Hepatitis B Foundation (HBF) Meetings with National Institutes for Health (NIH) On Research Opportunities For Finding A Cure For HBV March 12, 2018

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Hepatitis B Forum Meeting at EASL 2018

April 12, 2018

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July 2017

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AN OVERVIEW OF

A Roadmap for a Cure

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Research Agenda Published

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A Research Agenda for Curing Chronic Hepatitis B Virus Infection

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Meeting Report

Research priorities for the discovery of a cure for chronic hepatitis B: Report of a workshop

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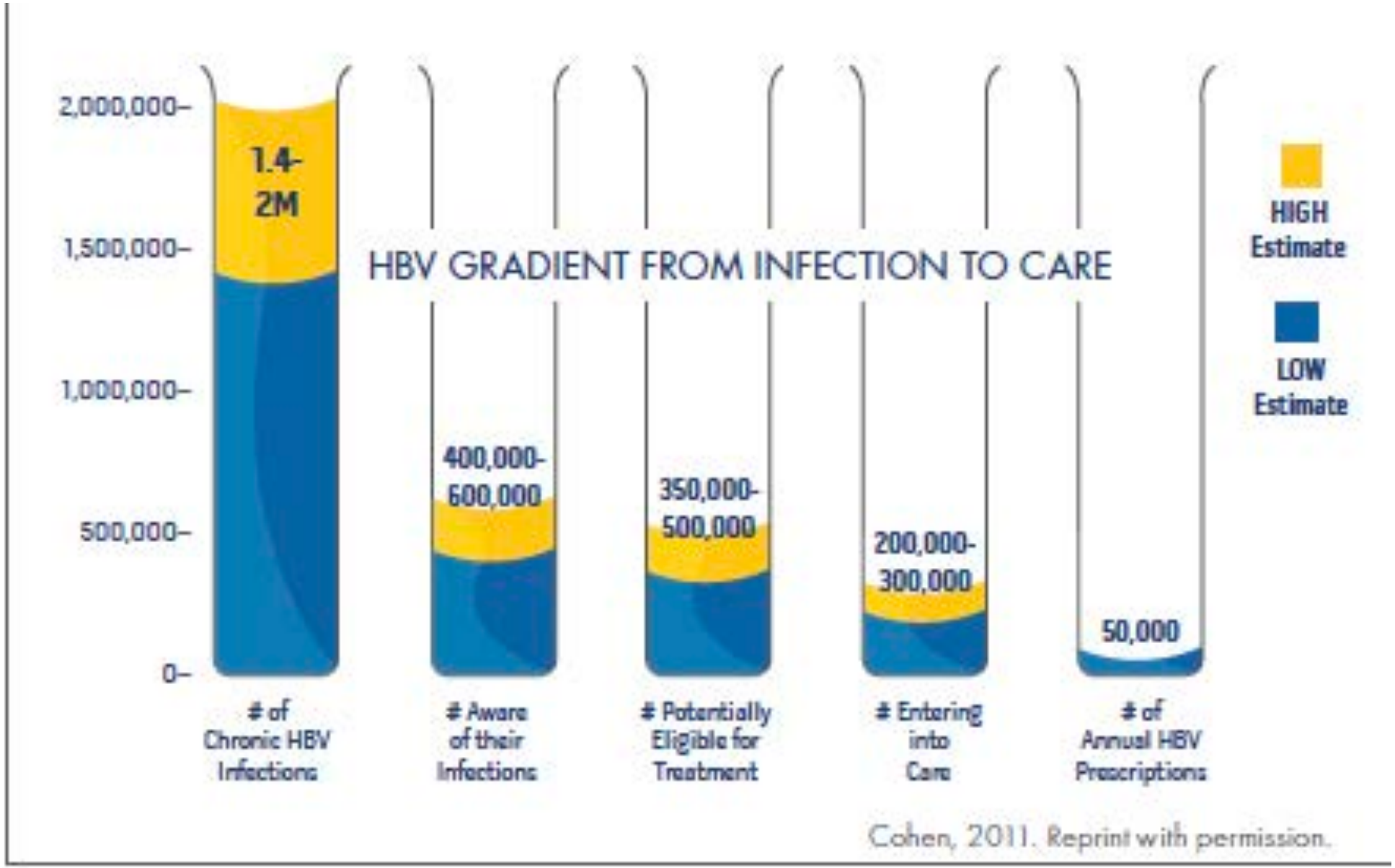

Cohen, 2011. Reprint with permission.

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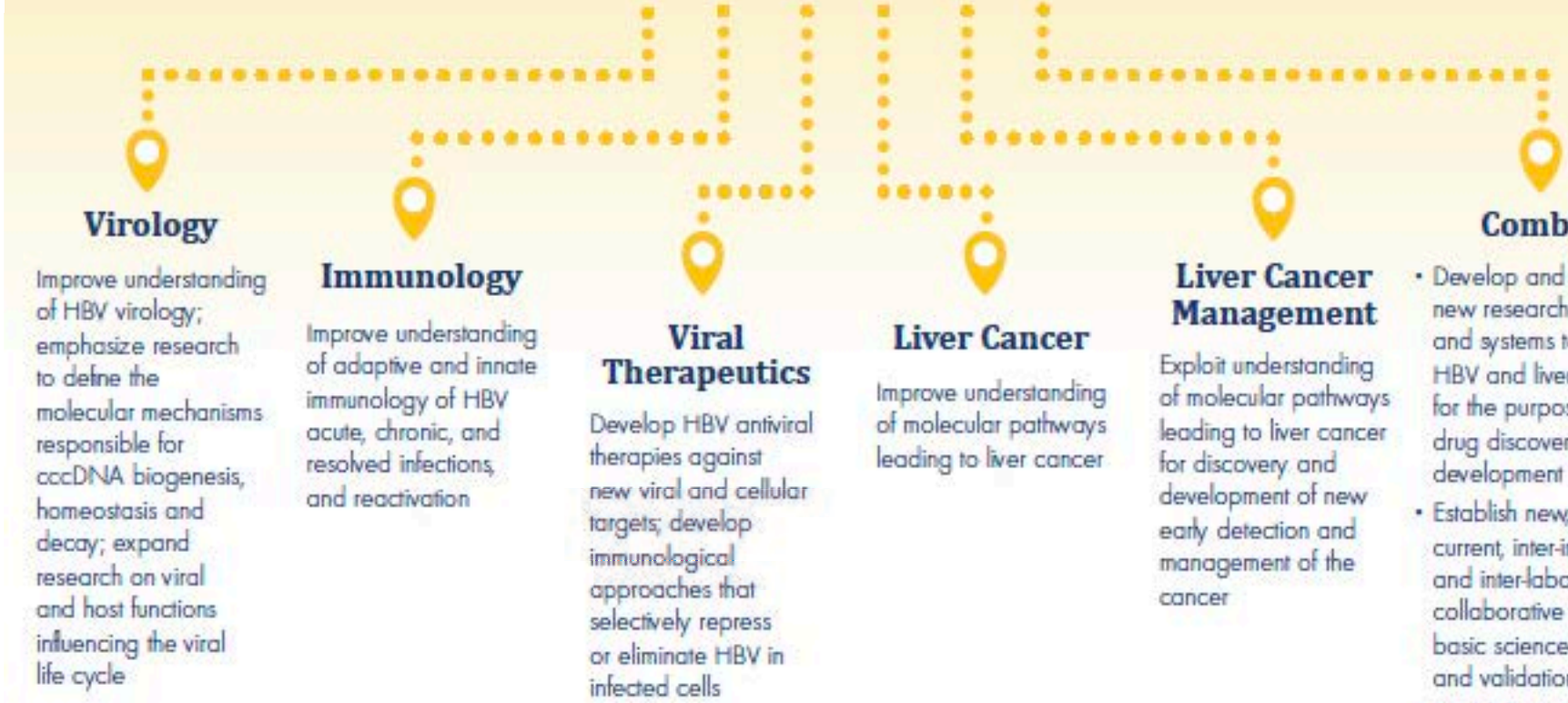
Table 1

Broad Areas of Research



Virology

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

Immunology

Improve understanding of adaptive and innate immunology of HBV acute, chronic, and resolved infections, and reactivation

Viral Therapeutics

Develop HBV antiviral therapies against new viral and cellular targets; develop immunological approaches that selectively repress or eliminate HBV in infected cells

Liver Cancer

Improve understanding of molecular pathways leading to liver cancer

Liver Cancer Management

Exploit understanding of molecular pathways leading to liver cancer for discovery and development of new early detection and management of the cancer

Combined

- Develop and standardize new research reagents and systems to study HBV and liver cancer for the purposes of drug discovery and development
- Establish new, and expand current, inter-institution and inter-laboratory collaborative networks for basic science discovery and validations
- Establish new, and expand upon current, clinical networks for therapeutic drug testing and validation, nationally and globally

Virology and Viral Therapeutics

Immunology

Liver Cancer and Cirrhosis

Research Reagents and Experimental Models

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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.*

	A) Current Level	B) Substantially Improved	C) HBV Cure
Death	188,000	93,210	18,800
Liver Cancer	120,000	78,204	12,000
Cirrhosis	206,200	114,088	20,620

*Adapted from NASEM, Toy, 2017

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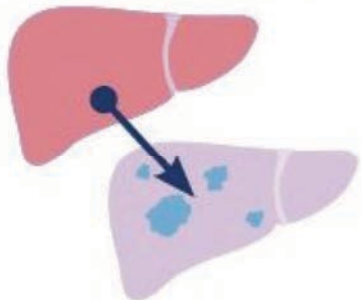
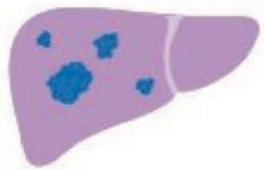
Table 3: Sample Costs Per Patient for Treating Chronic HBV

Liver Transplant
– charges
(UNOS, 2014)



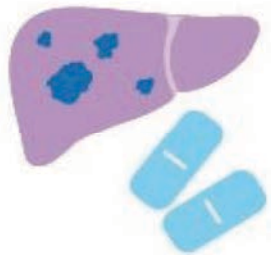
$739,000

Liver Cancer
(NASEM, Toy, 2017)



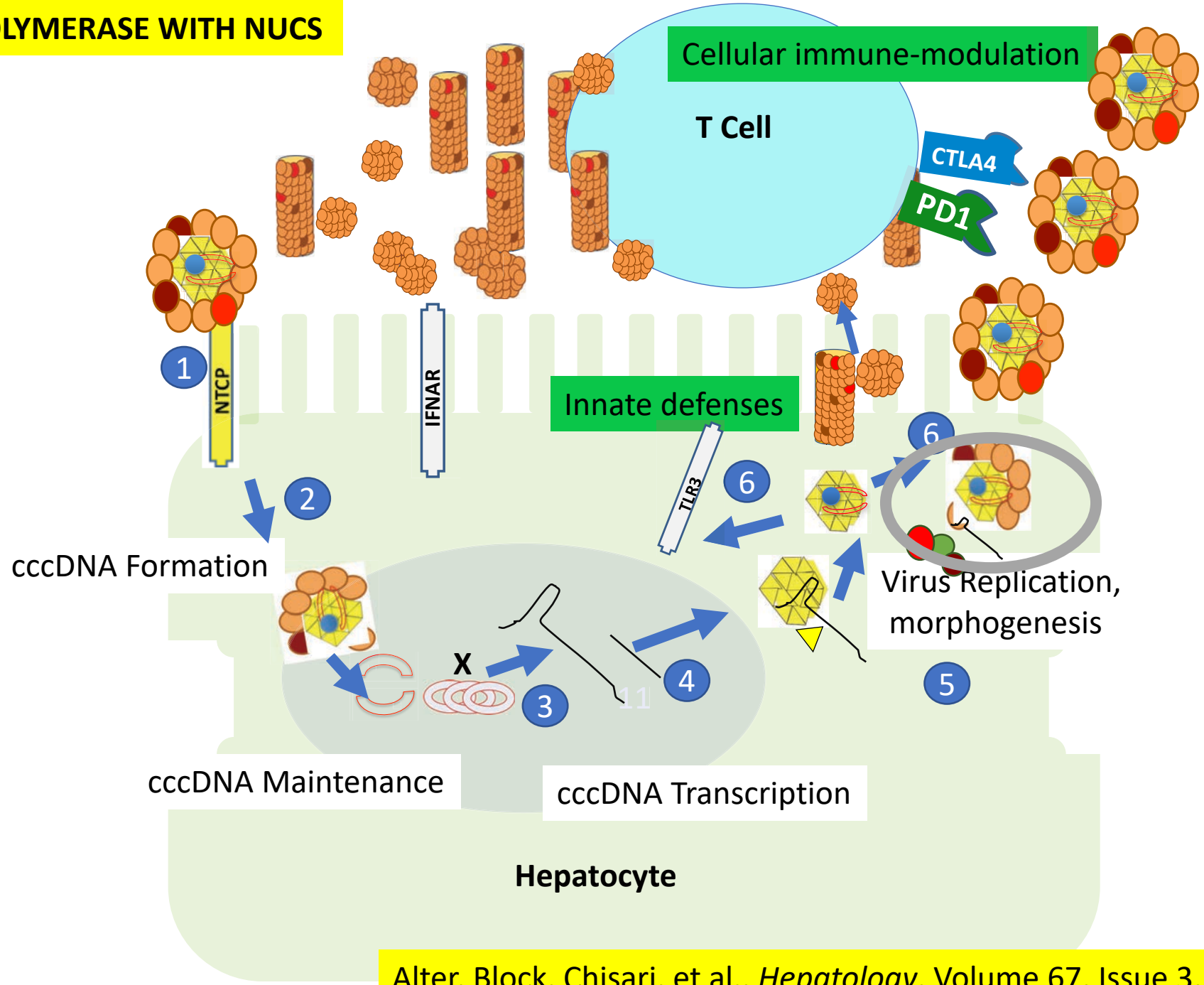
$46,538 (annual)
$232,690
(lifetime average)

FDA Approved Drugs,
e.g. Entecavir, Tenofovir
(NASEM, Toy, 2017)



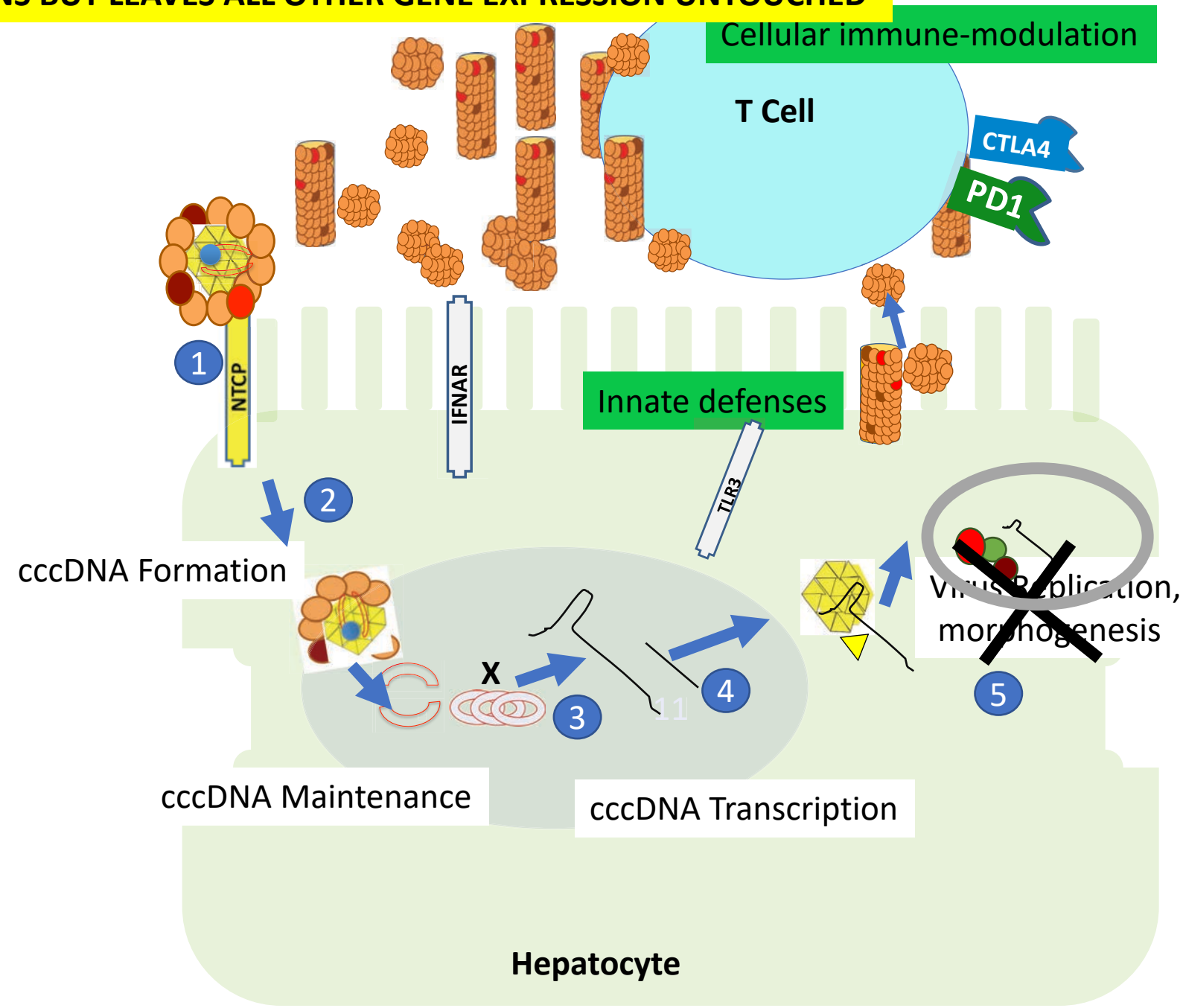
$8,400-$16,464
(annual)

INHIBITON OF THE POLYMERASE WITH NUCS



Alter, Block, Chisari, et al., *Hepatology*, Volume 67, Issue 3, January 24, 2018

PREVENTS NEW VIRIONS BUT LEAVES ALL OTHER GENE EXPRESSION UNTOUCHED



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HBV Therapy Top Priorities

cccDNA	
Project	Rank
Therapeutic benefit of inhibitors of cccDNA, alone and in combination	1
Basic academic research to define the molecular mechanisms responsible for cccDNA biogenesis, homeostasis, and decay, and to determine the half-life of preformed cccDNA in cell culture and animal models	1
Preclinical pharmaceutical research to discover and develop small molecules and biologics that directly target cccDNA life cycle vulnerabilities discovered in the priority above	1
Clinical research designed to test small molecules and biologics to either (a) eliminate cccDNA from the liver, or (b) reduce the number of cccDNA-positive hepatocytes (to a point at which all newly formed virus particles are neutralized by circulating anti-HBs antibodies)	1
Determination of mechanisms of cccDNA regulation	2
Basic academic and pharmaceutical research to determine if genetic, epigenetic, or other strategies that are known to (a) suppress cccDNA transcription, or (b) to prevent its recycling (e.g. capsid inhibitors) can eliminate cccDNA in HBV-infected cells in cell culture and animal models	2

HBx	
Project	Rank
Determine and validate the functions of HBx most important to its biological and virological roles	1
Specifically, confirm and expand upon understanding of HBx's HBV regulatory action on cccDNA other viral functions	1
Determine the benefit of HBx as an antiviral target, alone and in combination	1
Determine and validate role(s) of HBx in hepatitis B pathogenesis, including HCC	2
Develop antiviral agents that target HBx	2

HBs	
Project	Rank
Determine and validate role(s) of HBs in hepatitis B chronicity and pathogenesis, including HCC and immunosuppression	1
Develop and validate antiviral agents that target HBs	1
Benefit of HBs as an antiviral target, alone or in combination	2
Determine detailed molecular mechanisms of HBs morphogenesis and role in virion production and secretion	2

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2nd Level HBV Therapy Priorities

HBc	
Project	**Rank**
Benefit as an antiviral target, alone or in combination	1
Development of antiviral agents that target HBc	1
Determine if HBc has regulatory functions for viral and cell genes	2
Determine HBc role(s) in HBV life cycle, pathogenesis, and immunomodulation, beyond its role as a structural component of the virus	2

HBe	
Project	**Rank**
Benefit as an antiviral target, alone or in combination	1
Development of antiviral agents that target HBe	1
Determine if HBe has regulatory functions for viral and cell genes	2
Determine the role(s) of HBe in the HBV life cycle, pathogenesis and immunomodulation beyond its role as a structural component of the virus	2

RNaseH	
Project	**Rank**
Development of antiviral agents that target RNaseH	1
Benefit as an antiviral target, alone or in combination	2

Integrated HBV DNA	
Project	**Rank**
Can integrated HBV DNA cause independent production of HBsAg, making loss of HBsAg and/or measuring levels of HBsAg in some persons not a useful treatment endpoint or functional cure?	1
How can information about integrated HBV DNA be used in the management (treatment and risk assessments) of disease?	1
Better understanding of the role integrated HBV DNA plays in oncogenesis and in contributing gene products that affect chronic liver disease	2
Determination of the mechanism of regulation of integrated DNA expression	2

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Other HBV Therapy Priorities

Other Viral Targets	
Project	**Rank**
Development of strategies leading to the selective elimination of HBV-infected cells. Leading candidates are (a) therapeutic immunization, (b) checkpoint inhibition, and (c) bispecific antibody therapy that can deliver cytolytic or noncytolytic antiviral effector molecules selectively to infected cells	1
Identify viral gene products other than those currently known, that regulate HBV and its pathogenicity	1
How can information about other viral gene products and RNAs that regulate the HBV life cycle and host pathogenicity be used in the management (treatment and risk assessments) of chronic hepatitis B?	2

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HBV Immunological Priorities

Adaptive Immune Response	
Project	Rank
How can information about HBV immunovirology be used in the management (treatment and risk assessments) of HBV disease?	1
Role of T cells, T cell exhaustion, function of patient age, length of time of infection, other viral load issues	1
Possibility and benefits of restoration of immunorecognition of HBV	1
Safety of restoring cytolytic immune responses in patients with late-stage disease	1
Role of B cells, as antibody producers and other possible functions	2
Role of immunological checkpoints and other regulators of immunoresponsiveness in maintaining chronicity and disease	2

Innate Immune Response	
Project	Rank
Comprehensive analysis of the hepatic innate and adaptive immune systems, and their roles in chronicity	1
How can understanding the innate and adaptive immune systems help in the therapeutic management of HBV?	1
Role of innate defenses in regulating HBV infection, and in pathogenesis	1
Specific innate host defense factors that are responsible for the role of the innate defense response in influencing HBV acute and chronic infections, and in HCC	2
Nature and mechanism of HBV refractoriness to type I IFN	2

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Non-immunological Host Factors

Non-Immunological Host Factors	
Project	**Rank**
More complete understanding of the HBV life cycle, from receptor binding and entry, to nuclear transport and uncoating, and morphogenesis and secretion of virus and particles, with a focus on steps that are vulnerable to intervention	1
Determination of if and how information about the role of host factors in HBV virology can be used in the management (treatment and risk assessments) of HBV disease	1
Role of viral genotypes in pathogenicity, natural history and responsiveness to therapy	1
Role of host factors in determining outcomes (acute versus chronic, responsiveness to therapies, development of disease	2
Role of genetic factors in determining outcomes of disease natural history and responsiveness to therapy	2

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Priority Clinical Questions for HBV Therapy

Clinical Questions for HBV and HDV	
Project	**Rank**
Determine if people in different clinical stages respond differentially to different experimental therapeutics	1
What triggers seroconversion after years of chronic infection?	1
Explore molecular, cellular, and immunological mechanisms of reactivation in the absence of, and as a function of medical drug interventions	1
What does reactivation via medical interventions, such as immunosuppressive agents, anti-TNF, etc., teach about chronicity?	1
Does "functional" cure and management of HBV result in sustained clinical benefit to those with HDV?	1
Why do only subpopulations treated with IFN or NUCs become functionally cured?	1
Expansion of current, and development of new clinical trial programs and networks in the US and internationally, to evaluate HBV and HDV	1
Establish clinical centers, worldwide, that can carry out trials under FDA standards	2
Possibility that DAAs are sufficient to achieve functional (conditional) cure, and if responsiveness to the drugs varies with clinical stage	2
Are people responsive to treatments in a stage-specific manner?	2
Expansion of current, and development of new clinical networks and clinical programs that integrate basic and clinical studies to better understand HBV human biology and develop best management	2
Create a public database that will allow comprehensive and timely reporting of all drugs, new or old, showing association with HBV reactivation	2

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HDV Specific Research Priorities

Hepatitis D-Specific Antivirals and Immunology	
Project	**Rank**
Development of next generation anti-HDV agents based on HDV-specific gene products	1
Role of B and T cell exhaustion in chronicity and pathogenesis	1
How can information about HDV immunovirology be used in the management (treatment and risk assessments) of HDV disease	1

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HCC Priorities

Workshop participants considered the study of hepatocellular carcinoma and liver cirrhosis associated with chronic hepatitis B to be a high priority for discovering a cure.

Hepatocellular Carcinoma/Viral Oncology/Liver Cirrhosis	
Project	**Rank**
Development of safe and well-tolerated oral agents for primary prevention of HCC in patients at increased risk (those with chronic HBV and HDV, among others)	1
Development of safe and well-tolerated oral,agents for prevention of HCC recurrence post-surgical resection and liver transplantation in patients with chronic HBV and HDV (among others)	1
Test current promising and already available agents (including statins, and other complementary agents) in large RCTs for primary and secondary prevention of HCC and liver cirrhosis in persons with chronic viral hepatitis	1
Develop more effective screening and surveillance tools for HCC and liver cirrhosis (e.g., biomarker assays, imaging modalities)	1
Better understanding of molecular mechanisms leading to HBV/HDV-associated HCC	1
Development of more effective agents and locoregional therapies for treating established HCC in patients with chronic HBV and HDV (among others)	2
Develop HCC research and treatment clinical networks to share specimens, and clinical, histological, and imaging data.	2
Collect more detailed and more accurate HCC incidence data	2
Determine the role of metabolic liver diseases and obesity in contributing to hepatitis associated HCC	2

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HBV and HDV Research Tools

Reagents and technical capabilities for HBV & HDV research	
Project	**Rank**
Development of animal models of human HBV and HDV disease	1
Standardized virological and immunological assays for critical analytes [e.g., HDV RNA, HBV cccDNA, HBs (quantitative), anti-HDV, Ig, cytokine response] and T and B cells assays as new endpoints for therapeutic drug evaluation	1
Development of cell lines and primary human liver cell systems that support the full infectious cycle, and are authentic liver lines	2

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Three HBF Meetings at NIH March 12, 2018

- Anthony Fauci, MD, Director, National Institute of Allergy and Infectious Diseases (NIAID, NIH) and NIAID leadership
- Jay Hoofnagle, MD, Program Director, Division of Digestive Diseases and Nutrition, Liver Disease Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and relevant NIDDK leadership
- Douglas Lowy, MD, Acting Director, National Cancer Institute (NCI)

Hepatitis B Foundation (HBF) Attendees

- Timothy Block, PhD, President and Co-Founder, HBF and the Baruch S. Blumberg Institute
- William Mason, PhD, Emeritus, Fox Chase Cancer Center
- Alan Brownstein, MPH, Vice President for Public Policy, HBF
- Carol L. Brosgart, MD, Clinical Professor of Medicine, Biostatistics and Epidemiology, Global Health, UCSF and Member, Board of Directors, HBF
- J. Michael Hall, Principal, Madison Associates, Washington, DC
- Alyson H. Lewis, Legislative Director, Madison Associates, Washington, DC

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Hepatitis B Research at NIAID Summary

- Two program announcements released May 2017, in collaboration with NCI and NIAAA
- Upcoming RFA from Division of AIDS (DAIDS) with an HBV mono-infection component and an HIV/HBV co-infection component
- Support for a cross NIH effort with NIDDK and NCI to find a cure for hepatitis B (HBV)
- NIAID Attendance: Tony Fauci, Director; Hugh Auchinloss, Principal Deputy Director; Carl Dieffenbach, Director, DAIDS;Rajen Koshy, Program Officer; Sarah Read, Director, Therapeutics Research Program, DAIDS; Cristina Cassetti, Virology Branch Chief; Beverly Alston, Chief, Complications and Co-Infection Research Branch

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Hepatitis B Research at NIDDK Summary

- Supportive of a trans-NIH initiative of NIDDK, NIAID and NCI on finding a cure for hepatitis B. The scientific opportunities are ready and with some investment, we are poised to find a cure for HBV.
- We agreed that the HBF would take this trans-NIH research proposal to Francis Collins, MD, PhD, Director, NIH
- A cure would reduce the associated morbidity and mortality from cirrhosis, end stage liver disease, liver cancer (HCC) and liver transplantation
- We encouraged NIDDK to prioritize and increase funding for HBV research in their upcoming funding announcements
- They acknowledged their research priority constraints without additional funding
- Support for a cross NIH effort with NIDDK and NCI to find a cure for hepatitis B (HBV)
- NIDDK Attendance: Jay Hoofnagle,MD, Program Director, Liver Research; Gregory Germino, MD, Deputy Director, NIDDK; Stephen P. James, MD Deputy Director, Division of Digestive Diseases and Nutrition; T. Jake Liang, MD, Liver Diseases Branch Chief, NIDDK

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Hepatitis B Research at NCI Summary

- Discussed need to accelerate the pace of discovery to prevent and improve the outcome of liver cancer, as we face a rise in liver cancer incidence and deaths
- We agreed with Dr. Lowy's view that the three most important and promising areas of liver cancer research were
  - Molecular pathogenesis of liver cancer
  - Trade-offs of earlier vs. later treatments
  - HBV drug development
- Dr. Lowy agreed that the scientific opportunities are here now and that with investment, great progress could be made
- We acknowledged our appreciation for
  - The recent NCI RFA focused on liver cancer
  - The two program announcements in May 2017, with NIAID and NIAAA, on HBV co-infection
- Support for a cross NIH effort with NIDDK and NIAID to find a cure for hepatitis B (HBV)
- NCI Attendance: Douglas R. Lowy, MD, Acting Director, NCI

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Next Steps for Hepatitis B Cure Research at NIH

- Meet with Francis Collins, MD, PhD, NIH Director, to encourage a cross institute HBV Cure Agenda and Initiative
- Capitalize on the recent budget increase for NIH
- Final FY 2018 House and Senate Labor HHS Report Language for NIH comments on the impact of Hepatitis B morbidity and mortality, including liver cancer
  - House Report
    - NCI urged to target calls for proposals and to create and ad hoc special emphasis panel to review liver cancer applications
    - NIAID encouraged to issue targeted calls for HBV Research proposals in FY 2018 focused on therapeutic development for HBV and the many research opportunities identified by the scientific community
  - Senate Report
    - To increase the 5 year survivability of liver cancer, the NCI is urged to support liver cancer (HCC) research across its portfolio. Given that the majority of HCC globally is related to HBV, the NCI is urged to collaborate closely with NIAID and NIDDK
    - Given the global burden of HBV disease and being a leading cause of death worldwide, NIAID is urged to target calls for research proposals in FY 2018 focused on therapeutic development and research opportunities identified by the scientific community
    - The Office of the NIH Director is urged to ensure that NCI, NIAID, NIMHD (National Institute of Minority Health and Health Disparities), and NIDDK coordinate their strategic research agendas to find a cure for HBV. The Committee asked to be updated on these efforts for FY 2019 Congressional Justification

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Going Forward Towards HBV Cure

- Encourage all researchers in HBV disease and HCC to submit more grant applications to the US NIH (NIAID, NIDDK, NCI) to study HBV and liver cancer
- Today, 2018, and going forward, may be the best time in recent history to do this
  - NIH has received a **$3.1 Billion increase in funding**, of which **~$1 Billion is not "committed**" and may be used as the **"Institutes see fit to continue investments in research that will save lives, lead to new drug and device development, reduce health care costs, and improve the lives of all Americans "**
  - The experts believe the technology has now evolved to readiness for deployment to address the tough questions, as outlined in the Research Agenda (see report from the HBF Virtual Workshop) and in the two referenced publications (Hepatology and Antiviral Research manuscripts)
- The HBF will continue to urge NIH to issue "Requests for Applications" (RFAs) specific for HBV and HCC
- However, even in the absence of new RFAs, we were told by NIH leadership
  - The more applications NIH receives for HBV and HCC studies, the more HBV and liver cancer experts will be added to review panels; and, the more grants, then, that are likely to be funded

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July 2017

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CONQUERING HEPATITIS

NOW

AN OVERVIEW OF

A Roadmap for a Cure

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HBV Cure Resources

- Harvey Alter, Timothy Block, Nathaniel Brown, Alan Brownstein, Carol Brosgart, Kyong-Mi Chang, Pei-Jer Chen, et al. "A research agenda for curing chronic hepatitis B virus infection”,
  Hepatology 67, no. 3 (2018): 1127-1131
  - Open access: https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.29509
- Block, T.M., Alter, H., Brown, N., Brownstein, A., Brosgart, C., Chang, K.M., Chen, P.J., Cohen, C., El-Serag, H., Feld, J. Gish, R. et al., “Research priorities for the discovery of a cure for chronic hepatitis B: Report of a workshop”,
  Antiviral Research 150 (2018): 93-100
  - Open access: https://www.sciencedirect.com/science/article/pii/S0166354217307477
- “An Overview of A Roadmap *for* a Cure”, Hepatitis B Foundation, July 2017
  - email info@hepb.org or call +1-215-489-4900

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Questions