Hepatitis B Foundation Comments
Updating the Strategic Plan for Trans-NIH Research to Cure Hepatitis B
(NIH RFI Notice Number: NOT-A1-22-018)

We applaud the NIH for preparing the Strategic Plan for Trans-NIH Research to Cure Hepatitis B, released in November 2019, and for this important effort two years later to update it so it remains a robust road map to find a cure. This update offers the excellent opportunity to assess what has been learned since it was first released and to reassess and retarget the additional needed research.

The plan was issued to intensify innovative hepatitis B research to develop a cure defined as the sustained loss of detectable hepatitis B virus and hepatitis B surface antigens, after completion of a course of treatment. To assist with this update, the RFI requests information on four topics. This response comments on all four of those topics.

Topic 1: Recent significant research advances in hepatitis B as well as in other areas that could have implications for the development of a hepatitis B cure:
Progress in basic science and clinical research within and outside the HBV community can help in the pursuit of new therapeutics for HBV and the diseases with which it is associated. Most notably, the stunning efficacy of the mRNA-based vaccines may suggest new strategies for prevention as well as immune-therapeutic intervention and ways of producing therapeutic proteins in target organs. This work can complement and leverage other efforts to identify new HBV and liver cancer therapeutic targets, as discussed below.

Topic 2: Impact of COVID-19 pandemic on hepatitis B research, and possible solutions:
The COVID-19 pandemic has interrupted in-person components related to health care visits and clinical trials. Clinical trials have pivoted to include more patient-friendly strategies, such as "virtual" visits, home visits, and the integration of local labs for clinical trial monitoring. NIH should encourage the inclusion of these strategies in hepatitis B clinical trials, with a focus on assessing impact on clinical trial recruitment and completion. Additionally, COVID-19 has both highlighted and exacerbated health and access disparities, especially among communities that are disproportionately impacted by hepatitis B: foreign-born communities of color. It is imperative to include effective strategies in hepatitis B clinical research that specifically focus on inclusion of these communities. Working with experts in this field, and community-based organizations with expertise in reaching these communities, is one collaborative strategy that could lead to more effective inclusion plans. We also recommend the creation of a sub-group or task force, that includes community leaders and people living with hepatitis B; and creation of targeted RFPs that would fund studies to test strategies for more effective recruitment of diverse communities.

Topic 3: Emerging research questions and/or barriers:
The Strategic Plan (p.14) concluded that combination therapies that can suppress viral replication and stimulate the immune response to prevent viral spread are likely to be the most effective approaches to cure hepatitis B and that new therapies will need to be explored as potential combinations and developed together. Current treatments for hepatitis B work by inhibiting replication of the virus (specifically, by inhibiting the assembly of new viral DNA). The therapeutic benefit of targeting other viral and host functions that influence the viral life cycle remains largely unexplored. There are a handful of other virus-specific gene products that could

serves as therapeutic targets and cccDNA, HBx, and the hepatitis B surface, core and e antigens could be potentially therapeutically targeted. Additionally, there has been a general consensus for the need to prioritize research on understanding the biology of HBV cccDNA and the mechanism controlling its function and a growing appreciation that there is a need to understand the role of HBs in pathobiology of disease.

Immune responses are critical in both resolving HBV infection and, conversely, in promotion of HBV disease. While most HBV infections in adults induce a robust immune response that results in resolution of the infection, chronic hepatitis B is characterized by an unbeneficial and inadequate immune response to HBV. A better understanding of these immune responses is central to finding a cure and is an extremely high priority for both clinical and basic research. It is also important to note that different viral genotypes may behave differently with respect to HBV disease progression and treatment response. Understanding the role of viral genotype on the development of disease and on drug sensitivity could provide clues for new strategies of intervention.

Additional areas of research needed:

- More aggressive efforts to understand the mechanisms of HBV associated liver cancers in people with and without liver cirrhosis are needed.
- The usefulness of current and new interventions in reducing HBV associated HCC and whether or not early treatment with direct acting antivirals or other strategies can reduce cancer risk should be explored.
- Efforts to understand and treat disease in people with co-infections of HBV and Hepatitis delta or HBV and HIV are applauded and should be expanded.
- Efforts to understand and manage HBV reactivation are applauded and should be expanded.
- Efforts to understand and develop biomarkers of disease, specifically of interest is understanding the nature of flares following immune-therapeutic or medical intervention or cessation are encouraged.
- Studies to understand HBV DNA integration and its impact on the development of HCC.
- Studies to explore the clinical and quality of life impact on treating people in the immune tolerant phase or earlier in the disease process.
- Efforts to establish a scientific basis that undetectable viral load means that people cannot transmit the virus. This would be similar to studies that resulted in the HIV message “Undetectable=Untransmissible” (U=U). This would be an important message, with implications for treatment decisions and addressing disease-related stigma.

Topic 4: Resources necessary to advance basic, translational, and clinical research to cure hepatitis B:

HBF joins the research community in believing that curing HBV is a winnable battle and could happen in the next few years with adequate additional research. As the update of the Strategic Plan will highlight the research needed to find a cure, HBF urges targeted calls for this research and urges increased support for Program Projects, RO-1s, UO1 Cooperative Research Agreements plus the initiation of HBV programs similar to the Martin Delany Collaborations now funded by NIAID for HIV research. For Liver Cancer Research, HBF urges expansion of the Intramural Liver Cancer program, the HCC SPOREs, the new Diversity SPORE, the Translational Liver Cancer Network, HCC Epidemiology Consortium, the Large Genome Wide Association

Study expanded to include Hispanic and African descent populations and expanded support for Community Oncology Research Programs to help deliver care to people in underserved areas and areas of economic distress.

HBF estimates that annual increases of at least $40 million are necessary instead of the increases of $2 million experienced in recent years. Again, we applaud NIH's leadership to fund the research needed to find a cure. A coordinated drug discovery and development consortia and a clinical program consortium are needed to optimize progress.

Thank you for the opportunity to submit comments on behalf of the Hepatitis B Foundation, Baruch S. Blumberg Institute, and partners listed below.

Sincerely,

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American Association for the Study of Liver Disease (AASLD)
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