class of drugs that target specifically HCV-encoded functions and, in combination, can achieve a >90% cure rate of hepatitis C. Such a rapid pace from discovery to cure is rather unprecedented and is emblematic of the miracle of modern technologies and medical advances.

Looking back over the last two and one-half decades, this success certainly came with much blood, sweat and tears. First, extensive epidemiologic investigations underscored the global disease burden of this infection that remains an order of magnitude greater than infection with the highly touted human immunodeficiency virus. [1,2] The original stigma of HCV infection as a disease inflicting the fringes of society largely gave way to the general recognition that this virus infects all walks of life in both the developed and developing worlds. Unfortunately, this stigma remains a lingering concern to date. Second, clinical investigations identified the potential clinical consequences of chronic hepatitis C including cirrhosis, liver cancer, and death, which became a rallying cry among the medical and lay

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Conflicts of interest: The author discloses no conflicts.

communities for more research funding and effective treatments. Third, many governmental agencies and private biomedical research organizations invested in the basic science and clinical research that paved the road to success in hepatitis C. The saying of “a rising tide lifts all boats” certainly imprinted the annals of hepatitis C. The advances in modern molecular, chemical, cellular and structural biology certainly catalyzed today's success in the treatment of hepatitis C infection.[3]

Finally, the extensive collaborations among federal agencies, academic institutions, professional organizations, pharmaceutical industries, nonprofit foundations, and patient advocacy groups collectively created the “perfect recipe” for scientific discoveries, medical advances, and therapeutic development in the field of hepatitis C. This confluence of events cleared many barriers and propelled us to the success we now enjoy today. One formidable barrier was the lack of convenient model systems to study the virus and to test drugs. In response to this challenge, Bartenschlager and Rice, each taking a slightly different path, developed the HCV replicon system and constructed an infectious full-length HCV clone.[4,5] Their work permitted both the study of viral replication in cell culture and an unprecedented opportunity to develop virus-specific drugs.

Historically, many great scientific discoveries occurred rarely in isolation. Other breakthroughs in HCV cell culture systems came at the heels of the work of Bartenschlager and Rice. In particular, the discovery of a unique HCV isolate occurring in a Japanese patient with fulminant hepatitis C by Wakita et al[6] made possible the establishment of infectious HCV cell culture systems, which have been used widely to study HCV biology and therapeutic drug development.

Armed with these tools, many investigators in both the private and public sectors embarked on a long but exciting journey to identify the Achilles' heel of the virus and to design drugs to target these weaknesses. First was an inhibitor of the HCV-encoded protease,[7] which gave rise to the first DAA drug (telaprevir) approved for HCV treatment. Second was the discovery of a novel class of drugs targeting the NS5A protein of HCV[8], which was included in most of the approved interferon-free DAA regimens. Finally, accumulating scientific knowledge in developing a general class of drugs against viral infections, the nucleoside/tide analogs, led to the successful development of sofosbuvir,[9] which is to date probably the most effective of the DAA drugs. Michael Sofia, the lead inventor of the compound while working at Pharmassett, was the third awardee of this year's Lasker Prize.

As we congratulate and celebrate the achievements of these investigators, we should not lose sight that there is still much to do in the field of HCV research. We should not be complacent and jump to the premature conclusion of “mission accomplished.” The wide use of these life-saving drugs is still at an early stage in many regions of the world because of cost and other socioeconomic issues. In addition, we still do not know enough about how HCV interacts with the host, causes disease, and results in liver cancer, the deadliest cancer in the world, and how it is influenced by DAA therapy. To date, we still are not close to developing an effective preventive vaccine, which is essential for global control of HCV infection. More important, HCV infection provides an unparalleled opportunity to probe the mystery of human biology. Many unanticipated insights into the pathophysiology and

mechanisms of other human diseases have been revealed in the course of investigating HCV infection. If history were any lesson, it was the discovery of a virus (Rous sarcoma virus) causing tumorsin chickens back in 1911 that laid the foundation for modern oncology and many other disciplines in medical sciences.

Now it is only fitting that the Cinderella story of HCV has culminated in the second Lasker Award in the field of HCV research by recognizing the accomplishments of Ralf Bartenschlager, Charles Rice, and Michael Sofia. It is certainly not the end of the story but the future is indeed promisingly bright for a happy ending that the medical community should strive for and be proud of.

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