ECOFECT
UNIVERSITE DE LYON

DEVweCAN
Développement Cancer et Thérapies ciblées

TOUS MOBILISÉS POUR #IDEX LYON 2016

INVESTISSEMENTS D'AVENIR

Agence Nationale de la Recherche ANR

UNIVERSITÉ DE LYON

Towards a better understanding of chronic co-infections by hepatitis delta and B viruses: from eco-evolutionary aspects to the improvement of the treatment and prevention of associated liver diseases

InterLabex meeting

2016, December 13th

LBBE
BIOMETRIE ET BIOLOGIE EVOLUTIVE

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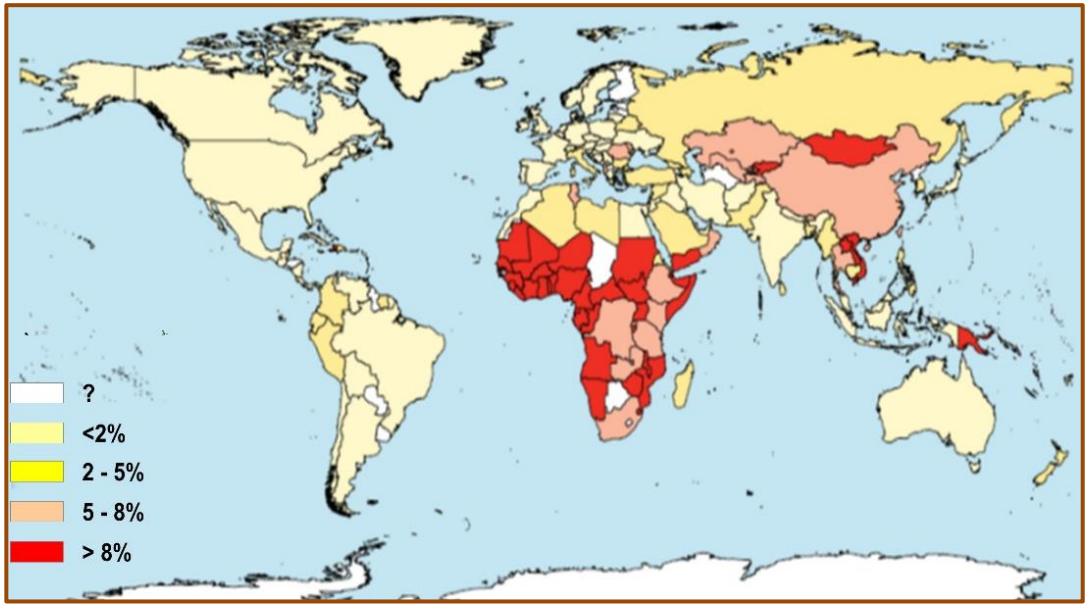
An emerging program on HDV research in Lyon ?

- ✓ **Set a “virtual HDV laboratory” in Lyon with international visibility to develop within 5 years an integrated and sustained program of research on HDV**
- ✓ **Gather the expertise of 6 research and clinical teams/units working in complementary areas of research (ecology, epidemiology, virology, immunology, oncology, medical research)**
- ✓ **4 main axes of research covering scopes of DevWeCan and Ecofect LabEx**
- ✓ **Build-up a long-term funding strategy on a “win-win” situation based on a “boot funding” from InterLabex initiative**

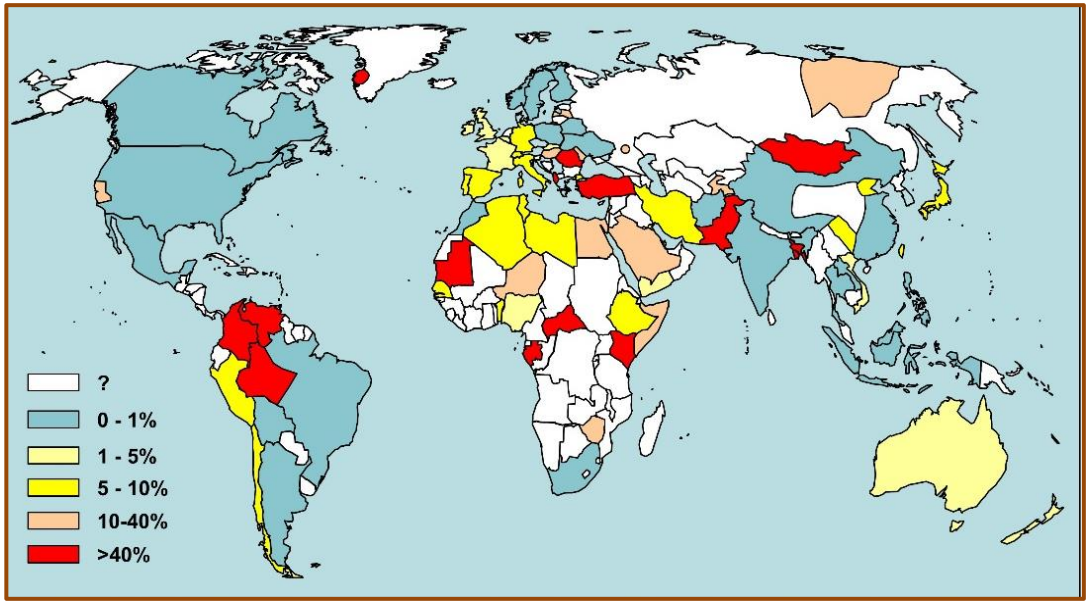
Epidemiology of HDV/HBV co-infection

HBV
250 millions



Partially undiagnosed

HDV(HBV)
15-20 millions

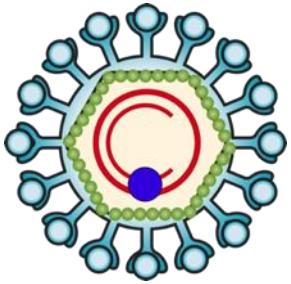


Globally undiagnosed

Schweitzer A et al. Lancet 2015; Alfaiate D et al. Antiviral Res 2015.

HDV is a satellite virus of Hepatitis B virus (HBV)

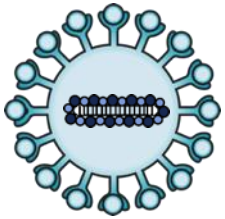
HBV



- ✓ Circular partially double-stranded DNA virus
- ✓ Genome = 3,2 kB, coding for:
  - Polymerase
  - Surface (S, M, L- HBsAg)
  - Core (HBcAg) and Precore (HBeAg)
  - HBx

- ✓ Around 250 millions chronic carriers
- ✓ No curative treatment
- ✓ Cirrhosis : 5 to 20 % in 10 years
- ✓ ≈ 50% of HCC are due to HBV worldwide (part due to HDV????)
- ✓ HCC incidence: 0.5-2% per year

HDV

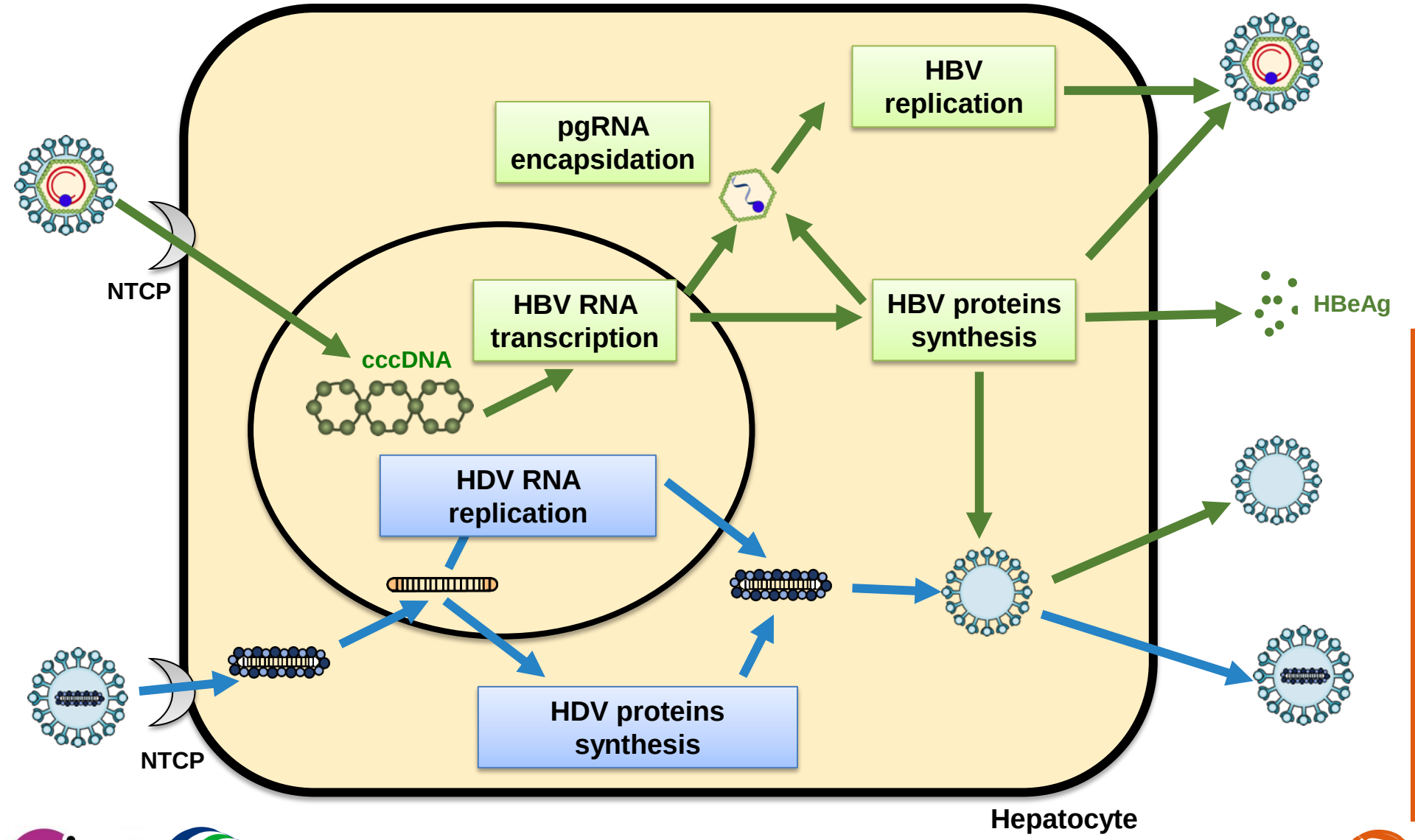


- ✓ Single-stranded negative sense RNA virus
- ✓ Genome = 1,6 kB, coding for:
  - HDAg – no enzymatic activity
- ✓ Depends on:
  - Cell RNA polymerases for replication
  - HBV envelop for spreading

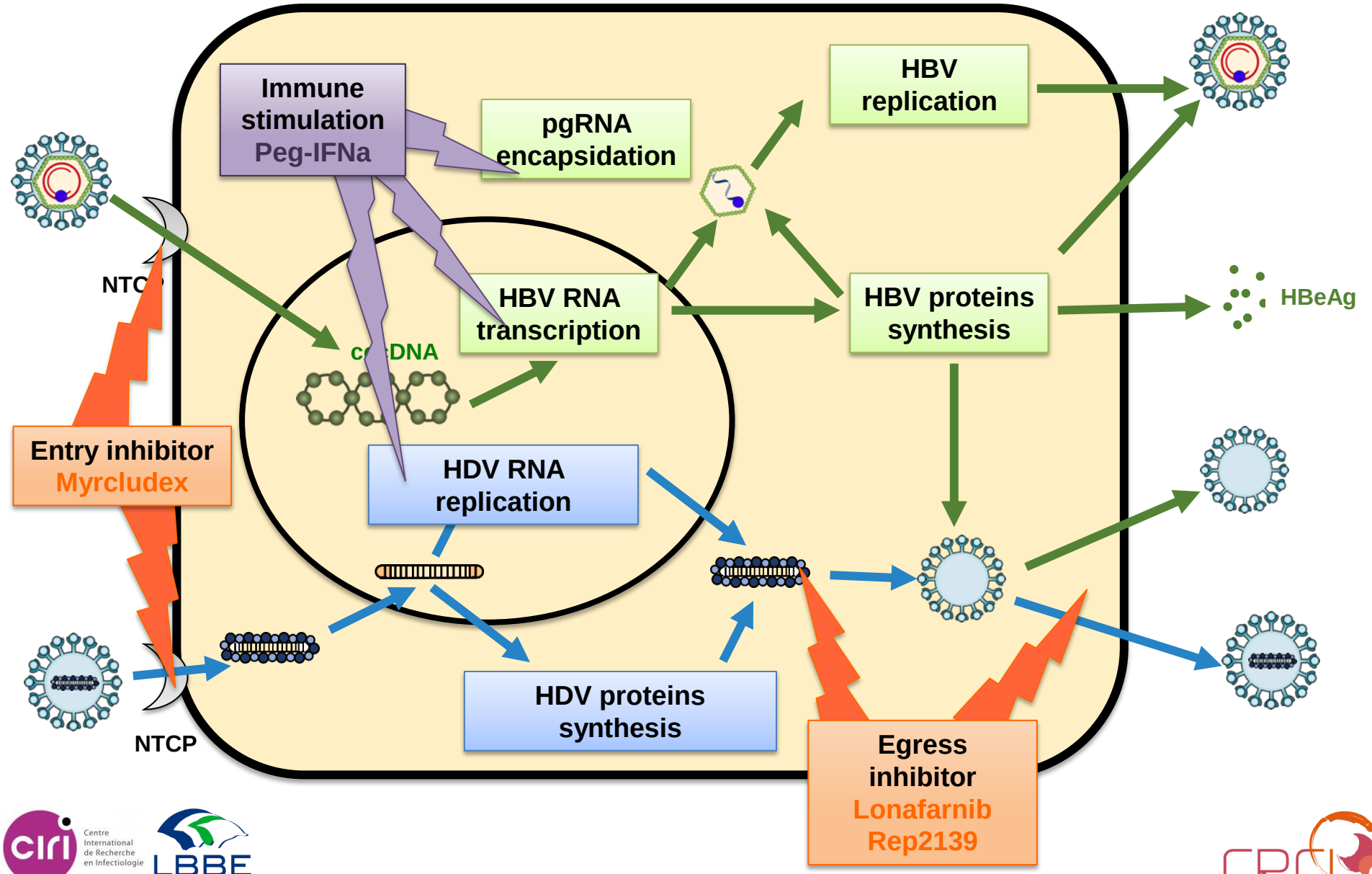
- ✓ ≈ 5-10 % of HBV chronically infected patients → 15-20 millions worldwide, but under diagnosed !
- ✓ High rate of fulminant hepatitis
- ✓ No efficient txt (Peg-IFNa <10 % efficacy)
- ✓ Cirrhosis : ≈ 70 % in 10 years
- ✓ HCC incidence: >> 5 %/year
- ✓ Very poor survival after 10 years (< 50%)

Abbas et al. World J. Gastroenterol. 2010; Schweitzer A et al. Lancet 2015; Wranke & Wedemeyer Curr. Opi. Virol. 2016

Schematic overview of HBV and HDV life cycles

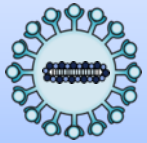


Existing and investigational anti-HDV drugs



HDV/HBV co-infections medical research challenges

HDV



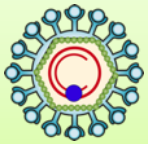
Hepato/liver

HBV/HDV increased pathogenicity (→HCC)

IFN-α treatment failure

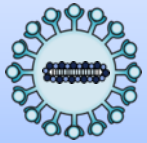
New anti-HDV therapies

HBV



HDV/HBV co-infections medical research challenges

HDV



Hepato/liver

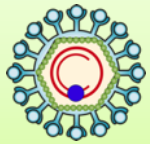
HBV/HDV increased pathogenicity (→HCC)

IFN-α treatment failure

New anti-HDV therapies

Better understanding of HDV biology

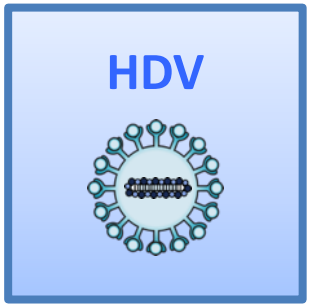
HBV



Four axes of research proposed in a long-term program

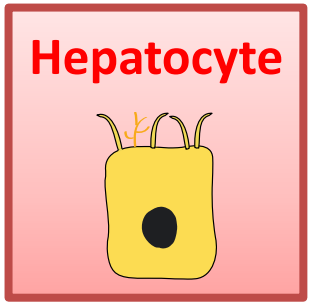
- ✓ **Axis#1: Eco-infectiology of HDV-related viruses in wild animal/human contact areas (Cosset/Pontier)**
- ✓ **Axis#2: Co-evolution of HDV and HBV genomes in human population in link with pathogenic geographical particularities (Deny/Combet/Scholtès)**
- ✓ **Axis#3: Interplay between HDV/HBV and liver (innate) immunity → relevance for immune-driven pathogenesis (Lucifora/Durantel)**
- ✓ **Axis#4: Genetic, epigenetic, and molecular patterns of HDV-driven carcinogenesis (Levrero/ Zoulim)**

Axis#3: Interplay between HDV/HBV and innate immunity



How and which kind of responses are induced by HDV ?

How the hepatocyte response influences HDV replication ?



more insight into

HBV/HDV increased pathogenicity

IFN-α treatment failure

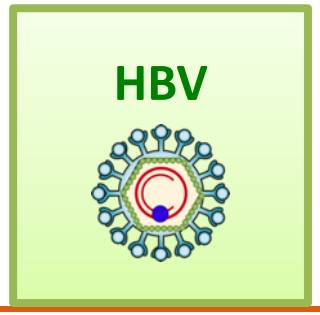
IFN-driven pathogenesis

How HDV interferes with HBV replication ?

How the hepatocyte response induced by HDV influences HBV replication ?

GILEAD

Private funding



anrs France REcherche Nord & sud Sida-hiv Hépatites
Agence autonome de l'Inserm

Academic funding

Infect-ERA

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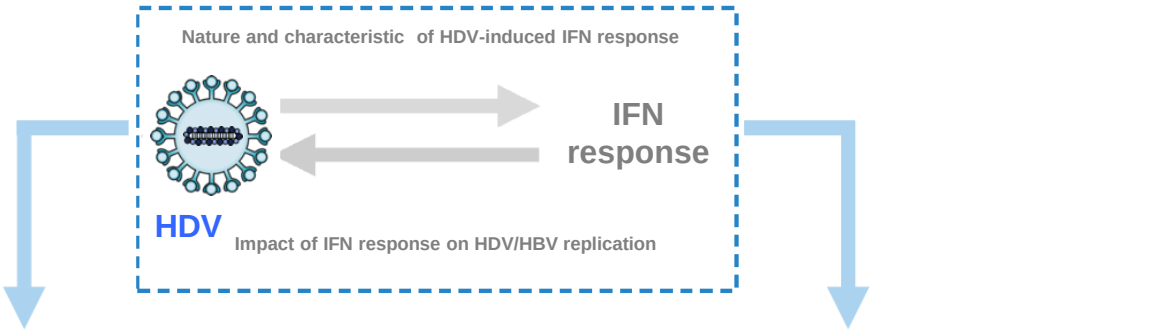
Axis#3: Main relevance of research

- ✓ As in the case of HIV or HCV, a **sustained viro-induced IFN response** has incidence on responsiveness to IFN treatment and pathogenesis
- ✓ **Peg-IFNa is not efficient** against HDV: understanding of underlying mechanism should help improving IFN based therapy and develop novel immune therapeutic options
- ✓ **Uncontrolled viro-induced inflammation** in liver is a main driver of pathogenesis
- ✓ **HDV/HBV co-infections** represent the **worst situation** with respect to development of HCC.
- ✓ 50% of patients if left untreated and/or without care die after 10 year! **Faster than any other liver infections!**
- ✓ Few research done in this area worldwide, because **HDV infections are neglected**



Define the role of HDV-driven sustained IFN response on pathogenesis

Restore permisiveness of HDV to Peg-IFNa in co-infected pateints OR develop novel immune-stimulatory strategies

Axis#4: Genetic, epigenetic, and molecular patterns of HDV-driven HCC

HBV-driven carcinogenesis: genetic and epigenetic patterns

- Complex mutational landscape
- Epigenetic changes
- Insertional mutagenesis
- Viral proteins (HBx, HBc)
- Co-morbidities (aflatoxin B1)

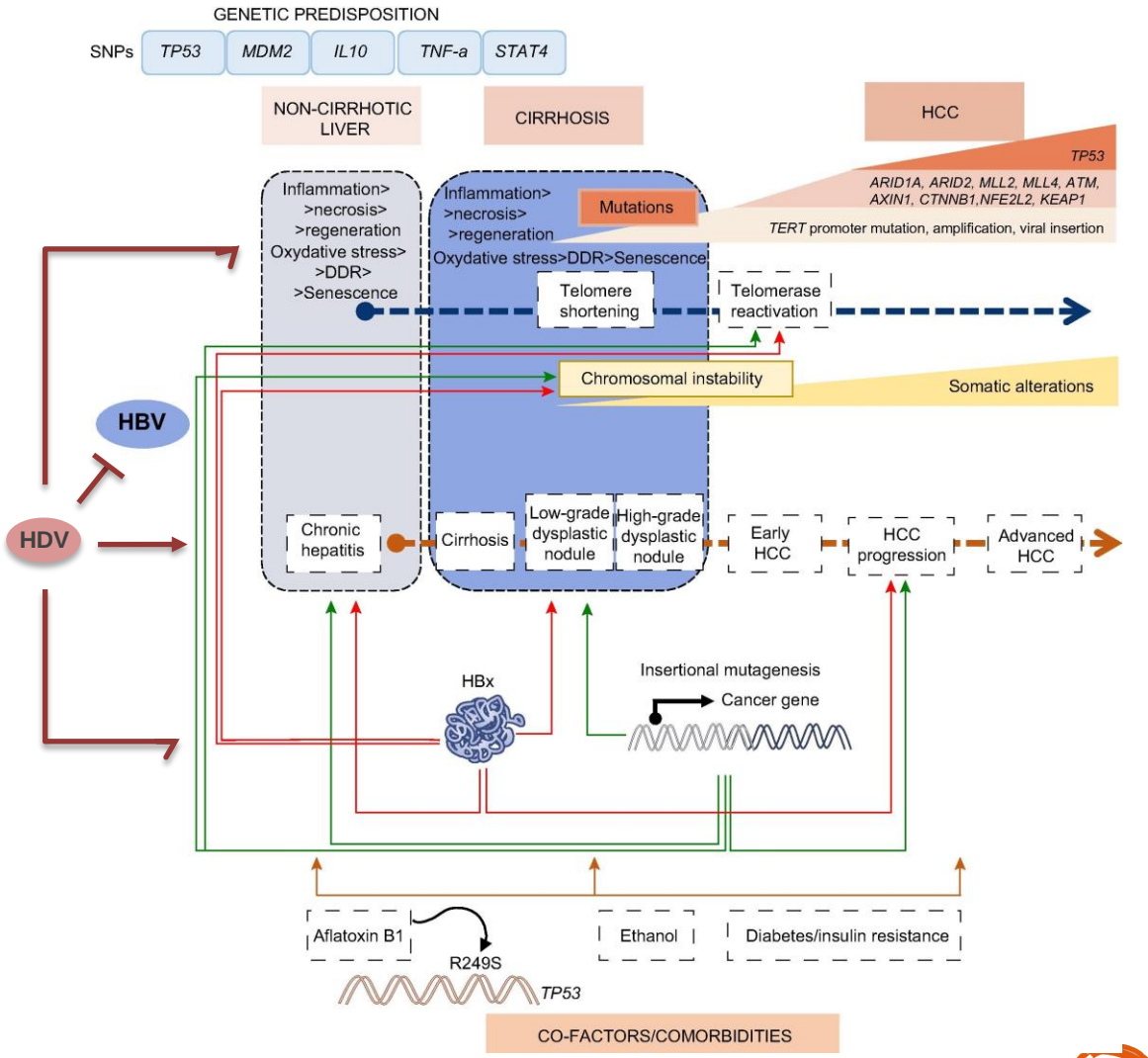
- HBV replication correlates with HCC

- Sustained HBV viral suppression
  - no inflammation
  - « regression of cirrhosis»
    but HCC risk is unchanged

- HBV / HDV co-infection:
  - more rapid and disease progression
  - increase HCC risk

- L-HDAg
  - high inflammation
  - NF-kB signaling
  - increased oxidative stress
  - ER stress

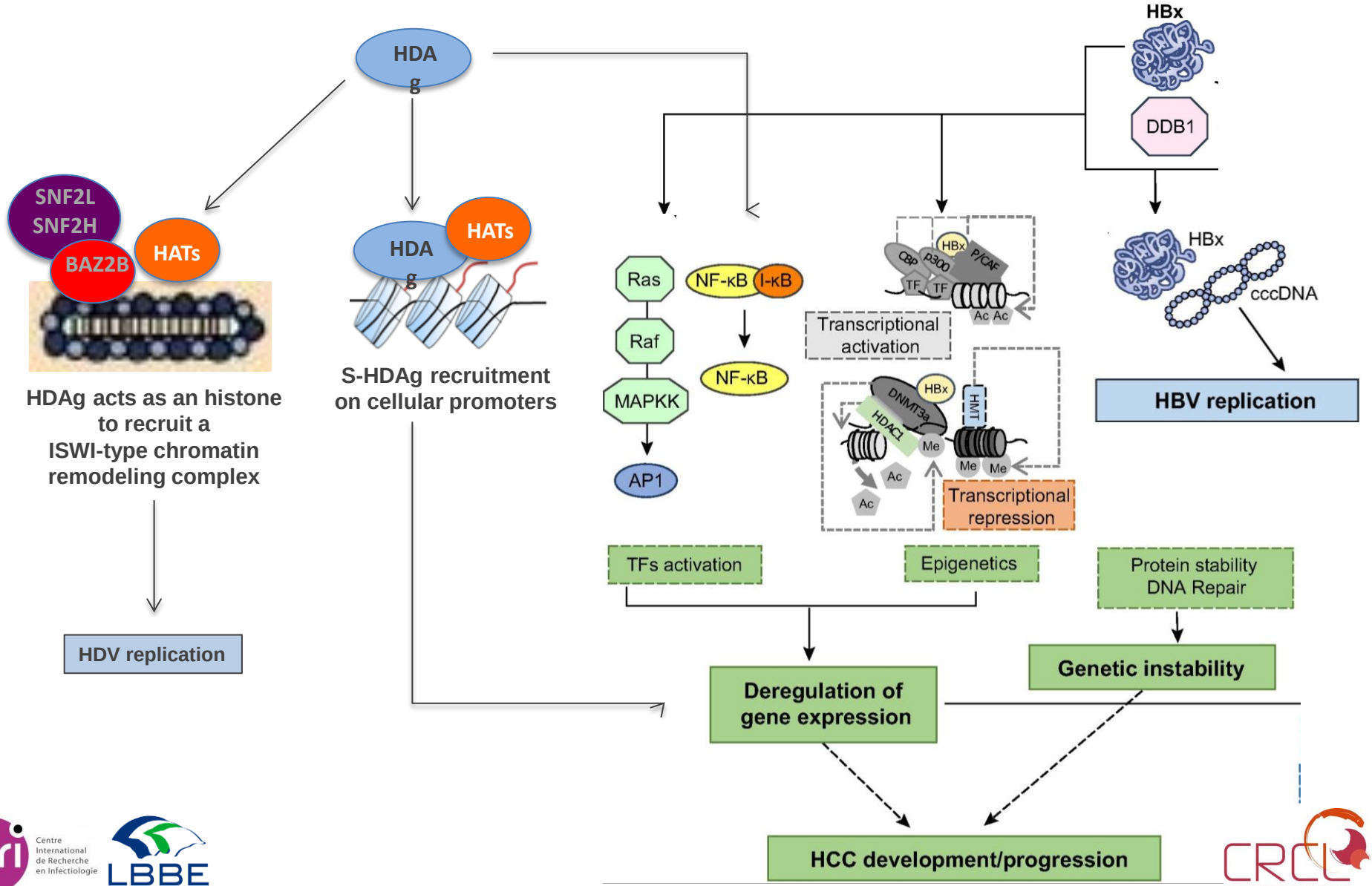
- S.HDAg
  - increased expression of “clusterin”
    - Hyperacetylation
    - epigenetic mechanism



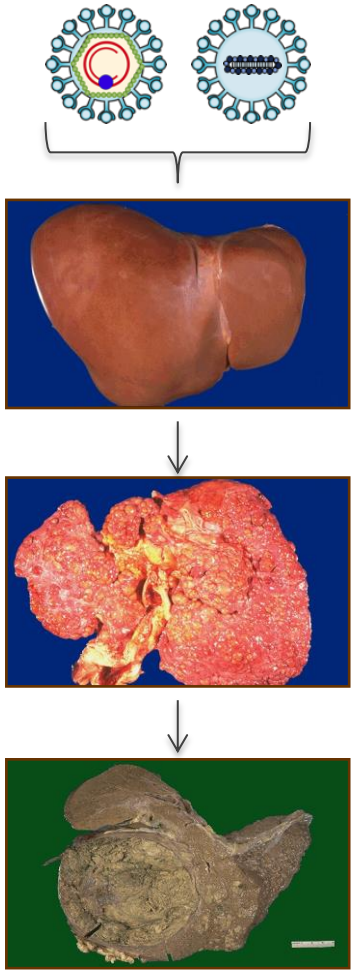
Levrero & Zucmann-Rossi, J. Hepatol 2016

Axis#4: Genetic, epigenetic, and molecular patterns of HDV-driven HCC

HDAg and HBx double role in viral replication and hepatocarcinogenesis



Axis#4: Genetic, epigenetic, and molecular patterns of HDV-driven HCC



blood, biopsies,
T/PT tissues from:

- Lyon / France
- Italy
- Turkey

- ✓ **Genetic landscape of HDV/HBV tumors**
  [Exome sequencing, MiSeq amplicon panels]
  (Collab. with Dr Jessica Zucmann-Rossi, Paris)
- ✓ **HDV/HBV tumors profiling**
  [RNAseq, miRseq]
  compare with infected cells, pre-neolastic lesions
  (Collab. with Dr Francesco Negro, Geneva)
- ✓ **Epigenetic profiles in HDV/HBV tumors**
  [HDAg ChIPseq, histone PTMs ChIPseq]
  cross analysis with HBx and HBc available and ongoing ChIPseq
- ✓ **HDAg interaction with cellular RNAs (mRNA, lncRNAs)**
  [HDAg RIPseq]
- ✓ **Validation and functional experiments in *in vitro/in vivo* HDVHBV models**
  [PHH, liver-humanized mice, transgenic mice…]

Prognostic and treatment allocation signatures

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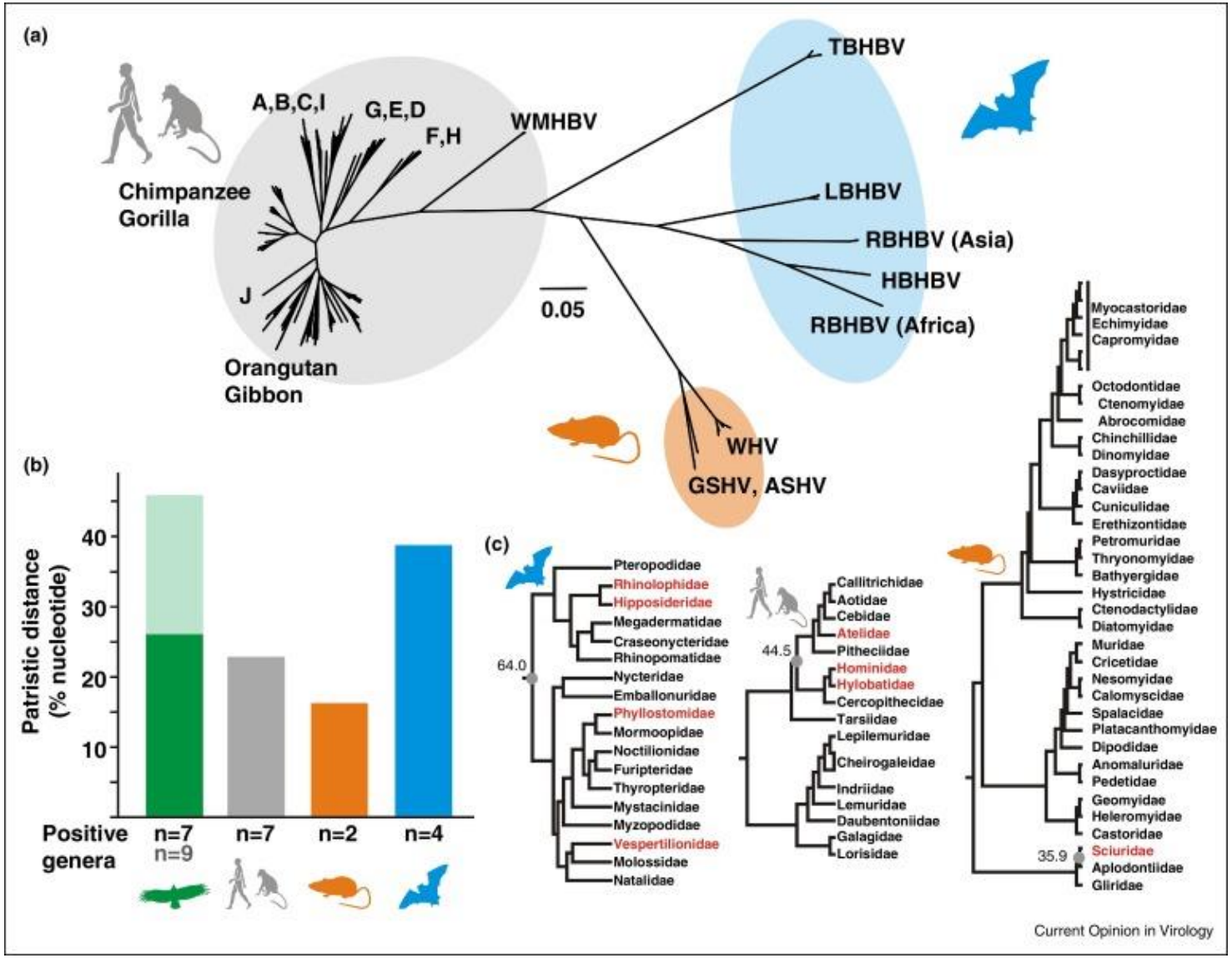
Axis#1: Eco-infectiology of HDV-related viruses



Rasche et al., Curr. Opi. Virol. 2016

Axis#1: Eco-infectiology of HDV-related viruses

Axis#1: Eco-infectiology of HDV-related viruses

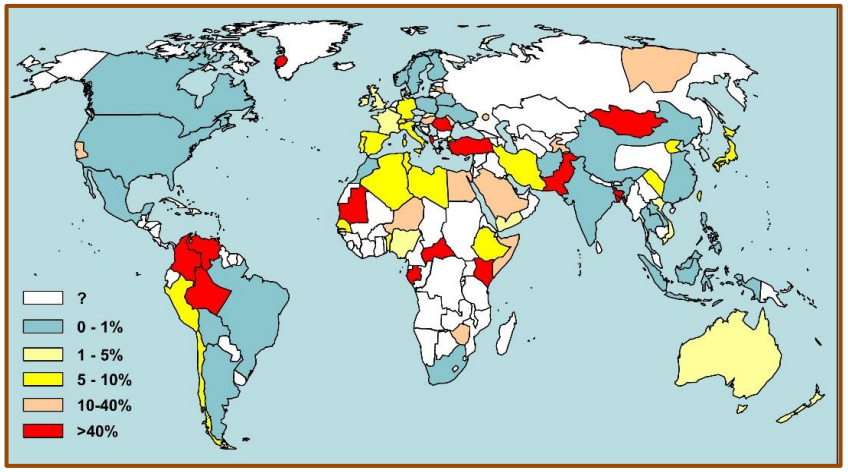
- ✓ **Define transmission and ecology of HDV-like viruses in their natural bat hosts (field studies in metropolitan France, French Guiana, Tunisia and Gabon)**
  - ✓ PCR assays as well as serological longitudinal studies in caves (aim: ca. 10,000 samples – faeces, serum)
  - ✓ Identification of bat species via high-throughput sequencing (>40 bat species)
  - ✓ Identification and quantification of HDV-like viruses by sequencing/qPCR
  - ✓ Phylogeny of HDV-like viruses

- ✓ **Determine intrinsic barriers and pathways to viral cross-species adaptation**
  - ✓ Understand the role of the HDV-like viruses' envelope glycoproteins found in bats in the potential crossing of the interspecies barrier
  - ✓ Characterize the cell entry molecular determinants of HDV-like viruses compared to the human HDV/HBV
  - ✓ Study HDV-like viruses in bat liver chimeric mice

- ✓ **Develop an integrative approach linking infectiology and eco-evolutionary biology to emphasize constraints shaping virus circulation between species**
  - ✓ Develop probabilistic models
  - ✓ Complete bat species phylogeny
  - ✓ Understand bat species ecology

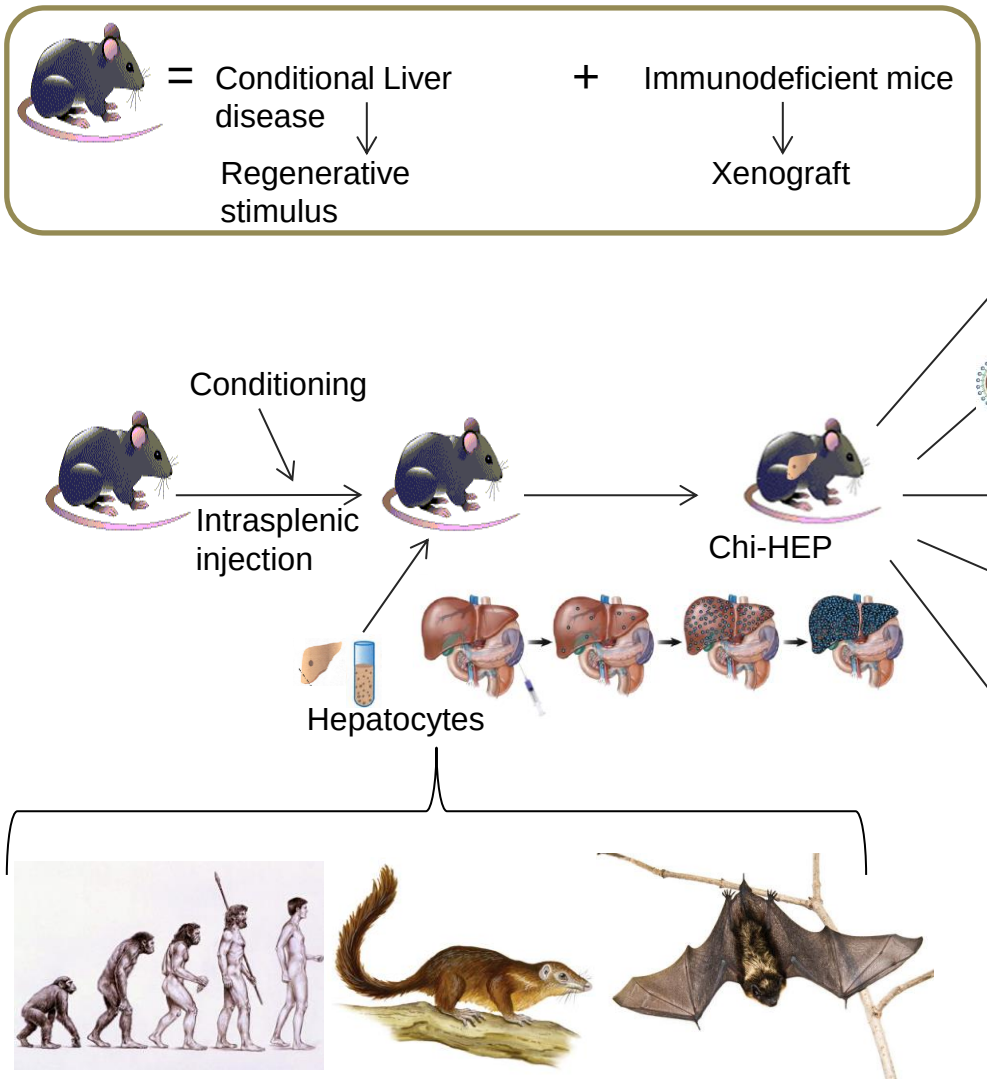
Axis#2: Co-evolution of HDV/HBV genomes in human pop.

- ✓ **Define several well annotated cohorts (n=20) of HDV/HBV co-infected patients (genotypically-paired with corresponding HBV-infected patients) from various geographical origins (France/Lyon, Italy, South America, Turkey, Eastern Europe…)**



- ✓ **Use NGS approaches to sequence full length HDV/HBV genomes in cross-sectional conditions**
- ✓ **Analyze co-evolution of genomes using mathematical/bioinformatic means in link with clinically determined pathogenesis**
- ✓ **Identify association of HDV/HBV genotypes/subtypes correlating with pathogenesis**
- ✓ **Additional markers to be found in same cohorts in link with axis#3 and 4**
- ✓ **Co-infections in liver humanized mouse model and *in vitro* to study early/late impact on hepatocyte physiology in link with pathogenesis/HCC**

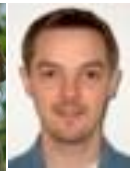
Axis#1 and 2: Chimeric mouse platform already set, to study cross-species strains and virus co-evolution



Model of implementation









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Labex ECOFECT
Dynamiques éco-évolutives des maladies infectieuses

DEVweCAN Développement Cancer et Thérapies ciblées

Boot funding 2017-2019 ?

anrs France REcherche Nord & sud Sida-hiv Hépatites
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