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Review

Critical challenges and emerging opportunities in hepatitis C virus research in an era of potent antiviral therapy: Considerations for scientists and funding agencies

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ABSTRACT

The development and clinical implementation of direct-acting antivirals (DAAs) has revolutionized the treatment of chronic hepatitis C. Infection with any hepatitis C virus (HCV) genotype can now be eliminated in more than 95% of patients with short courses of all-oral, well-tolerated drugs, even in those with advanced liver disease and liver transplant recipients. DAAs have proven so successful that some now consider HCV amenable to eradication, and continued research on the virus of little remaining medical relevance. However, given 400,000 HCV-related deaths annually important challenges remain, including identifying those who are infected, providing access to treatment and reducing its costs. Moreover, HCV infection rarely induces sterilizing immunity, and those who have been cured with DAAs remain at risk for reinfection. Thus, it is very unlikely that global eradication and elimination of the cancer risk associated with HCV infection can be achieved without a vaccine, yet research in that direction receives little attention. Further, over the past two decades HCV research has spearheaded numerous fundamental discoveries in the fields of molecular and cell biology, immunology and microbiology. It will continue to do so, given the unique opportunities afforded by the reagents and knowledge base that have been generated in the development and clinical application of DAAs. Considering these critical challenges and new opportunities, we conclude that funding for HCV research must be sustained.

1. Introduction – the public health imperative

Infections with hepatitis C virus (HCV) are a major cause of acute and especially chronic liver disease. The World Health Organization (WHO) estimates that at least 71 million people are persistently infected with HCV and are at risk for serious liver diseases, including potentially fatal hepatic cirrhosis and hepatocellular carcinoma (HCC) (WHO, 2017). At least 400,000 people die from HCV infection annually, almost half of the one million deaths attributable to HIV/AIDS in 2016 (UN AIDS, 2016). In the U.S., HCV-related deaths have exceeded HIV-

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related deaths for well over a decade, and opioid addiction is now driving dramatic increases in new HCV infections – truly a 'syndemic'. HCV-related deaths are increasing worldwide, while HIV-related mortality is declining according to the WHO, yet there are staggering disparities in both public health and research investments aimed at controlling these viruses. One in four cases of liver cancer, the second most common cause of cancer death worldwide and accounting for about 800,000 deaths annually, results from HCV infection, making HCV one of only 7 viruses (and the only positive-strand RNA virus) known to be oncogenic in humans. Yet HCV-mediated oncogenesis has received relatively little attention from the United States National Cancer Institute and many other cancer research agencies.

The recent development of highly effective direct-acting antivirals (DAAs) that cure the vast majority of HCV infections after only 8 weeks of oral therapy represents an outstanding success of modern medicine. It started with the discovery of HCV in 1989 (Choo et al., 1989) and the generation and rapid implementation of HCV screening tests to protect the blood supply (Kuo et al., 1989), and culminated 25 years later with the approval of interferon-free therapies that eliminate the virus in > 95% of treated individuals (reviewed in (Pawlotsky et al., 2015)). These drugs are the results of sustained and collaborative efforts between industry, academia, and government funding agencies, a joint endeavor that has unfortunately fallen victim to its success. Some now consider mistakenly that HCV is a vanquished pathogen, capable of being controlled or even eradicated on a global scale solely by antiviral therapy. This general perception has found its way into some funding agencies where the imperative for support of HCV research has been lost, and applications for support are confronted with the argument that HCV is no longer clinically relevant and further research is unnecessary. Such a view is naïve and short-sighted, and overlooks several major obstacles to global control of HCV with antivirals (Fig. 1). First, a large proportion of persistent HCV infections are clinically silent, often undiagnosed, and will not be recognized by patients or practitioners until liver damage is advanced. Second, DAAs are expensive, and will likely remain out of the reach of a majority of infected persons worldwide for many years (Iyengar et al., 2016). Third, clinically-relevant antiviral resistance, now relatively uncommon, will likely increase with broader use of DAAs. Forth, protective immunity after viral clearance is most often insufficient and reinfection with HCV, in the absence of a vaccine, is all too easy following curative DAA therapy (Midgard et al., 2016). Another factor, poorly understood and discussed in greater detail below, is that eliminating HCV infection with DAAs does not eliminate the risk of developing liver cancer. Finally, in the history of mankind no infectious disease has been eradicated by antimicrobial therapy, whereas this has been proven possible by vaccination.

Apart from the continuing need to develop more effective approaches to control the spread of HCV worldwide, the two-decade search for effective DAAs has provided investigators with a unique molecular "toolbox" that offers unparalleled opportunities to make important fundamental discoveries in virology, cell biology and immunology. In addition to its real and compelling impact on human health, the continuing value of HCV as a model pathogen should not be overlooked.

In this opinion paper we summarize important challenges in public health, translational and basic science, review some key aspects of HCV and briefly discuss new research opportunities that have emerged in the HCV field. We conclude that the mission is far from over, and that reductions in support for HCV research will compromise an opportunity to eradicate HCV on a global scale, and to make important discoveries that reach far beyond hepatitis C.

2. Important public health research challenges

At a first glance the availability of highly effective antiviral drugs might make the development of novel therapies for chronic hepatitis C obsolete. However, the costs are too high for most high-prevalence countries, which are often resource limited. Although costs have been lowered due to competition in the HCV drug market or facilitated access to generic drugs in some high-prevalence countries, a global eradication will not be possible unless these drugs become widely available with no strings attached. In principle, the conditions for such a strategy are good because treatment with pan-genotypic activity, minor side effects and minimal contraindications have recently become available. This should allow provision of treatment outside of specialized primary care centers.

Another major public health challenge is to reduce under-diagnosis. In fact, it is estimated that in most countries the rate of diagnosis of HCV infection is below 50% or just unknown (Bruggmann et al., 2014; Gower et al., 2014). While this requires nation-wide hepatitis-specific action plans that have been implemented only in 18 countries according to WHO (Lazarus et al., 2013), costs for diagnosis especially to measure viremia, an important marker to monitor antiviral therapy, is a major hurdle, especially in resource-limited countries where costs for HCV RNA testing may surpass the costs for HCV treatment. Thus, cheaper diagnostic tests to measure HCV viremia or core antigen have to be implemented that are also easy to use and do not require expensive equipment or specialized training. Such tests, ideally combined with antiviral therapy would be one important step to move treatment out of

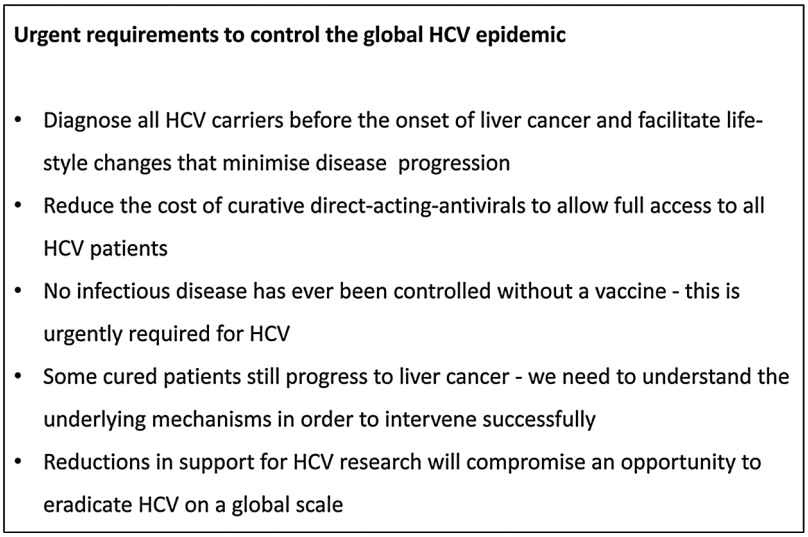

Fig. 1. Summary of the most urgent requirements to control the global HCV epidemic.