Recently, a fellow grant reviewer raised concerns about the significance of a basic research proposal on hepatitis C virus (HCV), stating, “There’s already a cure for HCV.” At the time, I found it ironic that this reviewer was known for their work on viruses unassociated with any human disease; nevertheless, the reviewer had a point: The HCV research community needs to justify its existence.

The conquest of HCV is one of the great success stories of basic, translational, and clinical virus research. Several HCV targets have been identified, potent inhibitors have been developed, and direct-acting antiviral (DAA) drugs have been approved and successfully deployed in the clinic. We are now in the postinterferon era of HCV treatment, with sustained virological response rates exceeding 90% after 8 weeks of combined DAA therapy. The current challenges are not to develop new antiviral strategies, but to optimize treatment regimens and deliver them cost effectively. Therefore, it is difficult to justify basic HCV research funding based on developing novel antiviral strategies. Yet, there are many unmet research priorities and important reasons to further study HCV, which I outline here.

Vaccine Development

With well over 100 million HCV-infected people, it is unlikely that expensive DAA therapies alone can eliminate the global burden of HCV-related disease. In the long term, a prophylactic vaccine is needed—not to prevent new HCV infections, which may be extraordinarily difficult—but to reduce the rate by which acute infections progress to chronic infections. The feasibility of this goal is supported by meta-analyses of animal challenge studies and prospective studies in humans. Nevertheless, there are barriers to vaccine development. First, the genetic plasticity of HCV leads to immunological escape within an infected individual, as well as multiple genotypic clades at the global scale; hence, effective vaccines will need to induce responses that are broadly cross-reactive. Second, because chimpanzee research has been banned in the United States, the field lacks an immunologically intact animal model of HCV persistence with which to test vaccine candidates.

Early vaccine studies showed that immunization with recombinant HCV E1-E2 glycoproteins can induce strong cross-neutralizing antibodies, accompanied with CD4+ T-cell help, that partially protects against the establishment of chronic infection. Another strategy currently being evaluated is a genetic vaccine to drive CD8+ T-cell responses against the HCV nonstructural (NS) proteins, NS3-5B. This approach has yielded promising results in preclinical chimpanzee challenge studies and in phase I human clinical trials, with a phase I/II clinical trial currently underway in at-risk intravenous drug users (NIH ClinicalTrials.gov identifier: NCT01436357). If successful, this strategy will be paradigm shifting, given that it will be the first antiviral vaccine that does not act by inducing antibodies to neutralize virus particles. Ultimately, a vaccine may need to be formulated to induce both broadly cross-reactive humoral and cellular immune responses to effectively reduce HCV chronicity.

The Unusual Structure of Infectious HCV Particles

One of the extraordinary features of HCV particles is their interaction with serum lipoproteins, which likely contributes to the inefficiency of antibody neutralization and difficulty in vaccine development. The current dogma in the field is that HCV particles are
hybrid lipoviroparticles that share features of both lipoprotein and virus particles. However, an alternate, less-radical hypothesis is that enveloped virus particles are simply tethered to lipoproteins via interaction with apolipoproteins. To date, experiments to discern between these possibilities have not yet been reported, and the nature of the virus-lipoprotein interaction remains unknown. In either case, HCV particles are unlike other known enveloped viruses. Understanding the structure of HCV particles is fundamentally important given that it will not only contribute to vaccine design, but also addresses a long-standing question of virus structural biology.

A second enigmatic feature of the HCV particle is the structure of the viral glycoproteins, E1 and E2, which mediate binding and entry of virus particles into host cells. It was widely anticipated that E1-E2 would share structural similarity to other viral glycoproteins that undergo acid pH-induced conformational changes to induce membrane fusion. In fact, structures for a small fragment of E1 and large portions of E2 were recently solved by X-ray crystallography, revealing novel structural folds without an obvious mechanism of membrane fusion. Because E1 and E2 are the targets of virus-neutralizing antibodies and key to naturally arising protective immunity to secondary infections, a more detailed understanding of their structure will provide a foundation for rational vaccine design. Completing the structure of the E1-E2 heterodimer is of fundamental importance because it should reveal a novel mechanism of membrane fusion.

The Mysterious Machinery of RNA Replication

All positive-strand RNA viruses share common features of genome replication, such as the need to encode an RNA-dependent RNA polymerase, the need to regulate genome translation versus genome replication, and the compartmentalization of RNA replication complexes within cytosolic membranes of infected cells. For HCV, RNA replication requires only five viral NS proteins: NS3, NS4A, NS4B, NS5A, and NS5B. We have developed potent DAAs to target the serine protease activity of NS3, NS5A dimer formation, and the RNA polymerase activity of NS5B, although we do not yet understand how these proteins fit together to function as a macromolecular machine. This is an important deficit, given that HCV has become an important model system for understanding positive-strand RNA virus replication. It took many years to develop DAAs against HCV, and, with the possible exception of the nucleoside analog polymerase inhibitors, these drugs will not be active against other viruses. Therefore, understanding the fundamental mechanisms of HCV replication will likely inform us about how to successfully target other viruses.

Perspective

For many years, HCV basic research was driven by the search for improved therapies, with most articles and grants in the field starting out with some variation of: (1) HCV is a major cause of chronic liver disease and cancer; (2) current therapies are insufficient; and (3) this work will lead to better therapies. Although this first statement remains true—and may be true for some time—it is thankfully time to retire the rest of this mantra. We should instead focus on unmet clinical priorities, such as an effective vaccine, as well as basic research to exploit HCV as a critical model system with which to understand an important category of human pathogens.

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REFERENCES

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