AN OVERVIEW OF
A Roadmap for a Cure

FEATURING #justB Storytellers
About this Overview

This overview of the research agenda has been condensed from two papers: the Hepatitis B Foundation white paper, *A Roadmap for a Cure: Priority Areas for Chronic Hepatitis B and Liver Cancer Research*, and the manuscript, *A Research Agenda for Curing Hepatitis B Virus Infection* (submitted for publication).

The professional judgment budget summary was drawn from an analysis of the research priorities identified in the *A Roadmap for a Cure* white paper, then aligned with existing NIH research grant mechanisms, funding levels, and duration. The full budget analysis is available from the Hepatitis B Foundation. Note that the *Professional Judgment Budget* was prepared by a committee distinct from the *Research Agenda*, and while it is based on the research agenda, the budget recommendations have not been reviewed or endorsed by the authors of the scientific research agenda.

Copies of the full-length versions of any of these papers, with complete authorship information and citations, are available from the Hepatitis B Foundation by emailing info@hepb.org.

The Real Stories featured throughout this document are from the Hepatitis B Foundation #JustB Storytelling Project. This project creates a national storybank of real people who share their stories to put a human face on this serious disease; decrease stigma and discrimination; and promote testing, immunization and treatment for hepatitis B to save lives. Stories are used with permission. For complete stories see [www.hepb.org/justB](http://www.hepb.org/justB).
In 2016, the World Health Organization and the U.S. National Academies of Science, Engineering, and Medicine declared that elimination of hepatitis B from the human population is possible. The strategies to achieve this will require both prevention and effective treatment. There is a growing sense of urgency and opportunity for finding transformational new therapies.

During the period of December 2016 to February 2017, the Hepatitis B Foundation convened a “virtual workshop” to consider the possibility of discovery of a cure for chronic hepatitis B infection, and the diseases with which it is associated, including liver cancer. More than 30 of the world’s leading experts contributed to the development of a detailed Research Agenda, a collective professional judgment on the research that is most likely to advance the discovery and development of curative therapies for hepatitis B. A brief summary of their recommendations is included in this overview. The Hepatitis B Foundation subsequently convened a second panel of five experts in health research funding to develop a Professional Judgment Budget detailing the funding needed to achieve a cure for HBV infection. Highlights of their analysis are also included in this report.

The time is right for an aggressive and vigorous research campaign to find a cure for chronic hepatitis B infection, because of the unacceptable morbidity and mortality of this serious liver disease in the U.S. and worldwide, and because recent advances in technology surrounding the problem make this a winnable battle. Indeed, there is an increasing optimism in the scientific community that a cure is possible.

Timothy M. Block, Ph.D.
President, Hepatitis B Foundation and the Baruch S. Blumberg Institute

ACKNOWLEDGEMENTS

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Professional Judgment Budget: The Foundation also acknowledges (alphabetically) Timothy Block, Alan Brownstein, Chari Cohen, J. Michael Hall, and Alyson Lewis for development of the professional judgment budget.

HBF is indebted to the individuals affected by HBV infection who were willing to share their personal stories, which are included in this report.

HBF also wishes to acknowledge Theresa M. Wizemann, Alan Brownstein and Jenny Kimbel for the preparation of this overview of the research agenda.
The Public Health Consequences of Hepatitis B

Hepatitis B continues to be a significant public health problem in the U.S., and around the world. More than 250 million people worldwide, and up to 2 million in the U.S., are living with chronic, life-long hepatitis B virus (HBV) infection. People who develop a chronic HBV infection have a significant lifetime risk of premature death from liver failure, cirrhosis, and primary liver cancer.

HBV infection is preventable with a safe and effective vaccine. However, vaccine coverage is incomplete, and new infections continue to occur in unvaccinated or incompletely vaccinated individuals (3 doses are required). For those with chronic HBV infection, there are now seven FDA-approved antiviral therapies that can help to keep the infection under control, and reduce the risk of liver damage or liver cancer. While these treatments are effective in managing the infection, there is still no cure for hepatitis B. People with chronic HBV face a lifetime of treatment and surveillance for disease progression. A complicating factor is that long-term use of antiviral drugs can lead to mutations in the virus that allow it to become resistant to the drugs (Weinbaum, 2008).

Although the burden of most other cancers is declining in the U.S., liver cancer incidence and death rates have continued to increase. Routine screening can detect liver cancer at an early stage, when it can be treated and potentially cured. While everyone with chronic hepatitis B should be monitored for liver cancer, only about 25 percent of HBV-infected individuals in the U.S. know that they are infected. Of those, less than 10 percent receive antiviral treatment, and very few receive ongoing screening for early detection of liver cancer. As a result of gaps in HBV screening, treatment, and disease monitoring, along with the current lack of effective therapies for liver cancer, the 5-year survival rate for individuals with HBV-associated liver cancer remains very low, about 16 percent (Cohen, 2011; McMahon, 2015; Ryerson, 2016).

“I think a breakthrough is going to happen in the next few years. We have to figure out how to attack each step of the hepatitis B virus life cycle so that we can develop new drugs that will be more effective than the ones we currently have.”

Anna Lok, M.D.
President of the American Association for the Study of Liver Diseases (AASLD), 2017

• Up to 2 million people in the U.S. are chronically infected with the hepatitis B virus (HBV).

• Worldwide, at least 250 million people are chronically infected with HBV.

• Up to 25% of people who have chronic HBV infection die prematurely from liver failure, cirrhosis, or liver cancer.

• Nearly 800,000 deaths worldwide each year are associated with HBV infection (8-10,000 in U.S.).

• More than half of the Americans living with chronic HBV infections are of Asian and Pacific Islander descent. Also at high risk are African immigrants.


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Finding a cure for both hepatitis B and HBV-associated liver cancer is critical to reducing the devastating loss of life and productivity caused by HBV infection.

**Curing HBV is a Winnable Battle**

Recent reports from the U.S. National Academies of Science, Engineering and Medicine (NASEM, 2016, 2017) and the World Health Organization (WHO, 2016) agree that HBV could be eliminated by 2030, if effective treatment is found for people who are already infected. Current treatment relies on a limited number of approved antiviral drugs that suppress the virus, but do not cure the infection. In addition, drug-resistant strains of HBV have developed. Clearly, new therapeutic drugs are needed that can be used alone, or in combination with current approaches, to achieve better disease management and, ultimately, a lasting cure for hepatitis B.

In 2016, the International Coalition to Eliminate HBV (ICE-HBV) published broad goals for research on HBV infection, and global strategies for a coordinated approach to advance a cure (Revill, 2016). The Hepatitis B Foundation sought to build upon this effort, defining specific areas of priority research to create a road map for policymakers, funding organizations, and those planning long-term research strategies.

**Surveying the Experts**

Working with more than 30 leading scientists and clinicians in the fields of hepatitis B and liver cancer research, the Hepatitis B Foundation prepared a research agenda for filling the major gaps in basic science and clinical knowledge of HBV biology. The experts identified research projects they deemed important to the goal of finding a cure for hepatitis B and HBV-related complications, especially liver cancer. Their feedback provided the basis of a comprehensive scientific Roadmap for a Cure, outlining specific research priorities, and providing the rationale for their selection. Highlights of this research agenda are presented here.

From a clinical perspective, the goal of HBV therapeutics is to reduce a patient’s risk of liver cancer, cirrhosis, and death due to liver disease. Ideally, the level of risk would be reduced such that it is comparable to that of someone who has never been infected with HBV, or perhaps more realistically, to that of someone who has fully recovered from an acute HBV infection (Block, 2013). Achieving this goal is ambitious, but the experts surveyed believe this is achievable with an aggressive, vigorous effort. Multiple parallel research approaches will be needed, because different strategies of treatment (including combination therapies) will be required depending upon the age of patients, length of time of infection, status of immune response, genotype of the infecting virus, and other variables (Bertoletti, 2015; McMahon, 2016).
Broad Areas for Priority Research Action

The research agenda developed by the experts is organized into six broad areas of research action (see Table 1). Each of these broad areas is further divided into specific subcategories that are discussed in detail in the full report. Highlights are provided below.

**Table 1**

<table>
<thead>
<tr>
<th>Broad Areas of Research</th>
<th>Combined</th>
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<tbody>
<tr>
<td><strong>Virology</strong></td>
<td>• Develop and standardize new research reagents and systems to study HBV and liver cancer for the purposes of drug discovery and development</td>
</tr>
<tr>
<td>Improve understanding of HBV virology; emphasize research to define the molecular mechanisms responsible for cccDNA biogenesis, homeostasis and decay; expand research on viral and host functions influencing the viral life cycle</td>
<td>• Establish new, and expand current, inter-institution and inter-laboratory collaborative networks for basic science discovery and validations</td>
</tr>
<tr>
<td><strong>Immunology</strong></td>
<td>• Establish new, and expand upon current, clinical networks for therapeutic drug testing and validation, nationally and globally</td>
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<tr>
<td>Improve understanding of adaptive and innate immunology of HBV acute, chronic, and resolved infections, and reactivation</td>
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<tr>
<td><strong>Viral Therapeutics</strong></td>
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<tr>
<td>Develop HBV antiviral therapies against new viral and cellular targets; develop immunological approaches that selectively repress or eliminate HBV in infected cells</td>
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<tr>
<td><strong>Liver Cancer</strong></td>
<td></td>
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<tr>
<td>Improve understanding of molecular pathways leading to liver cancer</td>
<td></td>
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<tr>
<td><strong>Liver Cancer Management</strong></td>
<td></td>
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<tr>
<td>Exploit understanding of molecular pathways leading to liver cancer for discovery and development of new early detection and management of the cancer</td>
<td></td>
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<tr>
<td><strong>Liver Cancer Management</strong></td>
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**Virology and Viral Therapeutics**

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 functions that influence the viral life cycle remains largely unexplored. There are a handful of other virus-specified gene products that could serve as therapeutic targets, and there are possibly more (Block, 2013). Other major HBV gene products that could potentially be therapeutically targeted include cccDNA, HBx, and the hepatitis B surface, core, and e antigens (HBsAg, HbcAg, and HBeAg, respectively).

One area of HBV research where there is general consensus is the need to prioritize research on understanding the biology of HBV **covalently closed circular DNA (cccDNA)**, and the mechanisms controlling its function. cccDNA is viral genomic DNA that persists in the cell nucleus of infected liver cells, and is essential for viral replication. cccDNA persistence is the reason that current antiviral therapies cannot be discontinued in patients with chronic infection, even after symptoms subside and levels of virus are low or undetectable.
It is cccDNA that is the source of rebounding virus levels after stopping antiviral treatment (McMahon 2016; Lok et al. 2016). A priority research question is if and how HBV cccDNA can be therapeutically targeted. It is thought that achieving sustained repression of HBV cccDNA within infected cells is a very high priority approach (Guo, 2015; Revill et al. 2016). However, much about cccDNA remains to be elucidated, and a better understanding might be the fastest route to a cure.

How HBV cccDNA can be therapeutically targeted is a priority research question because it is associated with virus levels rebounding after antiviral treatment is stopped.

There is a growing consensus that the viral protein, HBx, has essential function in the growth of the virus (Seeger, 2015), and is perhaps involved in enabling transcription of HBV cccDNA. If so, HBx could offer a viral protein target that, if inhibited, could repress HBV cccDNA transcription. As such, understanding whether HBx is a potential target for new therapeutics is another priority research question.

HBsAg is an essential viral protein needed for the secretion and infectivity of the complete, newly replicated viruses from the liver cell (Seeger, 2015). To determine whether it could be a potential target for therapeutic intervention, a better understanding is needed of the broader role HBsAg plays in altering the immune response and causing disease. HBCAg, another essential viral protein, is involved in formation of the virus capsid (the virus’s outer protein shell). Reports suggest that HBCAg might also be involved in regulating genes in both the virus and the patient, and altering the immune response. Although the current evidence for this is limited, this area warrants research attention, and there are several drugs targeting capsid formation currently in development (Liang, 2015). The HBeAg is derived from HBCAg, and is secreted from infected liver cells (Seeger, 2015). Although its function is unclear, HBeAg has been associated with higher levels of circulating virus in the serum of HBV-infected individuals, and with regulation of host immune recognition of the virus (McMahon et al. 2014). A better understanding of the role HBeAg plays in advancing disease is a research priority.

The research agenda also discusses potentially inhibiting the activity of ribonuclease H (RNaseH), an essential viral gene product, and exploring the role of integrated HBV DNA in the development of chronic HBV infection (viral DNA that is sometimes found inserted into host cell chromosomes). It is certainly possible that there are other virus-specified gene products that could also be potential targets for antiviral intervention.
Hepatitis D Virology parallels HBV virology. Approximately 15 to 25 million people are infected with the hepatitis D virus (HDV) worldwide, and HDV superinfection of chronic HBV is usually associated with a far more aggressive disease than HBV infection alone (Noureddin, 2014). HDV requires HBV co-infection of the same liver cells to complete its viral life cycle (Hughes, 2011). Thus, elimination of HBV would be expected to result in elimination of HDV. There are unique virological and clinical challenges associated with HDV infection, and key research areas for HDV parallel those for HBV.

Immunology

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 (Bertoletti, 2015), chronic hepatitis B is characterized by an unbeneficial and inadequate immune response to HBV (Chisari, 1995). 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 (Kim, 2011). Understanding the role of viral genotype on the development of disease and on drug sensitivity could provide clues for new strategies of intervention.

Liver Cancer and Cirrhosis

Cirrhosis and liver cancer are potentially fatal consequences of chronic HBV infection. The incidence of both diseases is growing at an alarming rate in the U.S. and worldwide, and is of extremely high public health importance. Advances in the effective management of HBV, risk screening, and cancer surveillance can go a long way preventing disease. However, once established, these diseases must be managed, and new, more effective treatments are needed. A better understanding of the molecular mechanisms of liver cancer and cirrhosis, development of new therapeutics, and improved diagnostics for early detection of liver cancer are all critical research areas.

Research Reagents and Experimental Models

The study of HBV and liver disease has been frustrated by a lack of critical research tools, ranging from experimental models to standardized controls. Current understanding of chronic HBV infection is largely based on observational clinical studies. The lack of biologically relevant animal models prevents better understanding of the immunological mechanism of chronic HBV infection. New animal models are needed that will allow, for example, for the critical experiments examining the impact of immune-restoration on the course of chronic HBV infection. While some research tools could be easily provided with minimal investment, new experimental systems will require greater investment of effort and funds, but will expedite the success of many of the proposed specific projects identified in the research agenda. In addition, current approaches to evaluating clinical trial endpoints may be inadequate for some of the potential therapeutic approaches being considered. Efforts to identify new biomarkers, or ways to redeploy currently available tests, will be important areas of research.
Investment for a Cure: A Professional Judgment Budget

The Hepatitis B Foundation’s research agenda is a roadmap to cure hepatitis B. It represents the professional judgment of leading scientists of the critical questions that need to be answered in virology, immunology and liver cancer to accelerate the progress to cure hepatitis B and effectively treat liver cancer. To answer these questions, a separate panel identified specific scientific projects and aligned them with existing National Institutes of Health (NIH) funding mechanisms. We assumed the maximum length for each grant, and a high mid-point (70% of max) for each funding level. Using NIH funding levels for the identified research projects, a professional judgment budget was prepared representing the increased investment needed over the next six years to follow this scientific roadmap to cure hepatitis B.

The professional judgment budget projects a nearly $39 million average annual increase totaling an additional $232 million of NIH support needed over six years through 2023. The funding outlined in the professional judgment budget will support basic scientific studies, as well as translational and clinical research designed to achieve specific milestones identified in the roadmap to a cure.

Investment for a Cure: Substantial Health and Economic Outcomes

Health Outcomes:

A cure for hepatitis B will save approximately 169,200 lives in the U.S. by 2030, as reflected in Table 2, below (current level of projected deaths at the current level – 188,000/column A less the reduction in deaths (column C – 18,800) if there were a cure). A review of Table 2 displays the consequences of not having a cure (or achieving an intermediate level of improved treatment and diagnosis) as well as the positive health outcomes if a cure for hepatitis B were in place.

- If by 2030, there is no cure or improved diagnosis and treatment of chronic HBV, the health consequences of chronic HBV will be staggering – see column A, Table 2 (NASEM, 2017)
- If by 2030, there is substantial improvement in treatment, outreach and diagnosis, the health outcomes are summarized in column B (WHO, 2016)

15 years ago I adopted a beautiful Chinese baby who was hepatitis B positive. Although my daughter’s initial medical records indicated she was healthy, I was told when I arrived in China that a blood test the day before had indicated she was hepatitis B positive. I cavalierly said, “Well, that’s ok, it’s a virus—she’ll get better, right?” I had so much to learn. One of the things I learned, however, was that managing a child’s hepatitis B is not life-consuming, especially if, as in my daughter’s case, there is no observable liver damage. I adopted a second daughter a few years later, who is also hepatitis B positive.

Why an HBV cure is important to me: An HBV cure is important to me because it will allow my daughters to enjoy their strength and energy, free from the shadow of a chronic condition.

Maureen, 63
West Roxbury, Massachusetts
www.hepb.org/justb/maureen
• If by 2030, there is a cure, chronic HBV would be largely eliminated, assuming that 10% of current rate of disease and death would remain primarily due to lack of access to therapeutic cure, small percent who do not respond to treatment and for those whose disease progression is beyond the range of treatment – see column C.

Table 2: Projected Health Outcomes for 2,000,000 Americans with Chronic HBV by 2030 using Three Levels of Diagnosis and Treatment: Current Level, Substantially Improved, HBV Cure.*

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<th>A) Current Level</th>
<th>B) Substantially Improved</th>
<th>C) HBV Cure</th>
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<tbody>
<tr>
<td>Death</td>
<td>188,000</td>
<td>93,210</td>
<td>18,800</td>
</tr>
<tr>
<td>Liver Cancer</td>
<td>120,000</td>
<td>78,204</td>
<td>12,000</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>206,200</td>
<td>114,088</td>
<td>20,620</td>
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*Adapted from NASEM, Toy, 2017

Economic Outcomes‡

Aside from the human toll described above, the economic burden of chronic HBV needs to be considered. One measure is the enormous costs associated with treating HBV as summarized in Table 3.

Table 3: Sample Costs Per Patient for Treating Chronic HBV

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<td></td>
<td>$739,000</td>
<td>$46,538 (annual)</td>
<td>$8,400-$16,464 (annual)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$232,690 (lifetime average)</td>
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The human and economic costs described provide compelling evidence for the importance of investing in a cure for hepatitis B. With the current scientific understanding of HBV, pursuing this Roadmap for a Cure offers a well-defined scientific strategy for curing HBV within a decade.

‡There are many sophisticated economic analyses that need to be performed to fully document the economic impact of curing HBV such as cost-benefit, incremental cost-effectiveness ratio (ICER) and quality-adjusted life–years (QALY) analyses.
Conquering Hepatitis B Now! – The Facts

The following facts have been established by the Hepatitis B Foundation and other highly regarded public and private scientific authorities in the U.S. and the world:

- Chronic Hepatitis B persists as an urgent public health threat, in the U.S. (2 million currently infected, with 8-10,000 deaths per year) and worldwide (250 million currently infected, with 800,000 deaths per year);
- Incidence of primary liver cancer in the U.S. is increasing, with a 5-year survival rate less than 15%;
- The potential for eliminating hepatitis B has been established by NASEM, WHO, and the International Coalition to Eliminate HBV;
- NIH funding for hepatitis B is only $49 million per year and has declined almost 16% since 2012.
- NIH has the research infrastructure needed to find a cure, with well-documented contributions in hepatitis research, and first-rate scientific capacity in understanding hepatitis B and liver cancer at NIAID, NIDDK and NCI; and,
- The Hepatitis B Foundation has developed A Roadmap for a Cure: Priority Areas for Chronic Hepatitis B and Liver Cancer Research based on the findings of a “virtual panel” of more than 30 leading scientific and clinical experts in hepatitis B and liver cancer.

It is now time to meet the challenge for hepatitis B — this can be achieved with the Hepatitis B Foundation’s Roadmap for a Cure as a guide for a trans-NIH coordinated research effort.

Conquering Hepatitis B Now! – Roadmap for a Cure

The Roadmap for a Cure is a comprehensive guide to the research necessary to cure hepatitis B, as well as estimates of the costs and time required. NIH has the research infrastructure needed to find a cure, with well-documented contributions in hepatitis research, and first-rate scientific capacity in understanding hepatitis B and liver cancer at NIAID, NIDDK and NCI.

To be able to achieve this goal and conquer hepatitis B, the following actions need to be taken:

- Develop a framework for a trans-NIH scientific meeting (including NIAID/NIDDK/NCI, and others) toward developing an HBV and liver cancer NIH Research Action Plan based on the Roadmap;
- Explore a potential future clinical trials network expansion to evaluate new and emerging therapeutic agents and combination therapies;
- Increase federal funding for hepatitis B research over the next six years at an additional $39 million per year needed to implement the Roadmap;
- Issue targeted requests for proposals for HBV/liver cancer research proposals (issued from NIAID, NIDDK and NCI); and
- Identify ways of attracting private industry investment in new drug discovery for HBV and liver cancer.

We have the scientific and technological capability to find the cure and win the battle against hepatitis B. It is now time to fund the Roadmap and eliminate HBV infection.

At four months old I was adopted from China, according to my medical record, I didn’t have hepatitis B. Two years later, my mother had me re-tested, and I tested positive. I’ve known about my hepatitis B since I was very young, with time I came to terms with it and yearly doctor visits just became part of my normal life. I’ve never had to be on medication as my viral load has always been low.

Why an HBV cure is important to me: An HBV cure is important to me because I want to be fully cured, I don’t just want to sero-convert and still be tested and observed. I want myself and others to be cured and not have to worry about it possibly becoming chronic.
After receiving my diagnosis, I struggled to find any hepatitis B specialists in my hometown in Kansas. The first doctor who treated me had very little experience with hepatitis B/HIV co-infections. She put me on a higher dose of medication, which led to me developing kidney disease. I finally found a caring and knowledgeable hepatologist 290 miles away in St. Louis. He let me know that new medicines are coming down the pipeline and enrolled me into his cohort study to monitor what makes hep B better or worse.

Why an HBV cure is important to me: I can’t imagine anybody going through the emotional roller coaster that I went through when I discovered my hep B diagnosis. It’s a lot to take in. It’s a battle. Every time I feel a pain on the right side of my abdomen, I ask myself, “Is it liver cancer?” It’s a paranoid way to live. Without a cure, this is a struggle. A cure is like saying to me, “I’m Free to live.”

References


Kim BK, Revill PA, Ahn SH. HBV genotypes: relevance to natural history, pathogenesis and treatment of chronic hepatitis B. Antiviral Ther. 2011;16(8):1169-1186


