ICE-HBV

International Coalition to Eliminate HBV

PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

HBV Cure Research 101

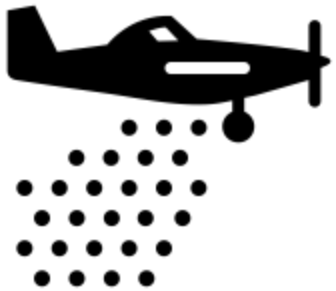
Fabien Zoulim, M.D., Ph.D.
Professor, Lyon University School of Medicine
Head of Hepatology Department, Hospices Civils de Lyon
Head of Viral Hepatitis Laboratory, INSERM Unit 1052 - CRCL

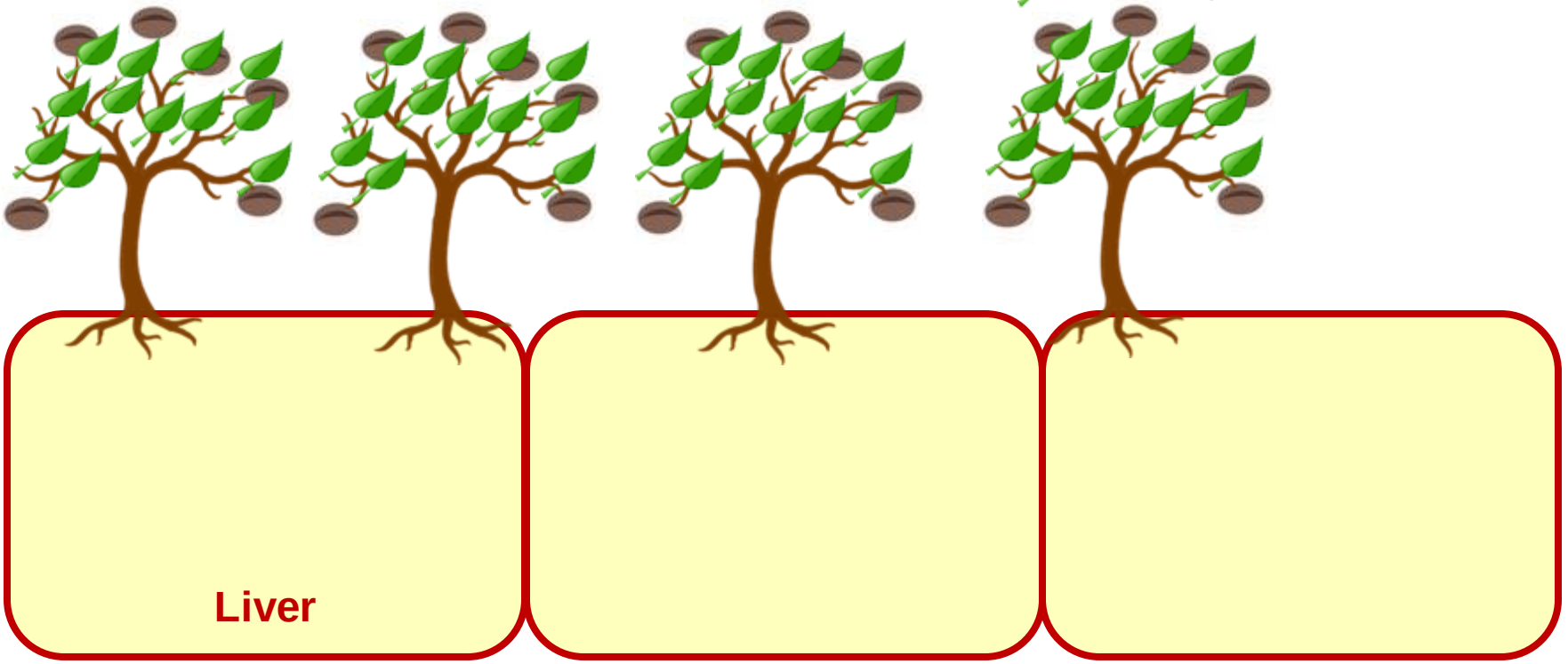
HBV Cure – Why do we need it?

- **Current drugs have big limitations**
  - Rarely cure patients and don't stop disease in everyone
  - Nucleos(t)ide analogs need to be taken for life
- **We really have only 2 flavors of drugs for HBV**
  - All nucleos(t)ide analogs work the same way on the same viral target
  - All interferon α derivatives stimulate the same set of cellular immune responses

Current Treatments

Reduce HBV DNA
Infection and HBsAg are still present



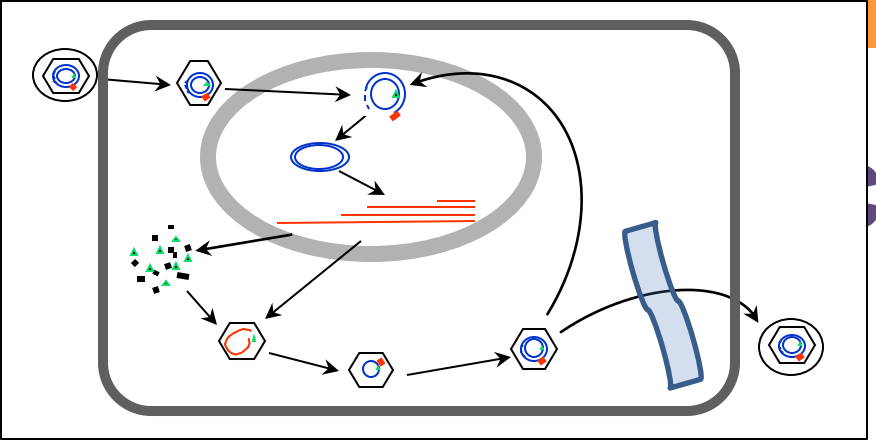


Hep B virus (HBV DNA)

cccDNA

Hep B surface antigen (HBsAg)

cle to curing HBV



cccDNA

HBV cellular replication cycle

- The central molecule in HBV replication is the viral “cccDNA”
  - It is the master copy of the viral genome in cells
- cccDNA appears to be long-lived in liver cells
- **Considered as a viral minichromosome and an archive of the virus responsible viral persistence**

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So how do we get rid of the cccDNA?

- **Nobody knows!**
- But….
  - *Clearance of an acute infection gets rid of the vast majority of the cccDNA safely, so the immune system can do it!*
  - The cccDNA is not always completely eliminated during resolution of an acute infection
  - The immune system can keep any residual cccDNA under control in almost all patients who resolved the infection

What is "HBV Cure"?

- The current goal is a **Functional Cure**
  - **A complete cure *eliminates* cccDNA, a functional cure does not**
- **The clinical definition** of a functional cure is undetectable HBV DNA and HBsAg in serum 6 months post-treatment
  - No disease progression
  - Decreased cccDNA in cells to very low levels (similar to resolution of acute infection)
  - Immune control of any residual cccDNA in the body

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What will cure therapies look like?

- **Combination therapy will be needed** because:
  - HBV's many genotypes and variable disease course mean no one drug will cure everyone
  - cccDNA's durability means we will have to hit it from multiple angles at the same time
- Cure therapy is likely to be long (a year?) and need exceptionally **safe drugs**

What types of HBV drug discovery are ongoing?

- Cure discovery research falls into 3 categories
  - Direct-acting drugs that target HBV itself
  - Host-targeted drugs that cause a patient's cells to block HBV replication
  - Immune-stimulating drugs that train the patient's immune system to attack HBV and control infected cells
- The work is being done in universities, biotech companies, and big pharma

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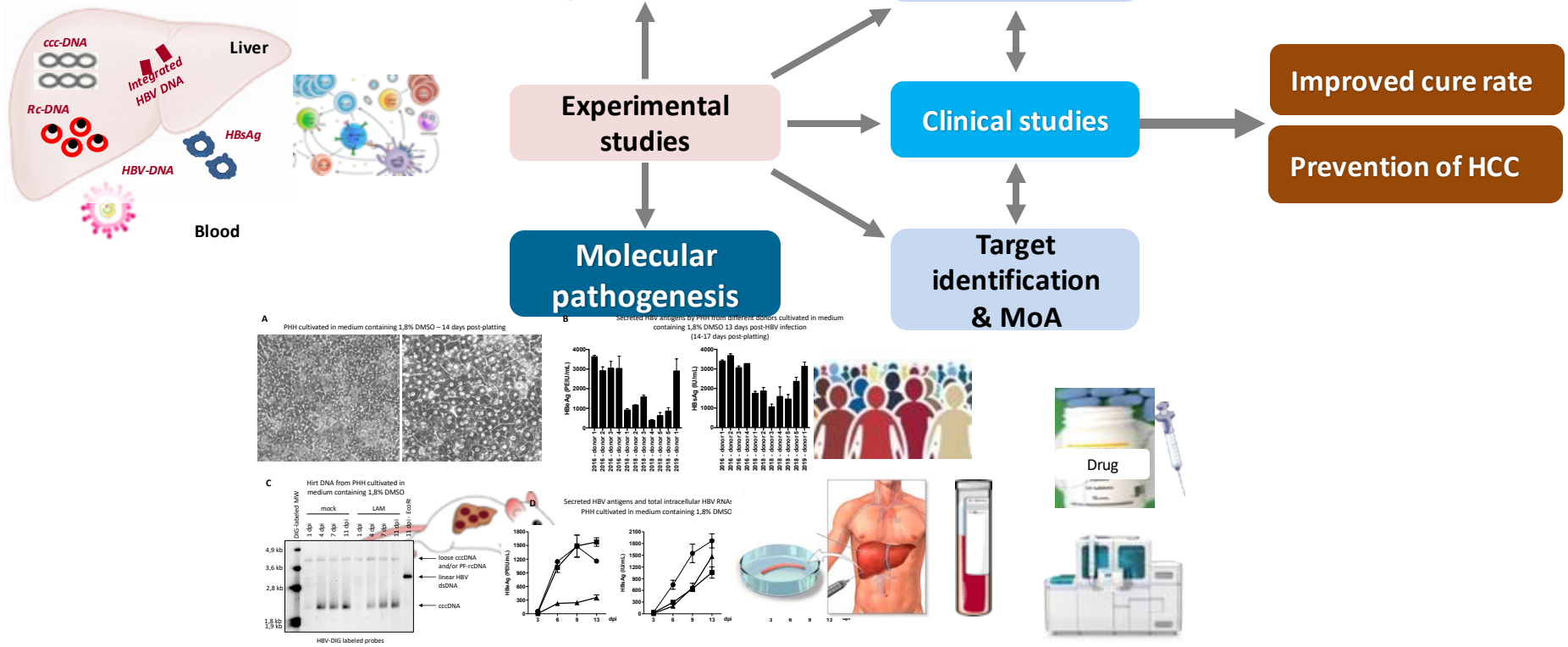
Reference site: www.hepb.org/treatment-and-management/drug-watch/

A translational approach for innovation in HBV & HDV therapies



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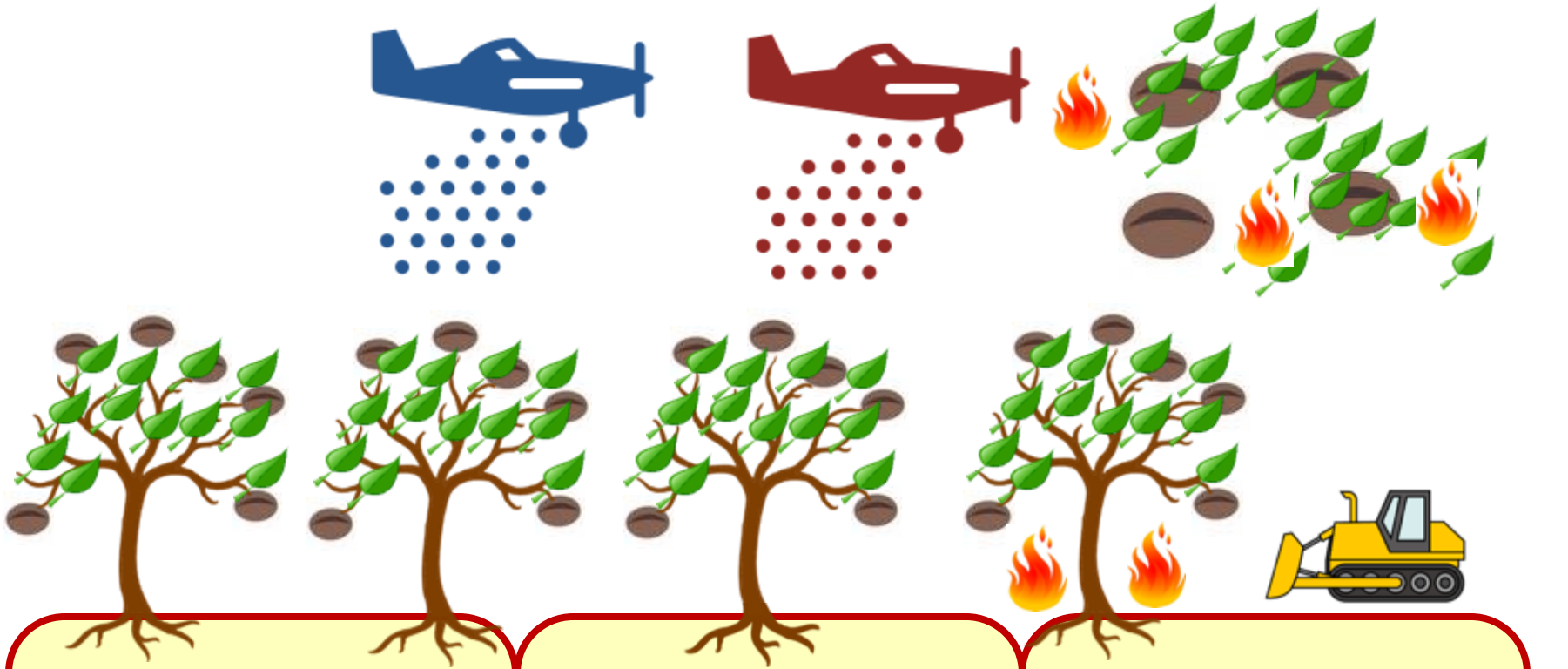
F Zoulim, ICAR 2020, Seattle Webinar

How can we cure the infection?



1) Remove the underlying virus multiplication

2) Suppress the virus protein production

3) Activate the immune response

Hep B virus (HBV DNA)

cccDNA

Hep B surface antigen (HBsAg)

New concepts of Combination Therapy to Cure HBV Consideration for clinical trial design

Replication inhibition ± **Antigen reduction** ± **Immune stimulation**

hNTCP

Entry inhibitors: bulevirtide

HBV polymerase

NUC: ETV, TDF, TAF, novel NUCs and RNAseH inhibitors

Nucleocapsids

CAM: ABI-H0731, JNJ-56136379, RO7049389

Transcription

FXR agonist: EYP001

Viral RNAs

siRNA: JNJ-3989 VIR-2218

ASO: GSK3228836

LNA: RO7062931

HBsAg release

NAPs: REP 2139 or REP 2165

STOPS

RNA destabilizers

FXR agonists

Invigorate immune responses

Innate immunity

TLR7: GS9620, RO6864018, RO7020531, JNJ6479464

TLR8: GS9688

Immune check points

Anti-PD1: nivolumab

Anti-PDL1

PDL1 LNA

Oral PDL1 sm

Stimulate HBV specific B/T cells

Therapeutic Vaccines

GS4774

TG1050

T101

SCI-B-VAC

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Fanning et al. Nat Rev Drug Discov. 2019 Nov;18(11):827-844; Roca Suarez et al, Liver International 2021

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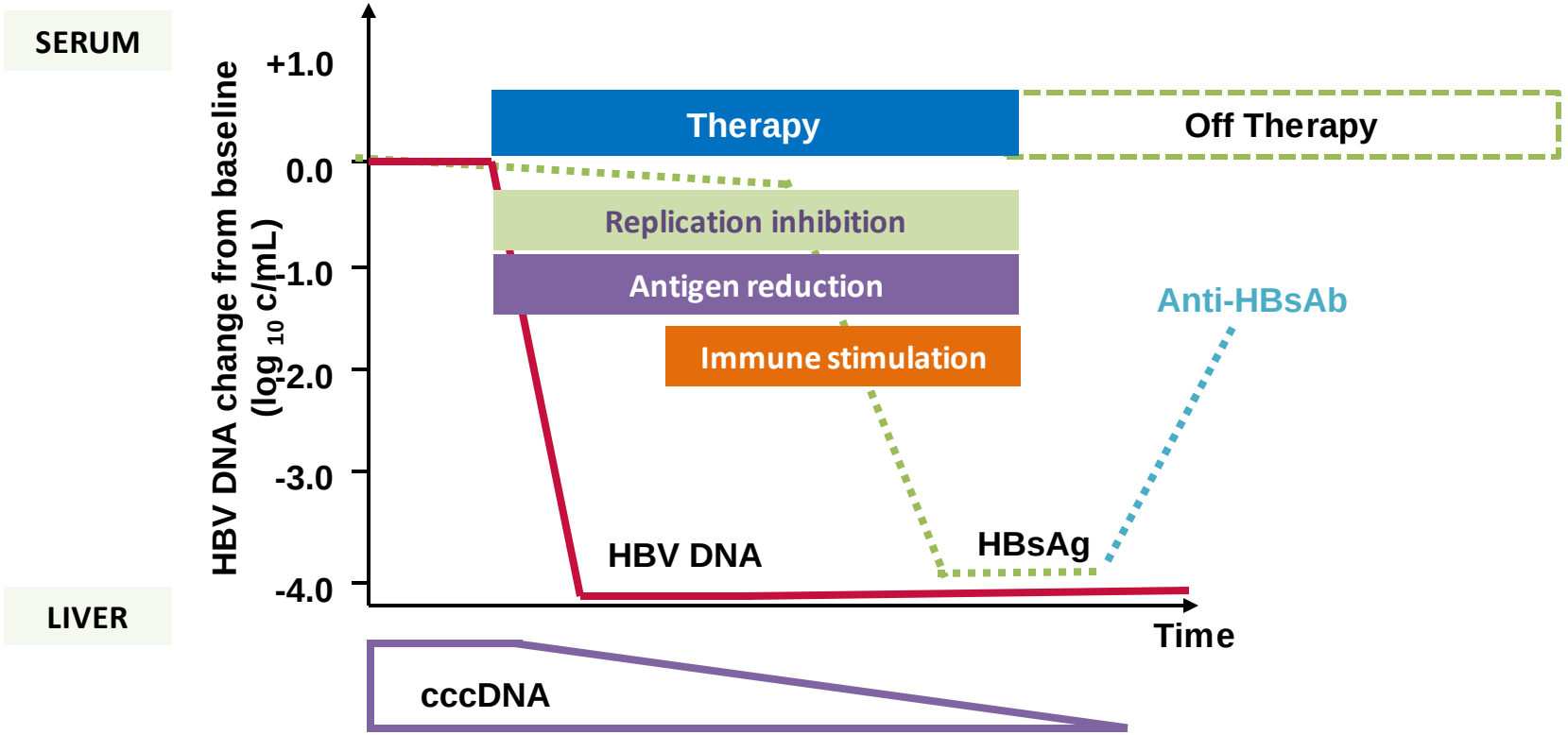
New Clinical Trial Design

Combination of direct acting antivirals and immune stimulation



Adapted from Testoni et al. Semin Liver Dis. 2017, Roca et al, Liver International 2021

Take-home messages

- The goal is a **Functional Cure**
- Combinations of drugs that work different ways are needed
- Understanding of how HBV persists has been improved
- Many promising drug candidates are being developed
- Functional cure rates up to ~30-40% have been seen in a Phase 2 study
- **There is HOPE!**

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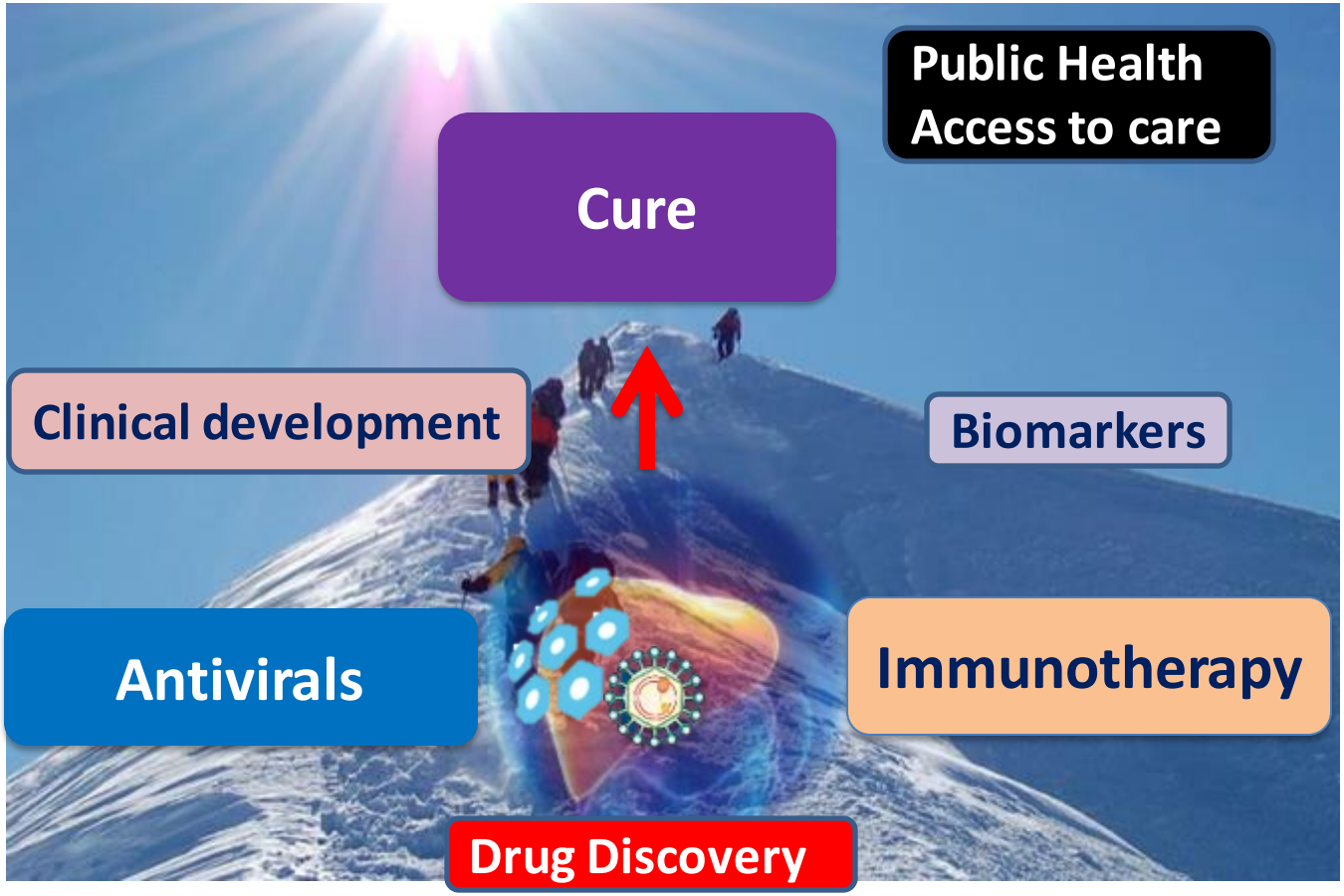
HBV cure: An attainable goal within the next decade !



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