Interferon-α Receptor Agonist Research Webcast

July 26, 2022

Nasdaq: ASMB

Today's Speakers

John McHutchison AO, MD

Chief Executive Officer

William Delaney, PhD

Chief Scientific Officer

Edward J. Gane, MBCHB, MD, FRACP, FAASLD, FRSNZ, MNZM

Professor of Medicine at the University of Auckland, New Zealand

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Agenda

- Leveraging Assembly Bio's Expertise in Small Molecules and Viral Hepatitis to Expand the Company's Portfolio
  - John McHutchison AO, MD, Chief Executive Officer at Assembly Bio
- The Role of Interferon in HBV Cure
  - Professor Ed Gane
- Assembly Bio’s Small Molecule Liver-Focused Interferon-α Receptor Agonist Research Program
  - William Delaney, PhD, Chief Scientific Officer at Assembly Bio
- Q&A
- Anticipated 2022 Progress
  - John McHutchison

HBV is a Major Global Public Health Problem

Prevalence: **296M**[1]

Up to 1M people die each year from HBV-related causes

Treatments are life-long and reduce but do not eliminate the virus, resulting in very low cure rates

~12M individuals infected with HBV are also infected with hepatitis delta virus (HDV) with limited treatment options and high risk for cirrhosis & HCC

Opportunity to improve outcomes and increase number of patients diagnosed and treated, with development of finite and curative therapies

No new MOAs approved for HBV in >25 years

Source: [1]WHO (2021)

Interferon's History as an HBV/HDV Antiviral

DEMONSTRATED EFFICACY

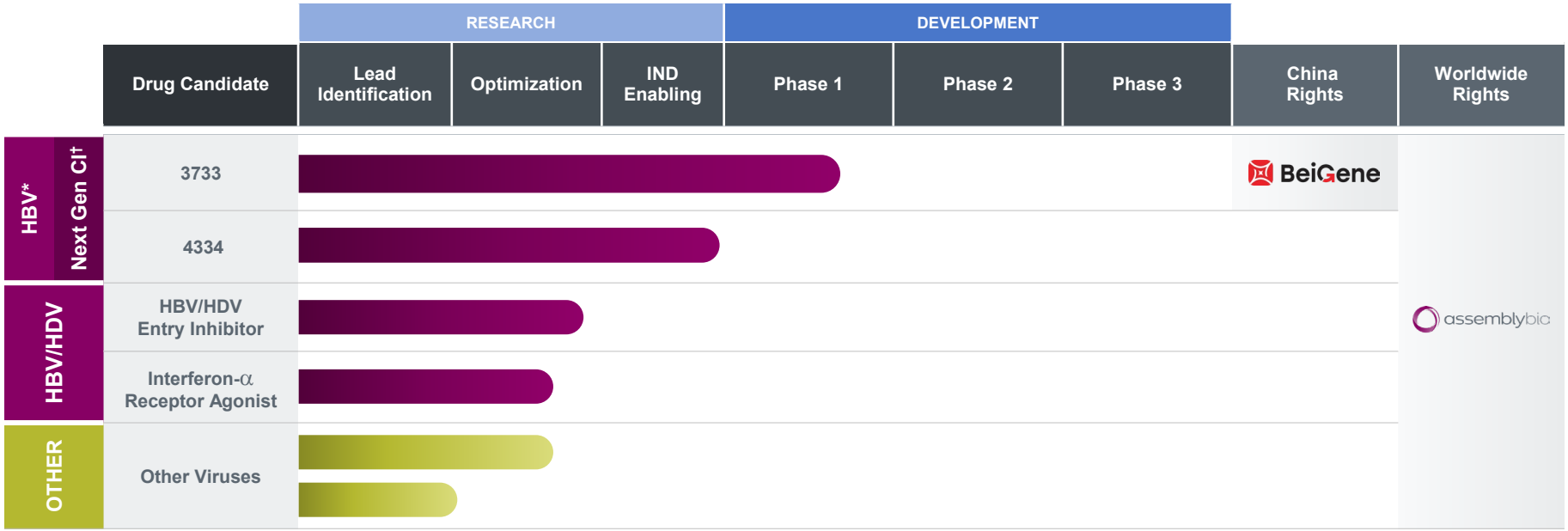
- Approved for treatment of hepatitis B for over 30 years
  - Also used off-label for treatment of hepatitis delta
- HBV: Highest rate of s antigen loss observed in controlled trials to date
- HDV: Results in hepatitis delta show RNA declines and improved clinical outcomes

POOR TOLERABILITY

- Substantial side effects, including flu-like symptoms, cytopenias, serious depression and psychiatric effects
- Multiple contraindications limit use
- Requires weekly injections resulting in systemic exposure for up to a year

ASSEMBLY BIO'S SOLUTION:
An Orally Available, Liver-Focused Small Molecule Interferon-α Receptor Agonist

Advancing a Clinical & Research Stage Portfolio of Small Molecules for HBV and Other Viral Diseases



*While Assembly Bio has discontinued further development of first-generation core inhibitor, vebicorvir (VBR), a Phase 2 triple combination study conducted in collaboration with Arbutus Biopharma evaluating VBR + NrtI + Arbutus' investigational RNAi is ongoing.

†Next Generation Core Inhibitors ABI-H3733 (3733) and ABI-4334 (4334)

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Edward J. Gane, MBCHB, MD, FRACP, FAASLD, FRSNZ, MNZM

- Professor of Medicine at the University of Auckland, New Zealand; Hepatologist and Deputy Director of the New Zealand Liver Unit at Auckland City Hospital.
- Trained in hepatology at the Institute of Liver Studies, King's College School of Medicine, London, where he completed his MD on the pathogenesis of hepatitis C-related liver injury.
- Appointed as Chief Physician for the first New Zealand Liver Unit at Auckland City Hospital in 1998, which provides a national transplant and HCC programme; helped set up the community-based national HBV Surveillance Programme, which is the largest in the world; chairs the Ministry of Health committee responsible for HCV elimination.
- Investigator for many international clinical trials with particular interest in early phase development of new direct acting antiviral therapies against chronic hepatitis C, hepatitis B, NASH and HCC
- Published more than 400 papers in peer-reviewed journals including The Lancet and The New England Journal of Medicine
- Awarded Member of the Order of New Zealand for Services to Medicine and 2017 New Zealand Innovator of the Year for his work towards HCV elimination; elected to the Royal Society (New Zealand) in 2018

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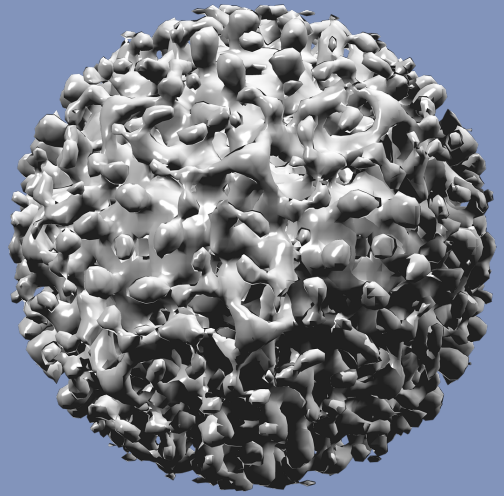
The Role of Interferon in HBV Cure



Professor Ed Gane,
University of Auckland,
New Zealand

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Wāipapa Taumata Rau
NEW ZEALAND

Safe, effective long-term oral therapy is available

Guidelines	Recommendations
APASL[2016]	Entecavir, or Tenofovir
EASL [2017]	Entecavir, Tenofovir, or TAF

Need for a finite CURE

1. Only
2. NUCs do **NOT** remove risk of liver cancer
3. Life long treatment ⇨ costs, risk of noncompliance
4. Life long treatment ⇨ cumulative toxicity (bone/renal)
5. Stopping NUCs ⇨ virologic rebound ⇨ severe flare

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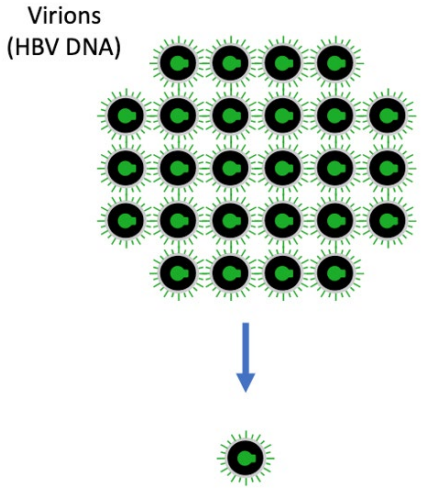
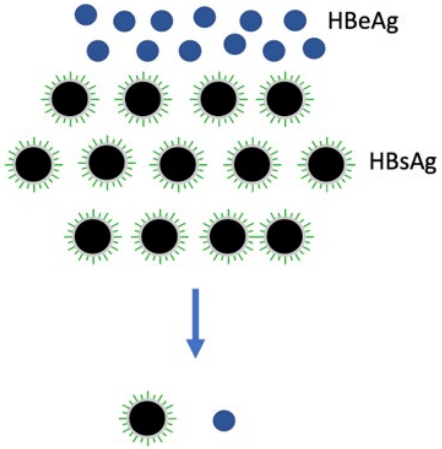
Therapeutic Approaches to HBV Cure

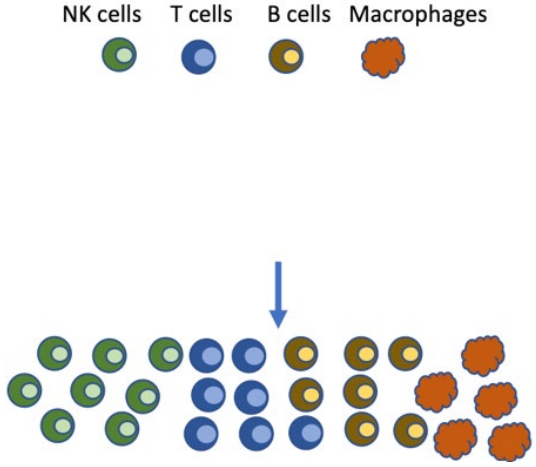
Inhibit Viral Replication



Lower Viral Antigen Burden



Boost Immune Response



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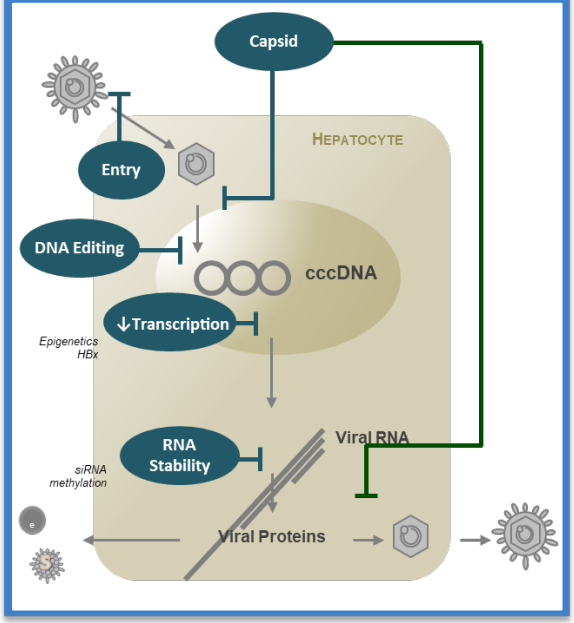
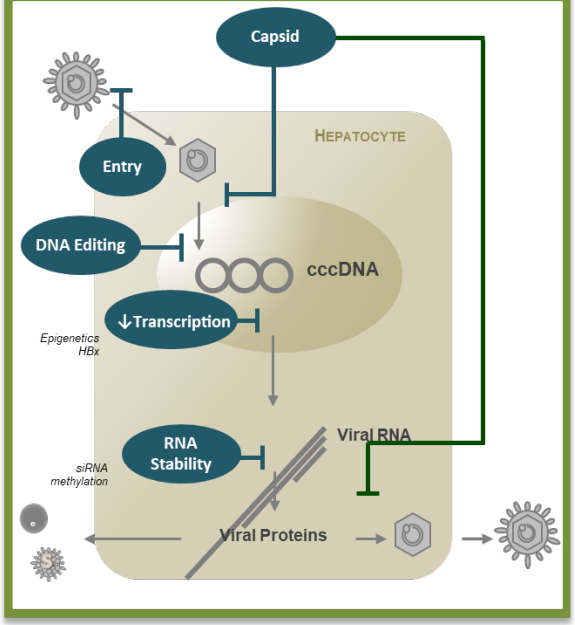
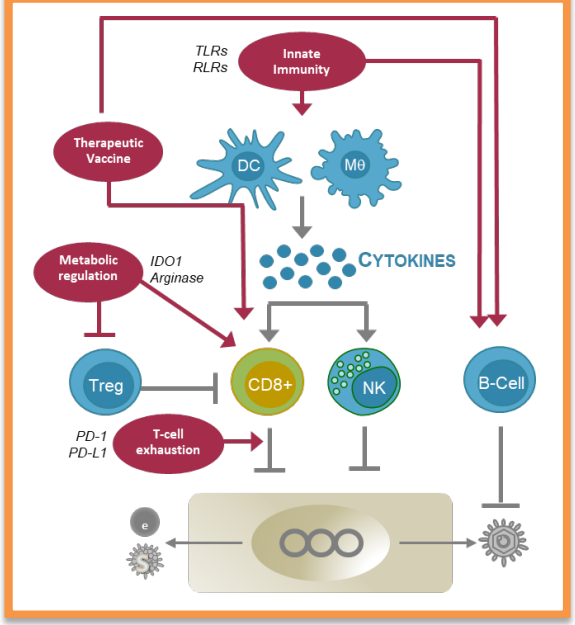


Lower Viral Antigen Burden

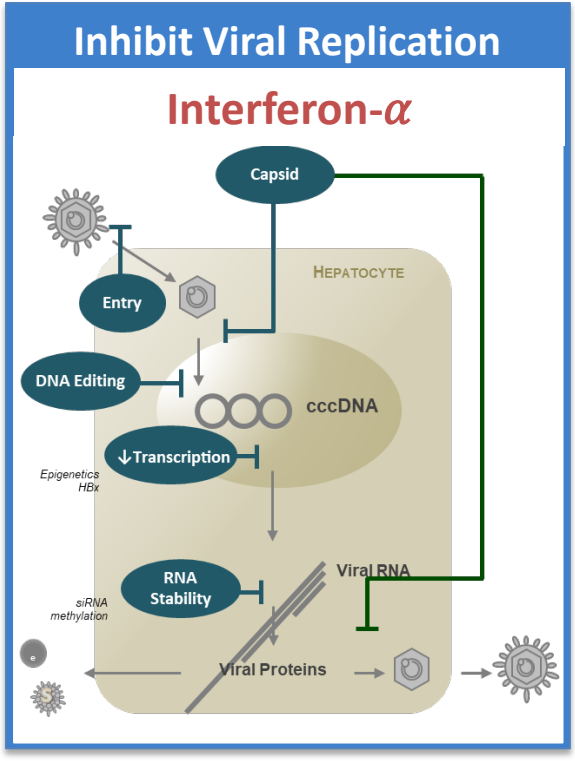


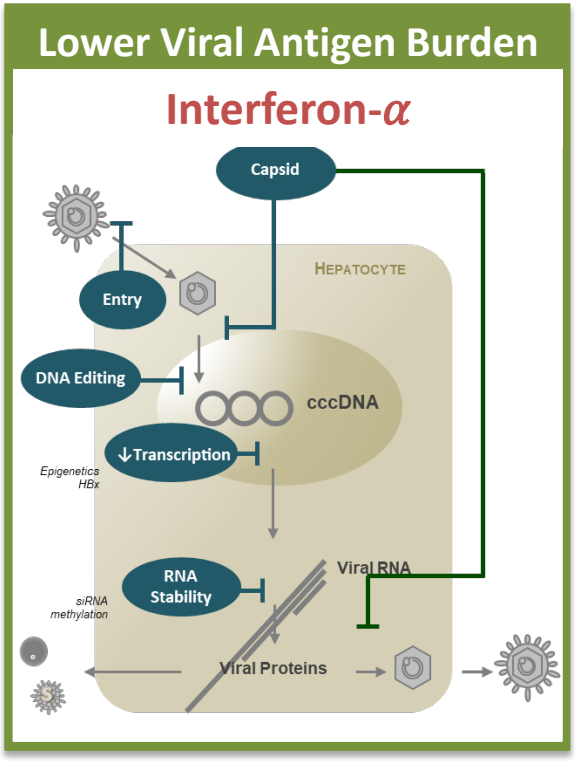
Boost Immune Response

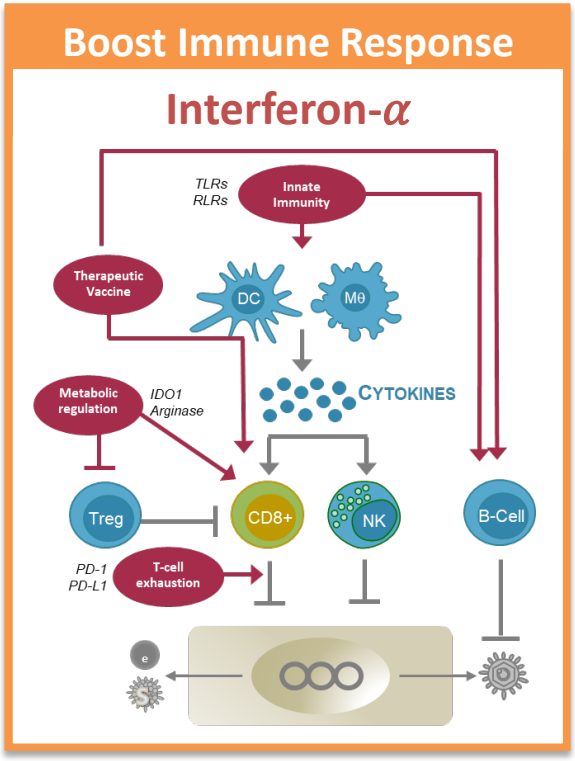


Lim S-G, et al. Nat Rev Gastro Hepatol 2022 (in press).

Therapeutic Approaches to HBV Cure







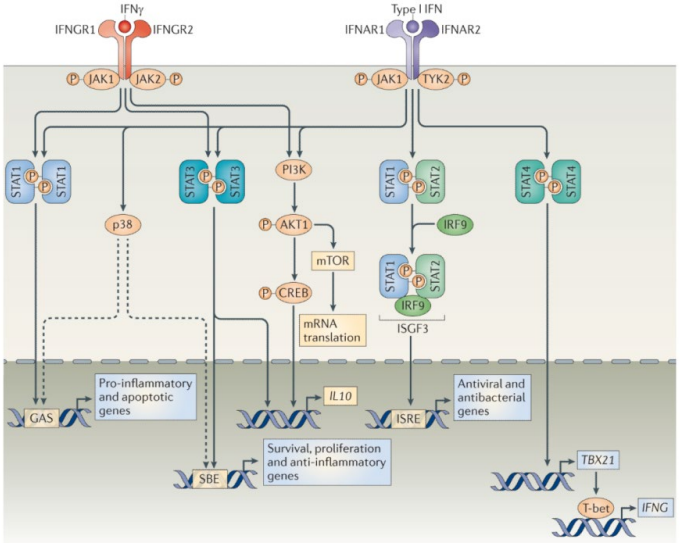
Lim S-G, et al. Nat Rev Gastro Hepatol 2022 (in press).

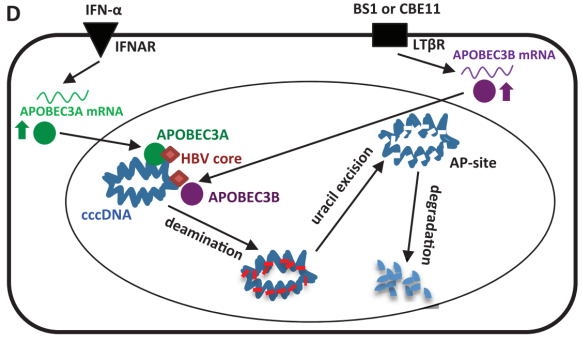
Interferon for CHB: Mechanisms of Action

1. Boost immune responses
   - Enhanced antigen presentation
   - Activation of NK cells
   - Increased cytokine production

2. Inhibit viral replication
   - Degradation of viral RNA
   - Inhibition of viral translation
   - Prevention of hepatocyte infection

3. Reduce HBV antigen burden
   - Reduction of cccDNA transcriptional activity
   - Induction of degradation of cccDNA

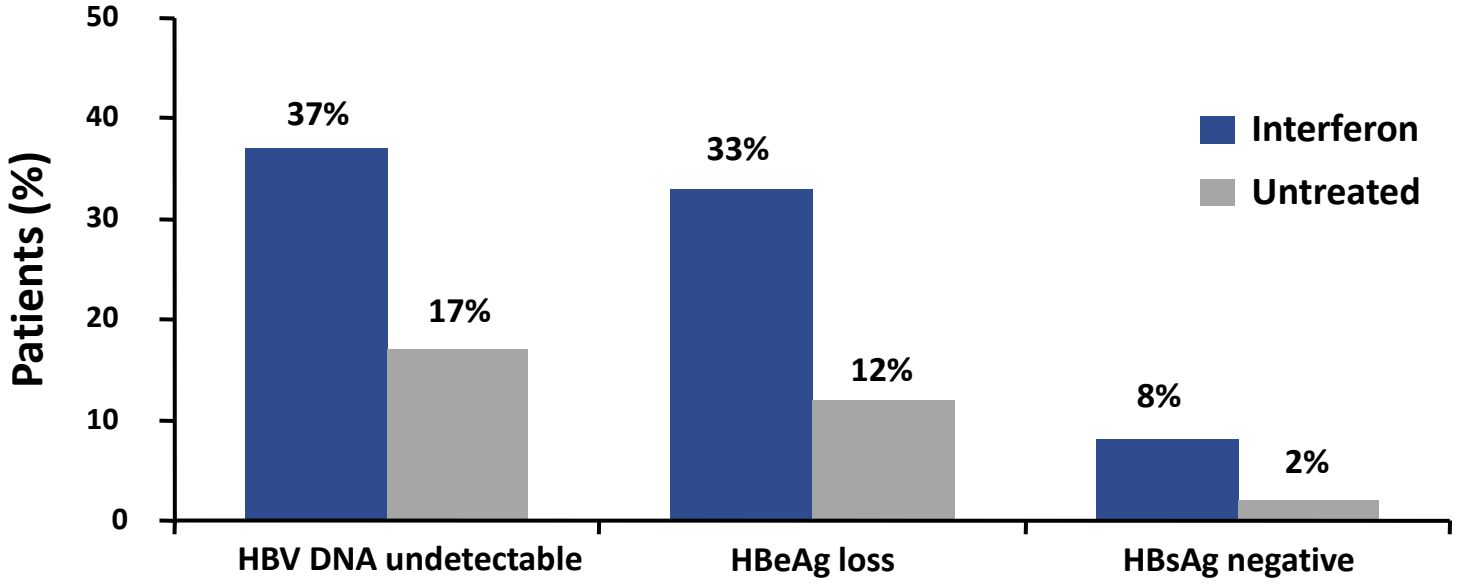




González-Navajas J, et al. Nat Rev Immunol 2012; 12(2): 125–135.
Lucifora J, et al. Science 2014; 343: 1221–8.

Interferon for CHB: Short-term Efficacy

- Meta-analysis of 837 patients (in 15 RCTs) treated with Standard IFN 5-10 MU tiw or placebo for 4 to 6 months

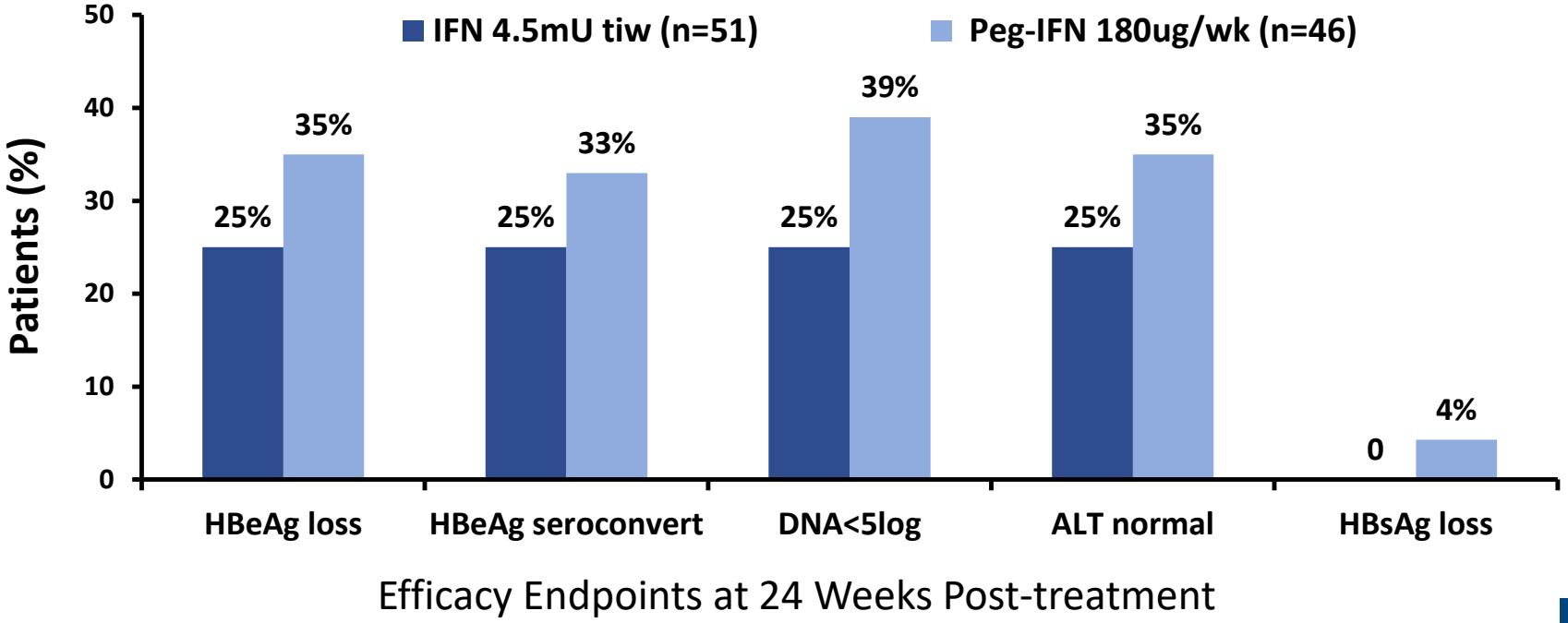


Efficacy Endpoints at 24 Weeks Post-treatment

Wong DKH, et al. Ann Intern Med 1993; 119: 312-23.

Interferon for CHB: Short-term Efficacy

- Peg-IFN 180mg/week for 24 weeks more effective than Standard IFN

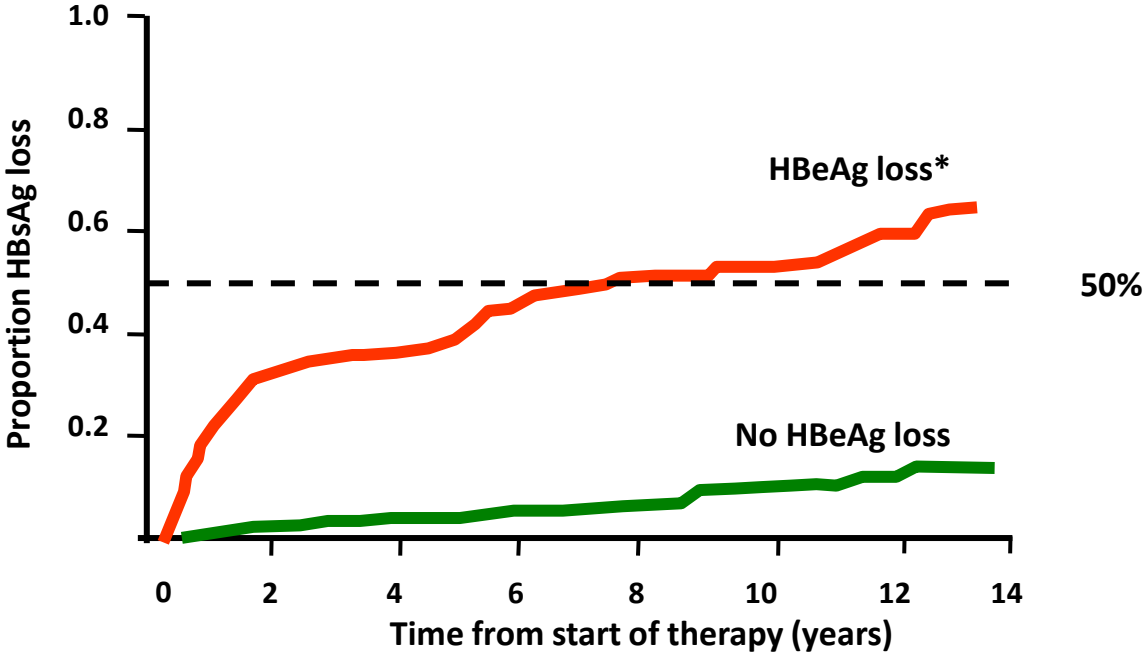


Cooksley G, et al. J Viral Hep 2003; 10: 298.

Interferon for CHB: Long-term Benefits

HBsAg seroconversion increases with time

- 165 patients treated with IFN 10MU tiw for 16 weeks

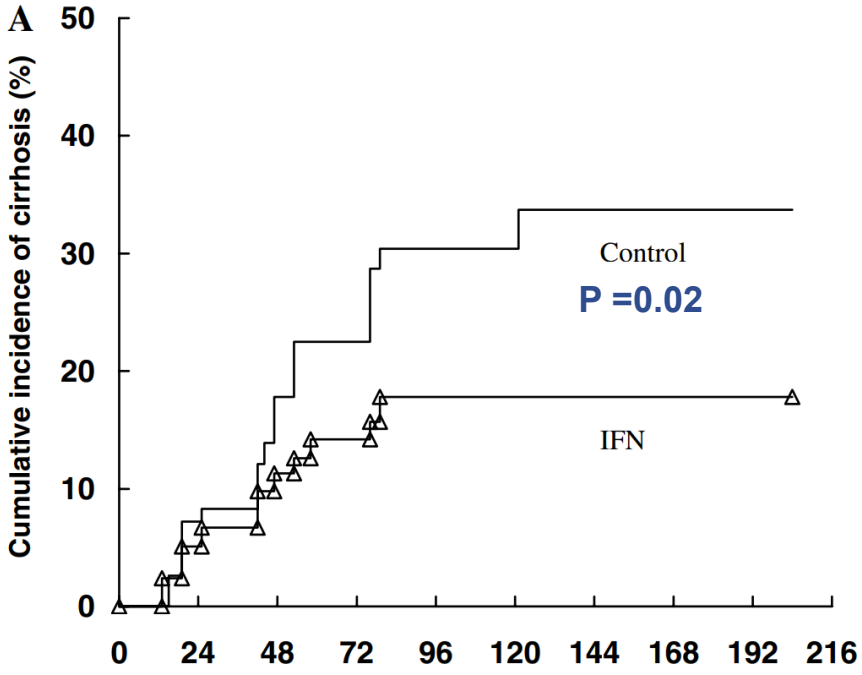


*HBeAg loss within 12 months of treatment

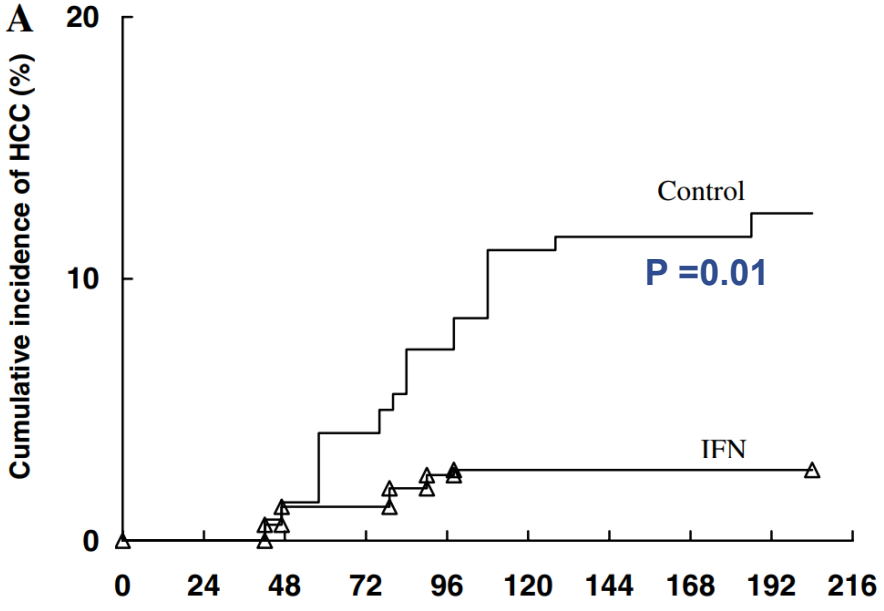
van Zonneveld M, et al. Hepatology 2004; 39: 804–810.

Interferon for CHB: Long-term Benefits

IFN reduces risk of cirrhosis



IFN reduces risk of liver cancer



Lin S-M, et al. Journal of Hepatology 2007; 46: 45–52.

Many Novel Therapies in Development to Combine to Cure HBV Infection

Inhibit Viral Replication

- **Peg IFN-α**
- NUC
- ASPIN
- CAM
- Entry inhibitor
- FXR agonist
- Transcription inhibitor
- HBx inhibitor

Lower Viral Antigen Burden

- **Peg IFN-α**
- siRNA
- ASO/LNA
- RNA destabilisers
- Nucleic acid polymers
- S-Ag Transport inhibiting oligonucleotide polymers

Boost Immune Response

- **Peg IFN-α**
- RIG-I agonist
- TLR7 agonist
- TLR8 agonist
- ALPK1 agonist
- Therapeutic vaccines
- Anti-PD-1/L1
- Anti-HBs
- TCR-redirected CD8 cells

Replication Inhibitor and Peg-Interferon-α

NUC | Pegylated Interferon

Systematic review/meta-analysis of combining IFN with NUCs in CHB

- Timing of Peg-IFN treatment determines rate of HBsAg loss

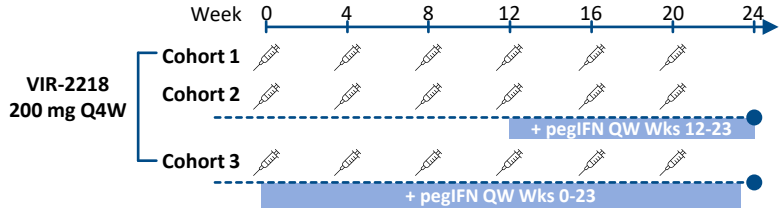
Strategy	Comparator	Number of Studies	Risk Ratio (CI) for HBsAg loss
Add IFN to NUC	NUC	15	**4.5x** (2.0 – 10.5)
Switch from NUC to IFN	NUC	12	**12.2x** (4.0 – 37.0)
Combined NUC + Peg-IFN	NUC	33	**15.6x** (3.2 – 75.5)

Liu J, et al. Hepatology International 2020; 14: 958–972.

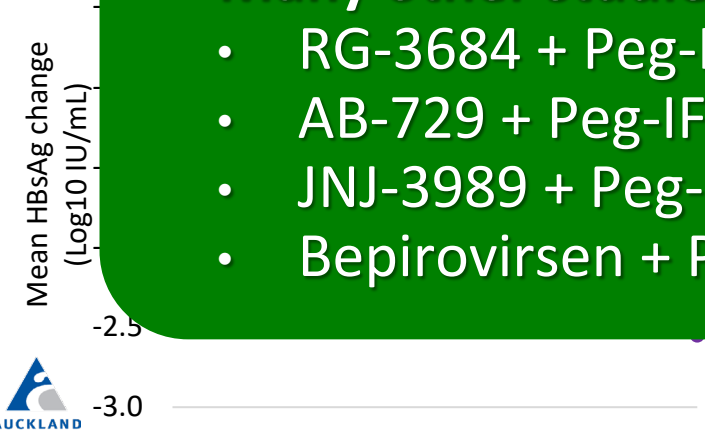
Translation Inhibitor and Peg-Interferon-α

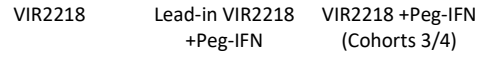
siRNA | Pegylated Interferon

- Adding peg-IFN might increase the rate of HBsAg decline and overcome the plateau seen with siRNA monotherapy at 3-6 months



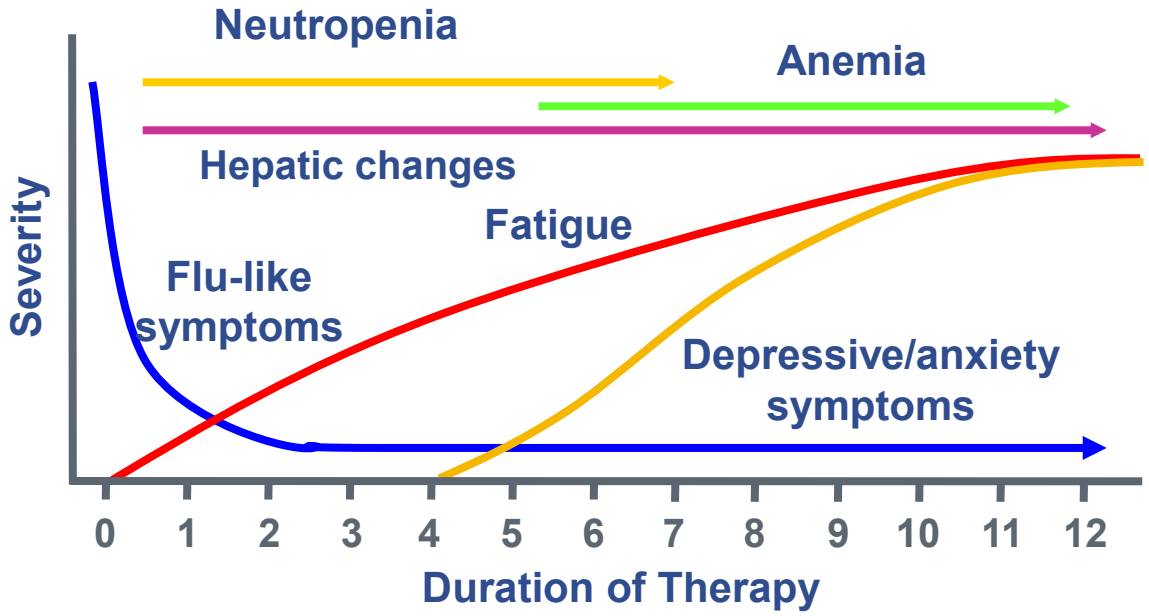
- **siRNA plus Interferon are synergistic**
- **Many other studies underway in patients with CHB**
  - RG-3684 + Peg-IFN *(NCT04225715)*
  - AB-729 + Peg-IFN *(NCT04980482)*
  - JNJ-3989 + Peg-IFN *(NCT05005507)*
  - Bepirovirsen + Peg-IFN *(NCT04676724)*





Yuen MF, et al. AASLD 2021.

Interferon has a predictable side-effect profile



Adapted from Fried MW. Hepatology 2002; 36(5 Suppl 1): S237-S244.

Safety of Peg-Interferon-α in Chronic HBV

	Chronic HBV *(n=448)*
Any adverse event	**88%**
Fatigue	40%
Headache	26%
Myalgia	26%
Anorexia	15%
Arthralgia	12%
Insomnia	8%
Irritability	7%
Depression	4%
Serious adverse events	**5%**
Dose reduction	**7%**
Discontinuation	**5%**

Marcellin P, et al. Liver Int 2008; 28:477.

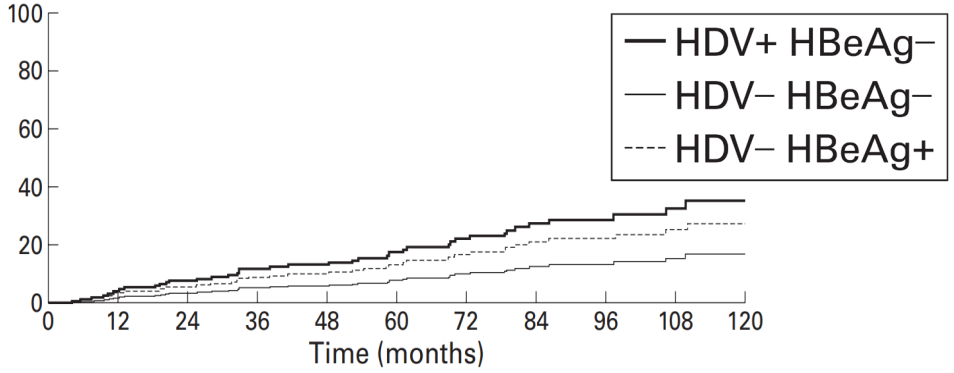
There are Many Contraindications to Interferon

- Advanced liver disease
- Severe cardiac or pulmonary disease
- Neutropenia or thrombocytopenia
- Uncontrolled thyroid disease
- Autoimmune disorders
- Psychiatric illnesses
- Solid organ transplantation
- Young children, elderly
- Pregnancy, breast feeding
- Ophthalmologic disorders

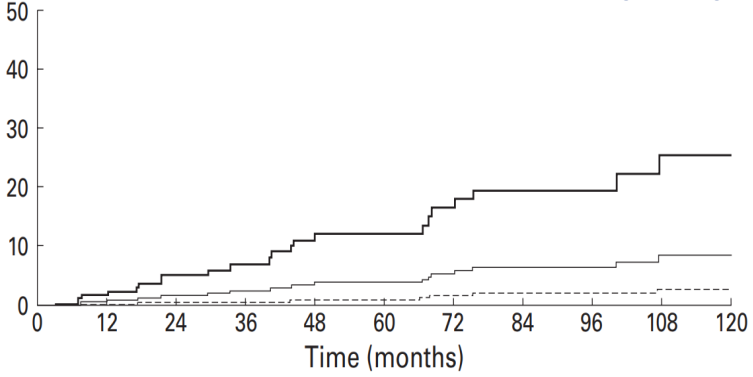
HBV-HDV (Delta) co-infection is associated with high morbidity and mortality

- 5% all HBV-infected patients = ~12 million patients in Mediterranean, Middle East, Pakistan, Turkey, Mongolia, western/central Africa, Amazonian basin and Pacific islands
- No proven benefit of nucleos(t)ide analogues
- More rapid progression to cirrhosis, decompensation, HCC, transplant and death

Incidence of Liver Failure



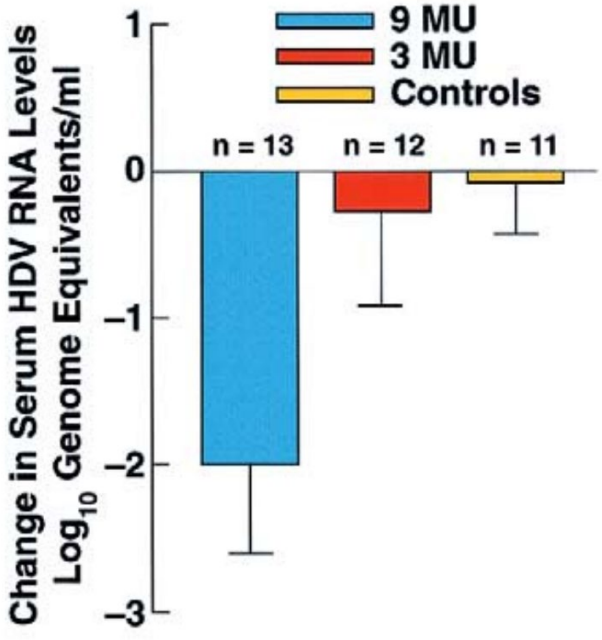
Incidence of Liver Cancer (HCC)



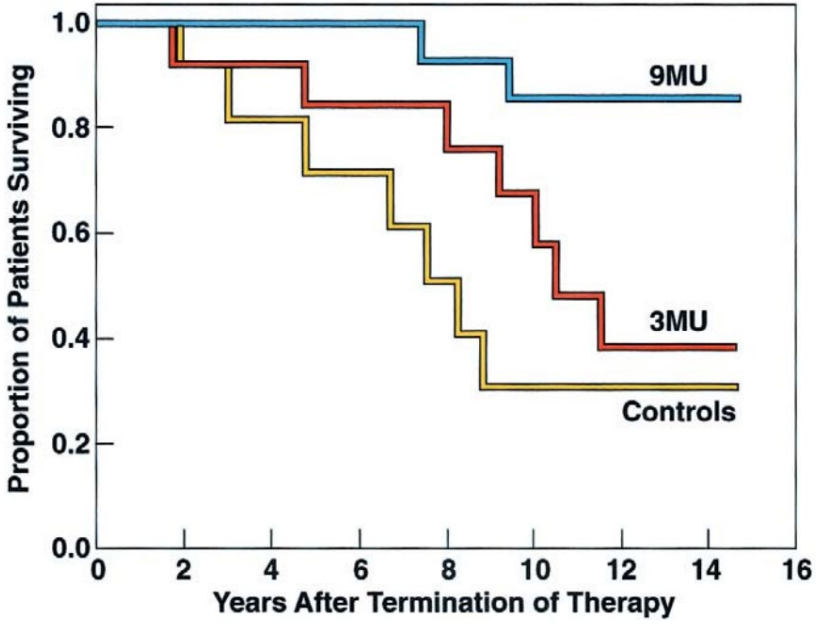
Fattovich G, et al. Gut 2000; 46: 420–426.

In HBV-HDV co-infection, IFN lowers serum HDV RNA and improves survival

Suppression of HDV RNA



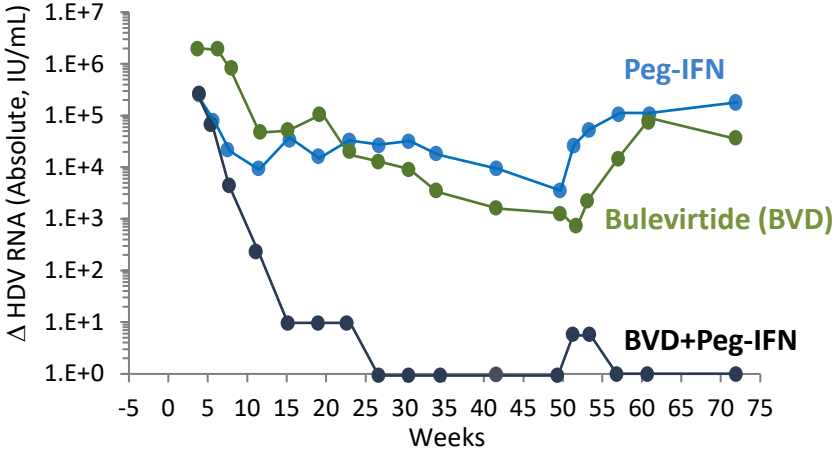
Improved Survival



Farci P, et al. Gastroenterology 2004; 126:1740-9.

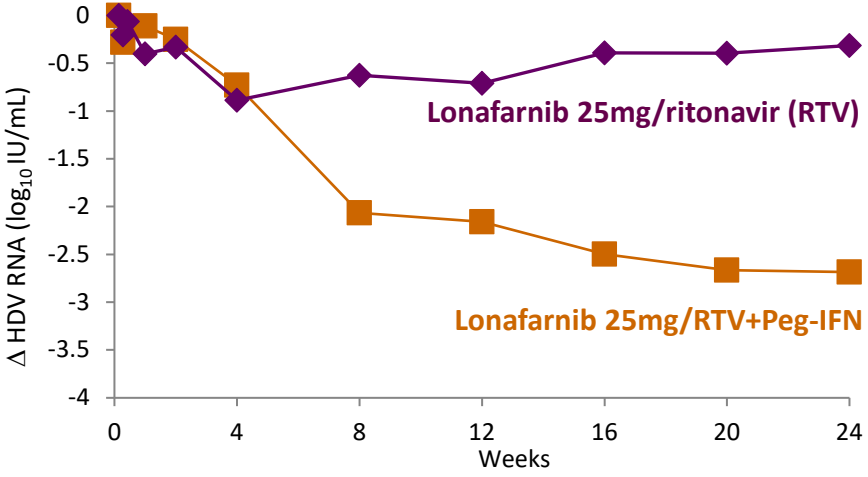
In HBV-HDV co-infection, IFN is synergistic with novel direct antivirals

With Entry Inhibitor



Wedemeyer H, et al. EASL 2020. #AS072.

With Prenylation Inhibitor



Yurdaydin C, et al. EASL 2018. #PS-161.

- IFN blocks both extracellular and cell division-mediated spread of HDV

Zhang Z, et al. EASL 2019. #SAT-202.

Summary

- IFN has pleiotropic effects on HBV and the host immune system
- IFN (alone or with NUCs) has led to the highest rates of HBsAg loss and improved clinical outcomes for patients with CHB
- IFN has synergistic antiviral activity when combined with novel therapies against HBV mono-infection and HBV-HDV co-infection
- The inconvenience, poor tolerability and multiple contraindications have limited the use of IFN for HBV in the clinic
- An improved, liver-targeting oral interferon with fewer systemic side effects could meaningfully contribute to a functional cure for patients with CHB

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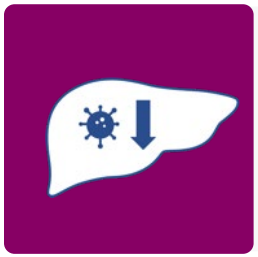
Clear Rationale for an Oral, Well-tolerated Liver Focused IFN-α Pathway Activator



Interferon-α is approved for treatment of cHBV:

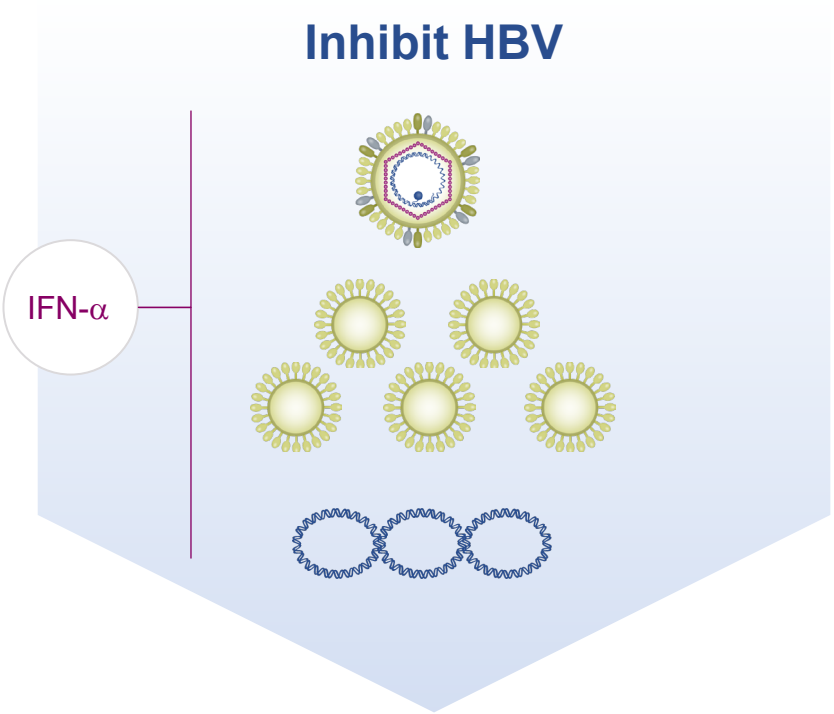
- PEGINTRON (peginterferon alfa-2b)
- Pegasys (peginterferon alfa-2a)

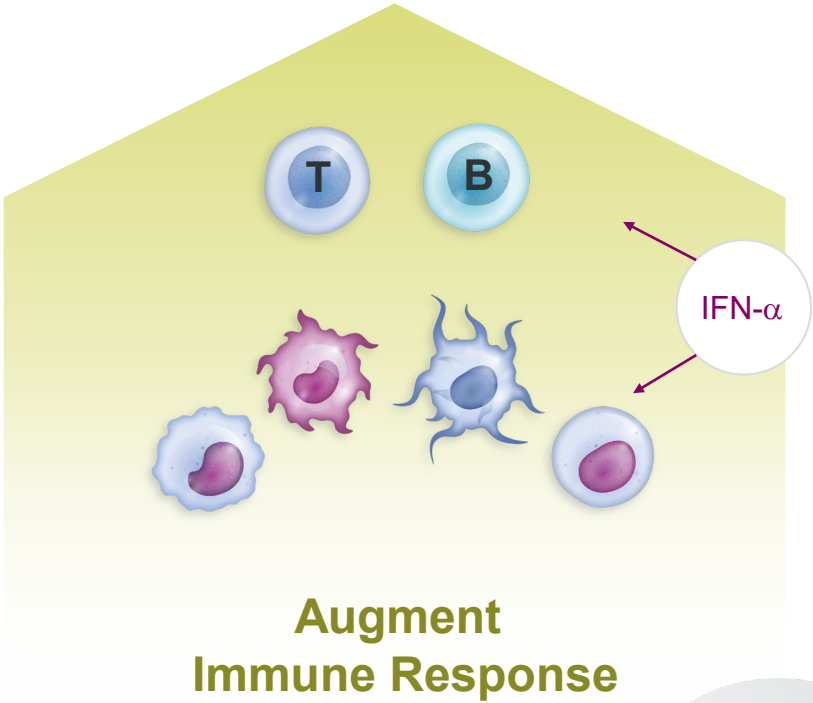
Highest rate of HBsAg loss/functional cure, though in a subset of patients

PEG IFN-α is delivered systemically by injection and has significant systemic side effects and tolerability issues that limit its use

An oral, liver-focused activator of the IFN-α pathway that retained the efficacy of IFN-α while improving tolerability would be a significant advance

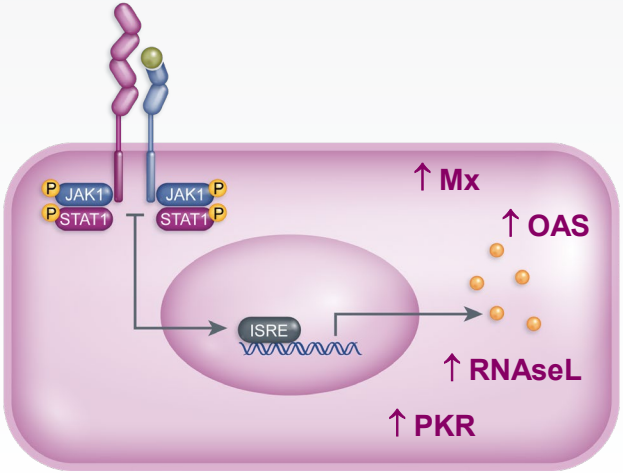
IFN-α Engages both Antiviral and Immune Modulatory Components of HBV Cure Strategy





IFN-α is a Critical Host Defense Cytokine Against Infection

1 Induce cellular antiviral state



2 Activate innate immunity

Macrophage: ↑ regulatory functions

NK Cell: ↑ recruitment & activation

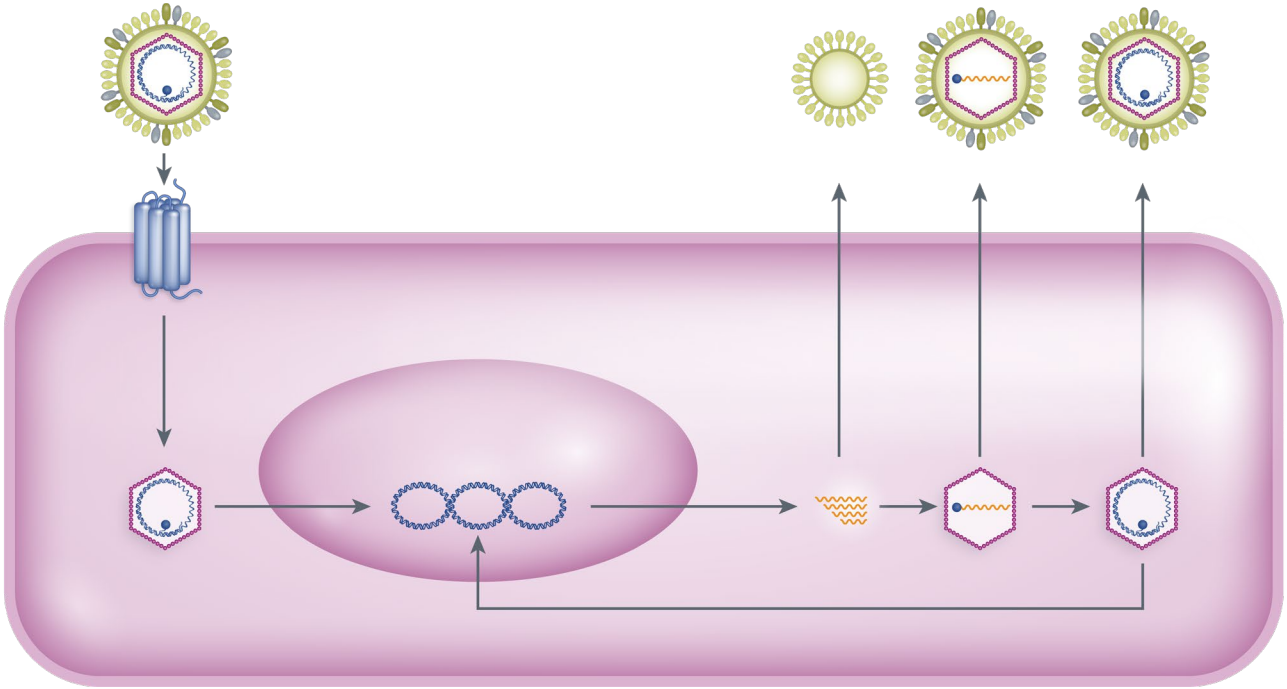
DC: ↑ antigen presentation, migration

3 Activate adaptive immunity

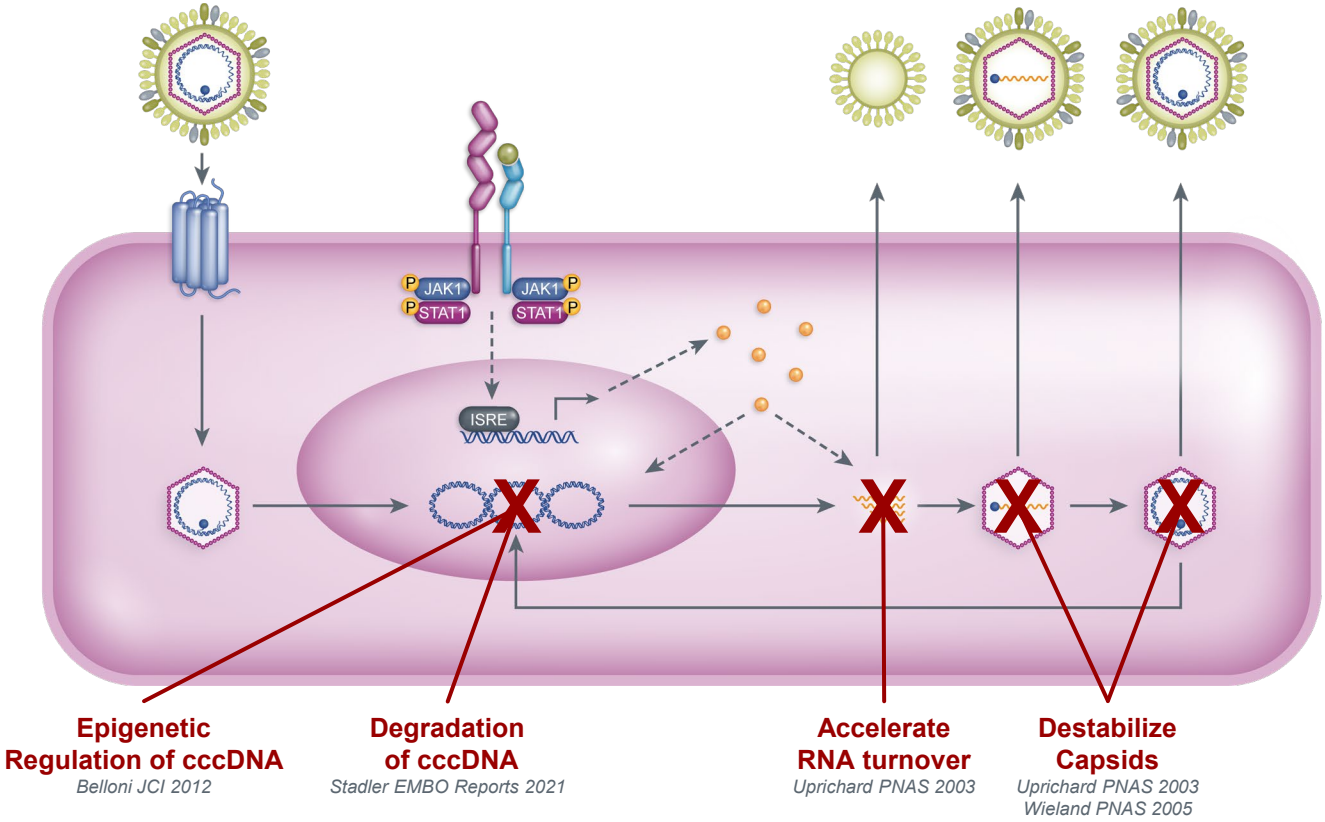
T ↑ Expansion, cytotoxic function

B ↑ Activation, Ab production

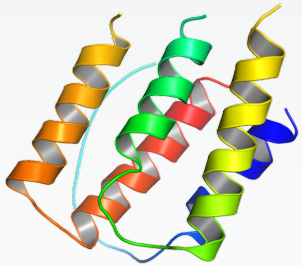
HBV Replication Cycle
Antiviral Mechanisms of IFN-α



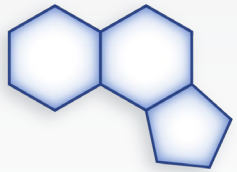
HBV Replication Cycle
Antiviral Mechanisms of IFN-α



Assembly is Developing a Small Molecule IFNAR Agonist



165 amino acids, MW = 19,241



MW = ≤500

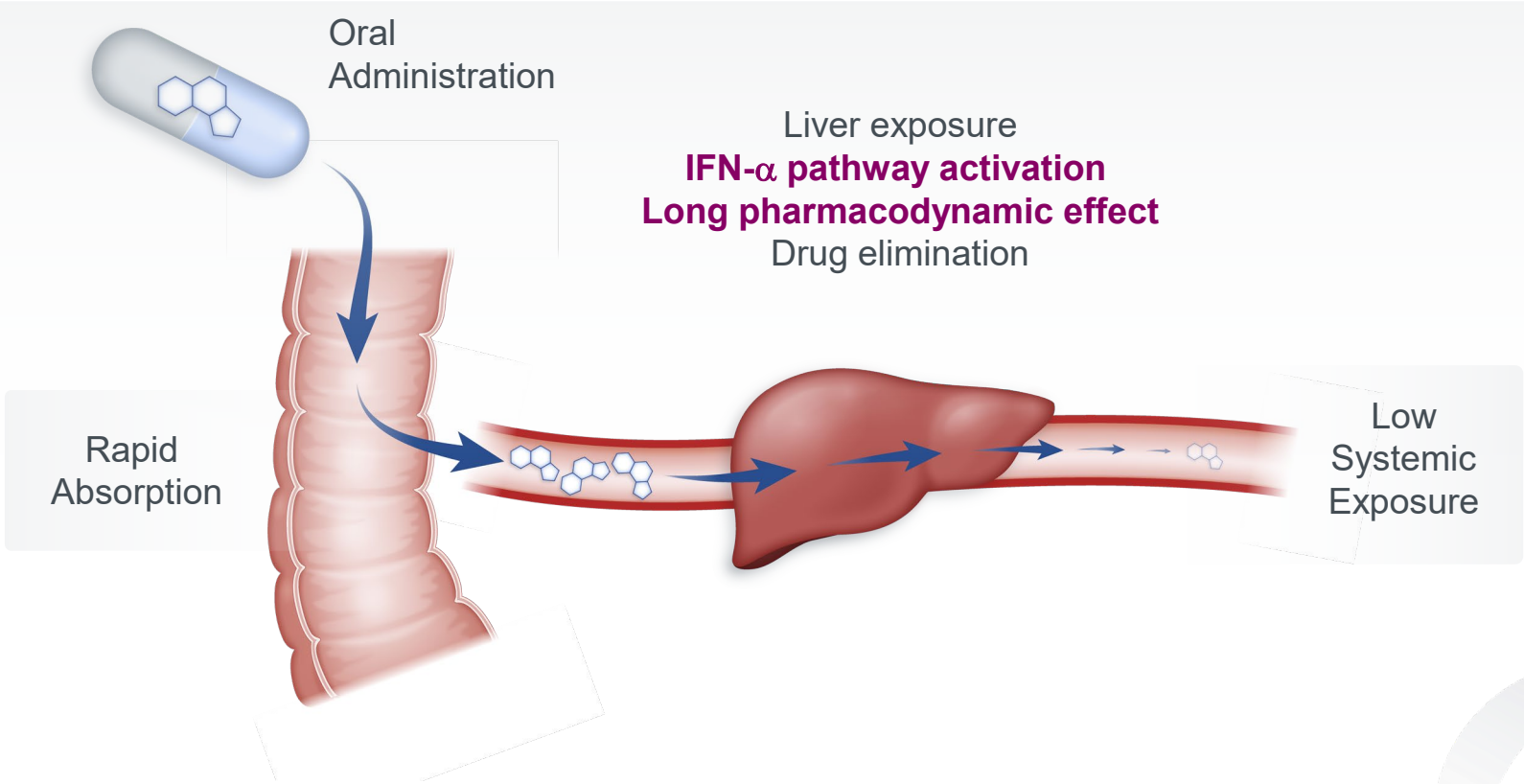
PEG-IFN-α

- Dosed as a weekly injection → high circulating interferon levels
- Tolerability issues → limited clinical use, discontinuations, limited duration
  - flu-like symptoms
  - changes in blood cell counts
  - depression

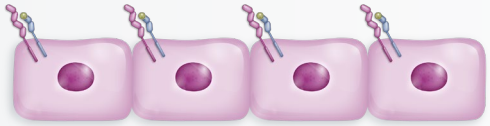
Small Molecule

- Liver focused PK exposure aims to
  - Activate antiviral effects in infected hepatocytes
  - Engage innate and adaptive immune responses in the liver
  - Avoid systemic immune activation leading to tolerability issues
- Oral drug provides convenience

Strategy for Liver-Focused Activation of the IFN-α Pathway



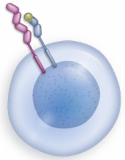
All Cell types in the Liver Express IFN-α Receptors Including Hepatocytes, Endothelial Cells, and Immune Cells



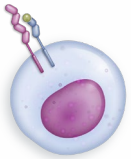
Hepatocytes

Liver Sinusoidal Endothelial Cells (LSECs)

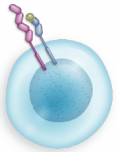
Kupffer Cells



T Cells



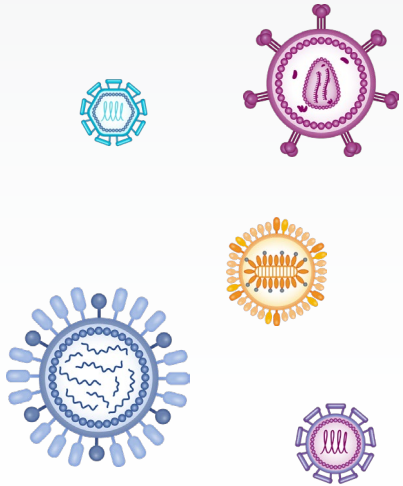
NK Cells



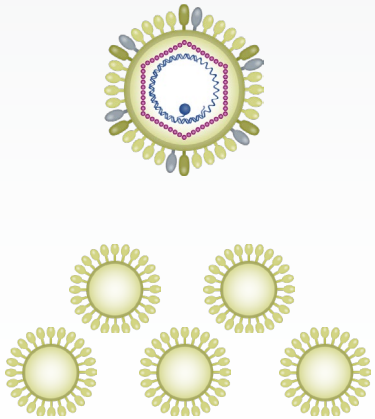
B Cells

Expected *In Vitro* Activities of a Small Molecule That Activates the IFN-α Pathways

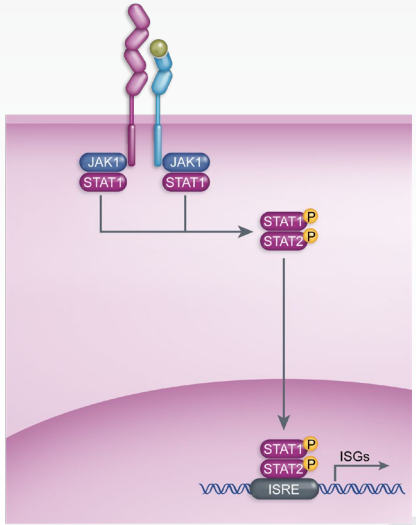
Broad Antiviral Activity



Inhibition of HBV Replication and Antigens



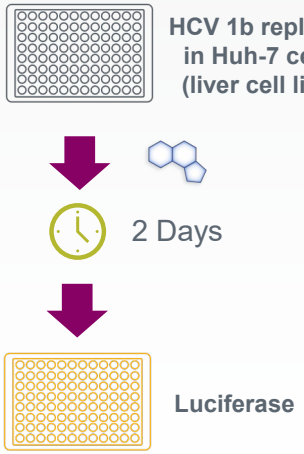
Signaling through JAK/STAT; ISG Induction



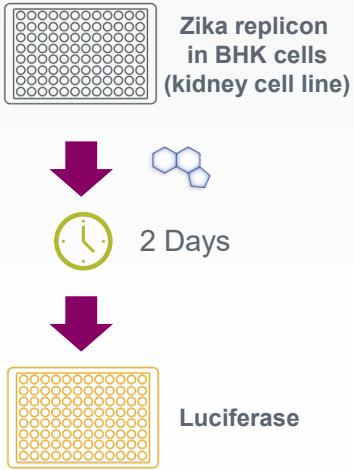
Establishing the Broad Antiviral Activity of our Small Molecule IFNAR Agonists

Cell-based Preclinical Antiviral Activity

HCV Replicon Antiviral Assay



Zika Replicon Antiviral Assay

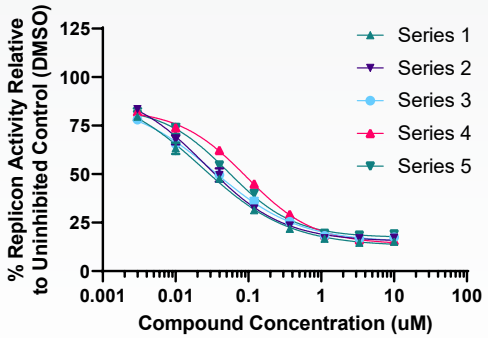


EMCV Whole Virus Antiviral Assay

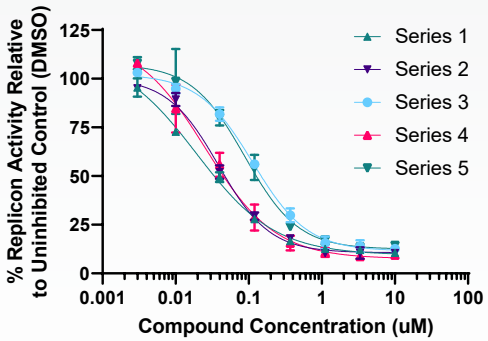
Broad Antiviral Activity of Multiple Lead Compound Series

Cell-based Preclinical Antiviral Activity

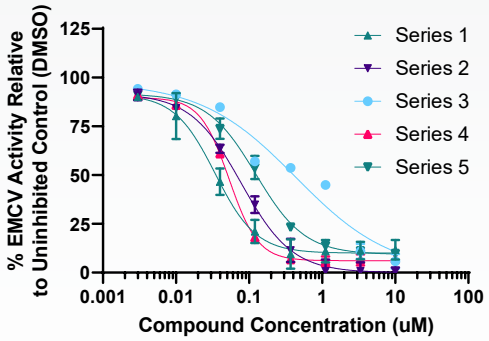
HCV Antiviral Activity



Zika Antiviral Activity



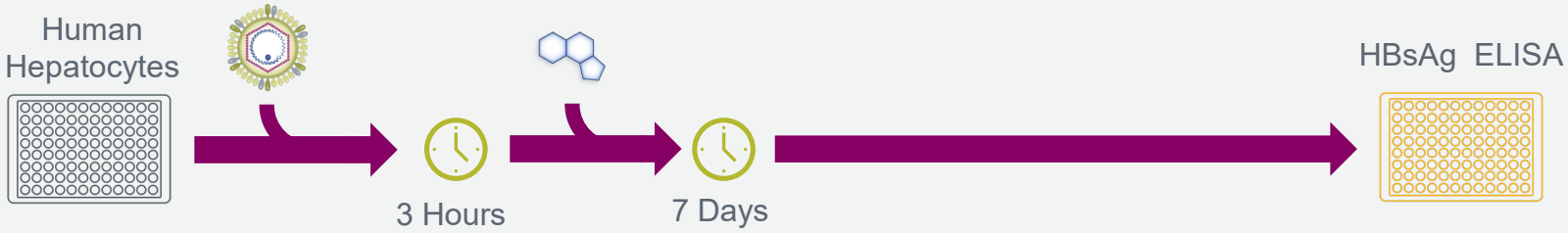
EMCV Antiviral Activity



Further Specific Evaluation of Activity Against HBV

Cell-based Preclinical Antiviral Activity

Early Treatment Assay (pre cccDNA formation)

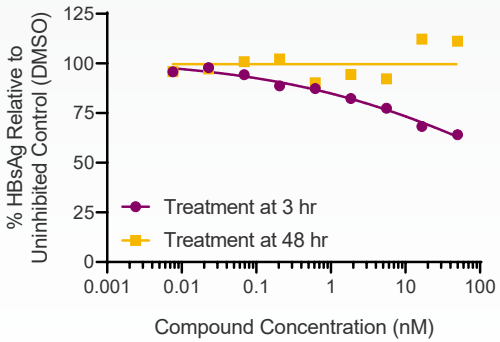


Late Treatment Assay (post cccDNA formation)

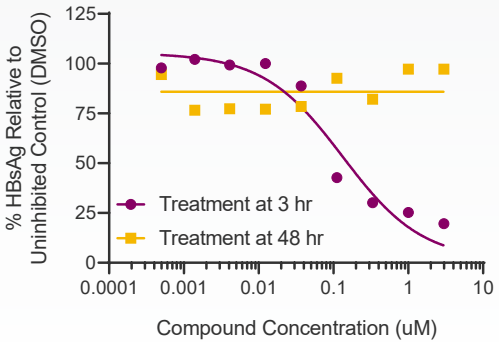
IFNAR Agonists Inhibit HBV Antigen Production Whether Added Early or Late

Activity is Distinguished from that of Nucleoside Analogs and Core Inhibitors

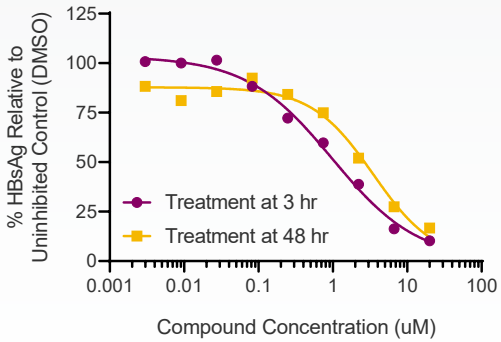
NrtI (entecavir)



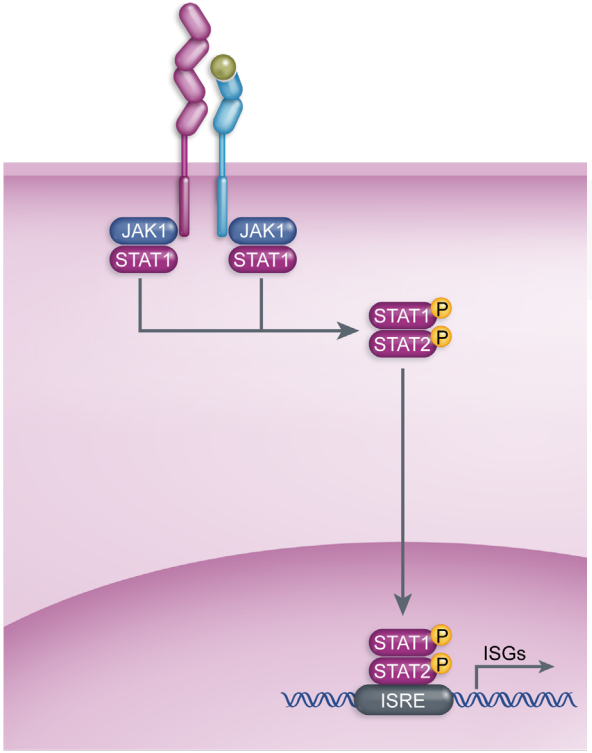
Core Inhibitor (3733)

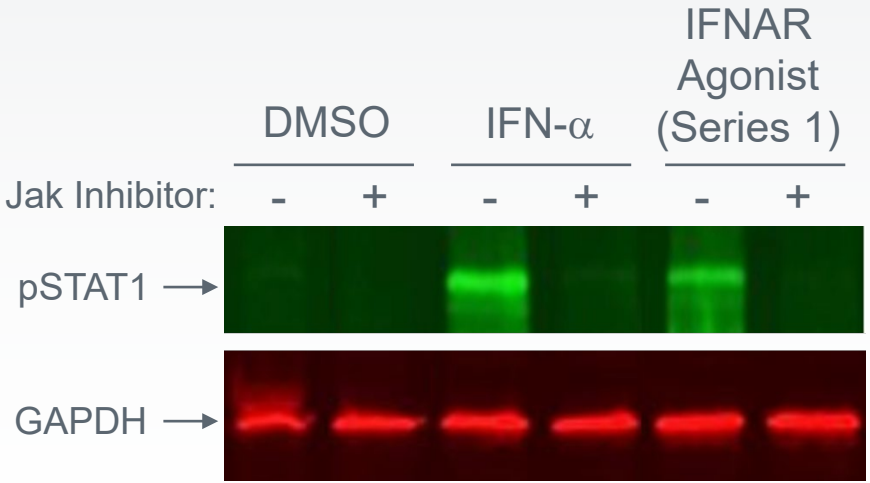


IFNAR Agonist (Series 1)

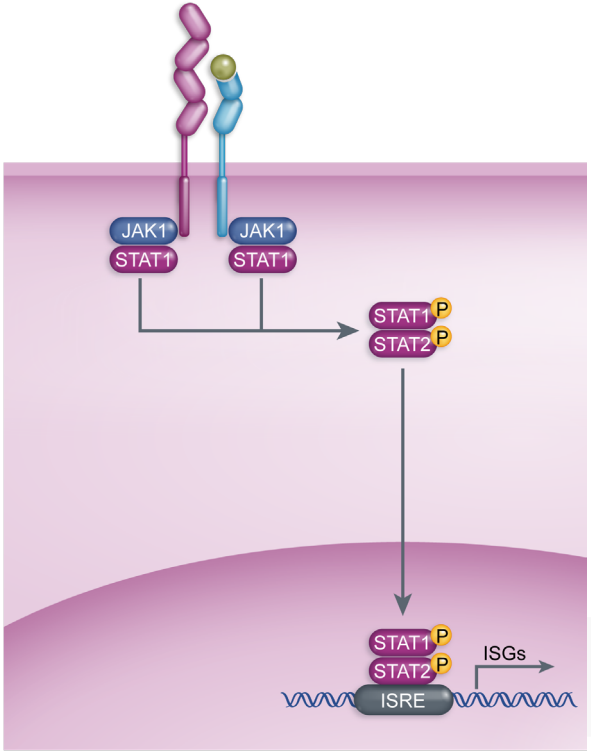


Small Molecule IFNAR Agonists Act Through Jak-STAT Signaling

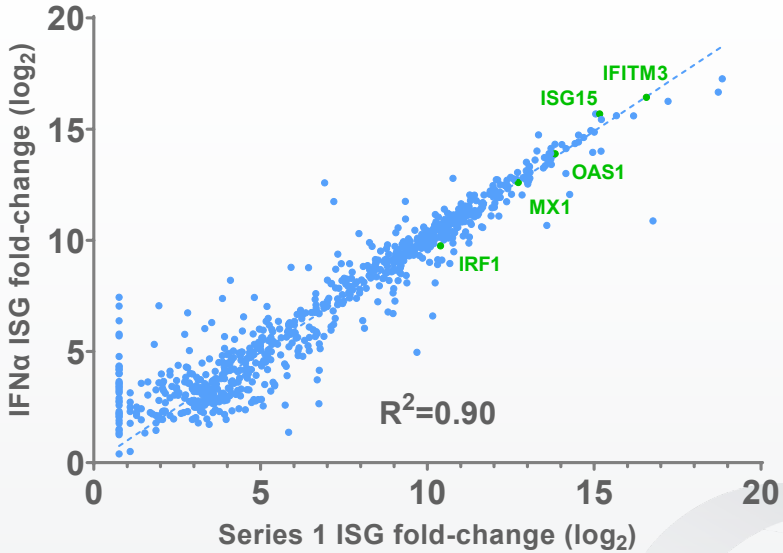




Small Molecule IFNAR Agonists Induce Transcription of Expected Interferon Stimulated Genes



Induction of interferon-stimulated genes in human hepatocytes



IFNAR Agonist Target Product Profile

Activity Profile

- *In vitro* antiviral activity against HBV and HDV comparable to IFN-α
- *In vitro* immune gene induction comparable to IFN-α
- Selective *in vivo* induction of interferon stimulated genes in the liver versus periphery

PK Profile

- Orally administered with rapid absorption
- High liver exposure
- Limited systemic exposure
  - short terminal half-life

Safety Profile

- Well tolerated (enhanced tolerability compared to PEG-IFN)

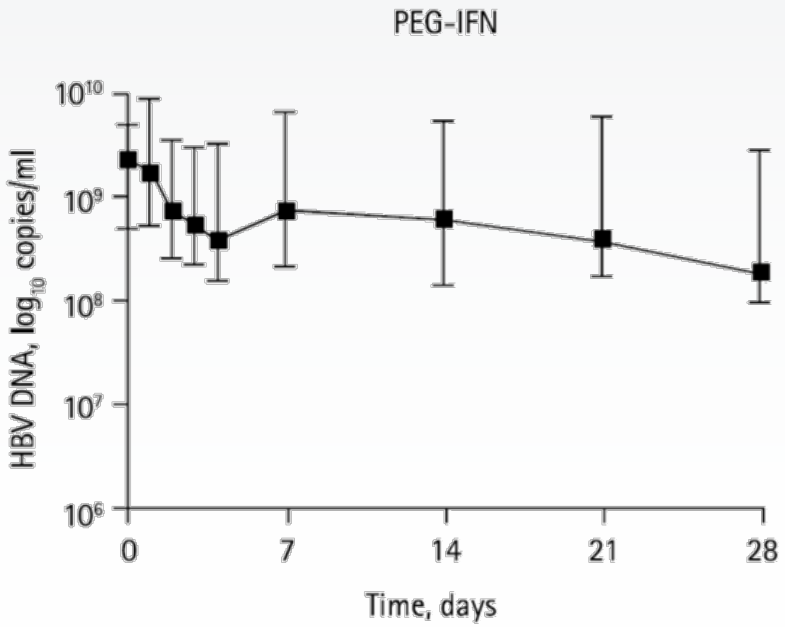
IFNAR Agonist: Progress and Goals

Project is in Lead Optimization

- Multiple chemically-differentiated lead series
  - Confirmed activation through IFN-α signal transduction pathway
  - Broad activity against multiple viruses including HBV demonstrated
  - Optimizing PK ($T_{1/2}$ can be tuned based on chemical structure)
- Compounds actively being profiled in preclinical PK/PD studies

- Anticipate advancing compounds into preclinical safety profiling in 2023 to enable development candidate nomination as quickly as possible

HBV DNA Decline During 28 Days of PEG-IFN Therapy



n=19 Patients

Median HBV DNA reduction = 0.45 $\log_{10}$

Ter Borg et al. Antiviral Therapy; 12:1285-1294

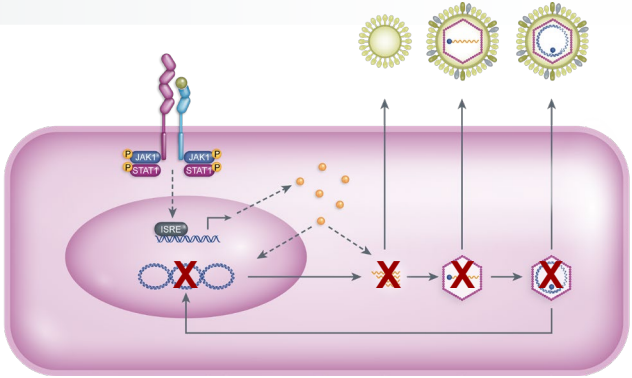
Small Molecule IFNAR Agonist: Summary

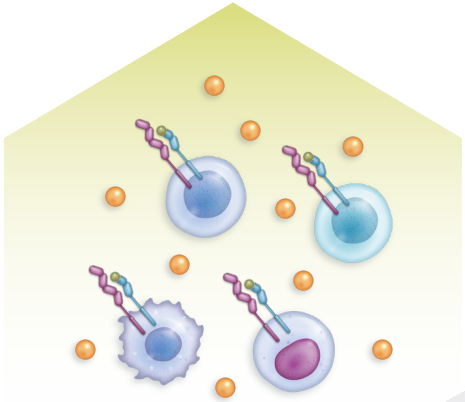
IFN-α is an approved drug for HBV with a demonstrated ability to achieve functional cure

Despite efficacy, use of IFN-α is limited due to poor tolerability and contraindications

An oral, small molecule agonist that engages IFN-α pathway in the liver while reducing systemic exposure and side effects would overcome the major limitation of PEG-IFN

We have discovered novel potent small molecule IFNAR agonists and are aiming to advance compounds into preclinical safety assessments in 2023





Agenda

- Leveraging Assembly Bio's Expertise in Small Molecules and Viral Hepatitis to Expand the Company's Portfolio
  - John McHutchison AO, MD, Chief Executive Officer at Assembly Bio
- The Role of Interferon in HBV Cure
  - Professor Ed Gane
- Assembly Bio’s Small Molecule Liver-Focused Interferon-α Receptor Agonist Research Program
  - William Delaney, PhD, Chief Scientific Officer at Assembly Bio
- Q&A
- Anticipated 2022 Progress
  - John McHutchison

Q&A

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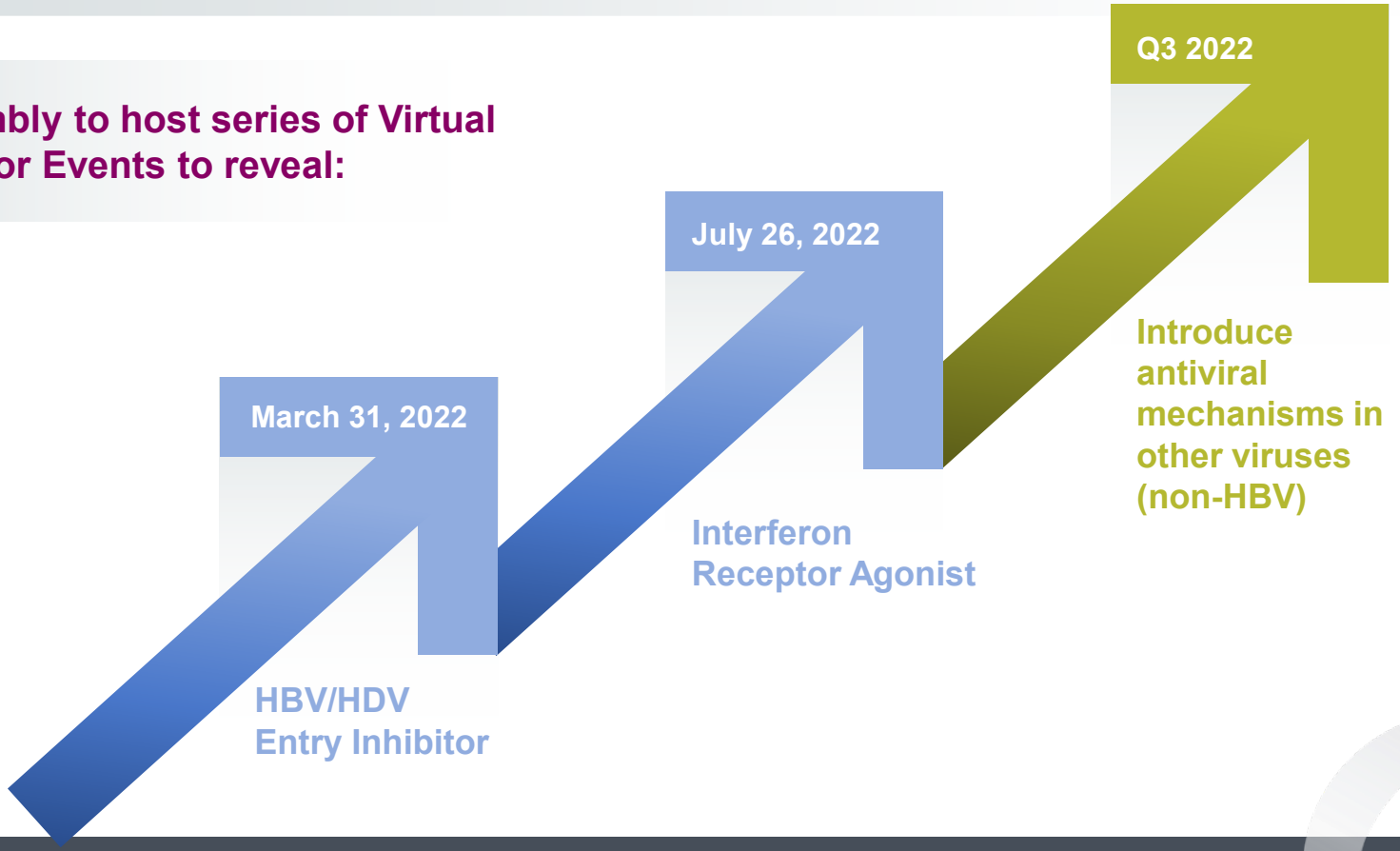
Expanded Research Engine - Expectations for 2022

Assembly to host series of Virtual Investor Events to reveal:



Key Objectives and Anticipated Progress

2022

- ✓ Initiate Phase 1b Study – 3733
- ✓ Introduce HBV/HDV entry inhibitor program
- ✓ Introduce orally-bioavailable small molecule interferon-α receptor (IFNAR) agonist
- ○ Introduce R&D initiatives aimed at other viruses (non-HBV) – Q3 2022
- ○ Initiate Phase 1a Study – 4334
- ○ Interim Phase 1b Data – 3733

Cash Runway

Cash/equivalents anticipated to fund operations into 1H 2024

Interferon-α Receptor Agonist Research Webcast

July 26, 2022