France
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Hépatites

Agence autonome de l'Inserm

PARIS HEPATITIS CONFERENCE
January 13-14, 2014

Translational Research in viral hepatitis: the French ANRS experience

Pr. Jean-François DELFRAISSY
Director of ANRS
Internal Medicine Department
CHU Bicêtre – Paris XI - ANRS

- **Public Agency aimed at funding researches in all areas relevant to HIV/AIDS and hepatitis**
- **Annual budget of research: 46 Millions euros**

  (total equivalent to 130 millions euros with salaries)
- **Supported by :**
  - **Ministry of Research +++**
  - **Ministry of Health**
  - **Ministry of Foreign Affairs**
  - **Institutional partners : INSERM, CNRS, Pasteur Institute, IRD, Universities**

% Distribution of funds according to research area 2013 (46 M €)

- Basic Science HIV 14 %
- Vaccine HIV-HCV 12 %
- Clinical trials and cohorts (HIV) 26 %
- Epidemiology/socio-behavioral science 8 %
- Resources limited countries (HIV-Hepatitis) 21 %*
- Hepatitis B and C 19 %

GLOBAL HEPATITIS 24% : 11,5 M €

GLOBAL BASIC SCIENCE : 39% : 17 M €

*Not including external contributions (EDCTP, Total foundation, Gates Foundation…)

ANRS «Scientific performance »

- 550 publications/year
- Approximately 50% of publications have IF > 5.
- 1% of ANRS publications are in the 10 top international journals
- 6,2% of ANRS publications (HIV/AIDS and hepatitis) are in the 1% group of excellence (number of citations), higher than the national average in the field of biology/health
- France is ranked 2nd or 3rd international position in the field of HIV and 2nd in the field of hepatitis

- Hepatitis : 140 publications/year : Clinical 40, Basic and Translational 100

AGENDA of the ANRS : 2011-2013
5 main priorities for HEPATITIS

1. Molecular mechanisms involved in cell-virus interactions
2. Relationships between fibrosis, inflammation and viral replication
3. Strategic evaluation of new molecules anti HCV (Cohorte, coinfections...)
4. New tools for prevention
5. HBV Cure (2014 and….)

The Coordinated Action (AC) in the field of viral hepatitis

Basic Research:

-AC 29: Entry and assembly mechanisms of hepatitis viruses in their target cells (J Dubuisson)

-AC 33: Resistance to antiretrovirals of Hepatitis B and C viruses (JM Pawlotsky and F Zoulim)

Clinical Research:

-AC 7: Cohorts (G Chêne)

-AC 24: Clinical trials in viral hepatitis infection (M Bourliere)

-AC 5/24: Clinical trials in HIV-Hepatitis co-infection (M Bourliere and JM Molina)

FUNDING : Two calls each year, with peer review

BASIC AND TRANSLATIONAL RESEARCH

- INSERM-CNRS Research Units Network

-Mechanisms of entry and **assembly**

- Humanized mouse models

- Genome wide association study

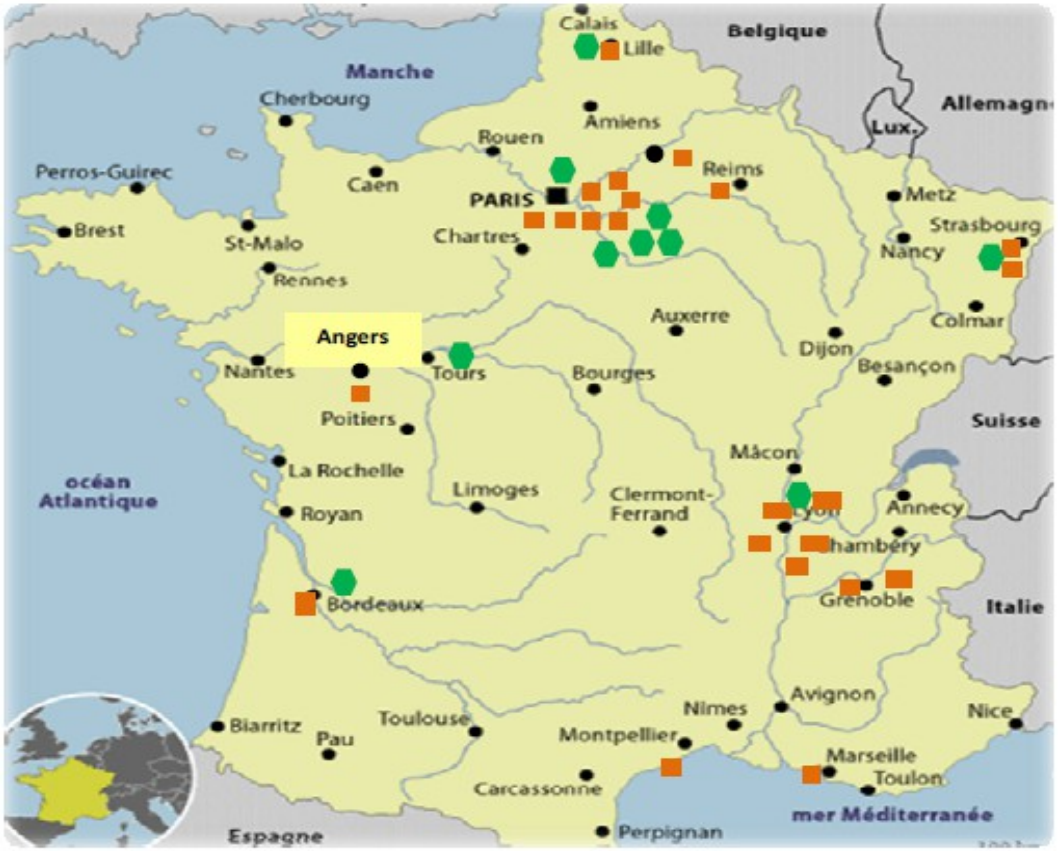
- Ultra-deep pyrosequencing

- From Cohorts to basic science

- HBV Cure

- New tools for testing and prevention

INSERM, CNRS, UNITS, INVESTIGATED IN HEPATITIS FIELD RESEARCH



CNRS, INSERM, UMR

INSERM

Coordinated action 29 (AC29)
« Mechanisms of entry and assembly of hepatitis viruses »

- **Characterization of the role of HCV cellular entry factors**

- **EGF receptor and HRas signaling play a major role in HCV entry**
- *Lupberger et al., Nat Med, 2011; Zona et al., Cell Host Microbe, 2013*

- **The LDL receptor is involved in a non-productive entry pathway**
- *Albecka et al., Hepatology, 2012*

- **Only highly mobile CD81 molecules are involved in HCV entry**
- *Potel et al., Cell Microbiol, 2013*

- **SRB1 receptor plays a role at different steps of HCV entry**
- *Dao Thi et al., JBC, 2012; Zahid et al., Hepatology, 2013*

- **Characterization of HCV envelope glycoproteins**

- **Identification of crosstalks between HCV envelope glycoproteins**
- *Albecka et al., J Virol, 2011; Maurin et al., JBC, 2012; Wahid et al., J Virol, 2013*

- **HCV envelope glycoproteins form large oligomers on the virion**

Coordinated action 29 (AC29)
« Mechanisms of entry and assembly of hepatitis viruses »

- **Neutralizing antibodies & escape from neutralization**

- **Structure of HCV neutralizing epitope in interaction with a Mab**
- *Krey et al., PLoS Pathog, 2013*

- **A « glycan shield » protects neutralizing epitopes in HCV**
- *Helle et al., J Virol 2010; Anjum et al., JID, 2013*

- **Escape from antibody neutralization by altering interaction with HCV entry factors**
- *Fafi-Kremer et al., J Exp Med, 2010; Fofana et al., Gastroenterology, 2012*

- **Vaccines inducing neutralizing antibodies**

- **Chimeric subviral HBV particles containing HCV envelope proteins**
- *Beaumont et al., Hepatology, 2013*

- **Retroviral pseudotypes containing HCV envelope proteins**

ANRS Consortium “Humanized mouse models for the study of viral hepatitis“

Goal : merge several French projects of development of an animal model for HCV and HBV infection into one single project

- Objectives
  - To improve human hepatocyte repopulation in the different mouse models (uPA and FAH)
  - To make a side by side comparison of the two mice models for HCV and HBV infection
  - To create new models or to optimize existing models that harbor human immune cells and human hepatocytes (HIS/HUHEP mice)
  - To investigate HBV and HCV infection in such HIS/HUHEP models
  - To select and share the best model(s) to investigate human immune responses and virus-induced and immune-mediated liver disease in HIS/HUHEP mice infected with human hepatotropic viruses.

France REcherche Nord & sud Sida-hiv Hépatites

Agence autonome de l'Inserm

ANRS consortium

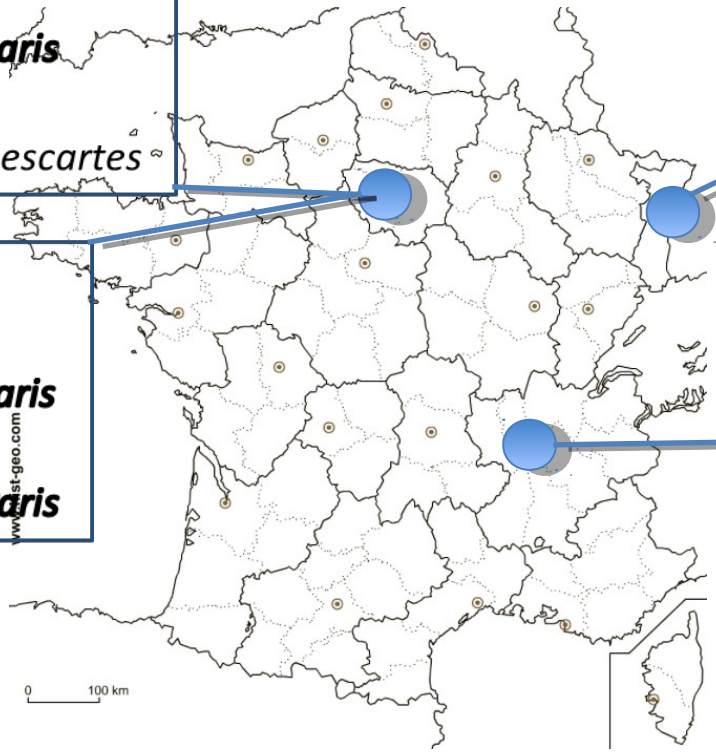
« Humanized mouse models for studying viral hepatitis »

Partner 1:
J Di Santo
H Strick-Marchand
Inserm U668, Institut Pasteur, ***Paris***
D Kremsdorf
Inserm U845, Université Paris-Descartes

Partner 3:
T Baumert
E Robinet
L Mailly
Inserm U1110, ***Strasbourg***

Partner 4:
S Garcia
CNRS U1961, Institut Pasteur, ***Paris***
ML Michel
Inserm U845, Institut Pasteur, ***Paris***

Partner 2:
FL Cosset
E Verhoeyen
Inserm U758, ENS, ***Lyon***



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ANRS consortium

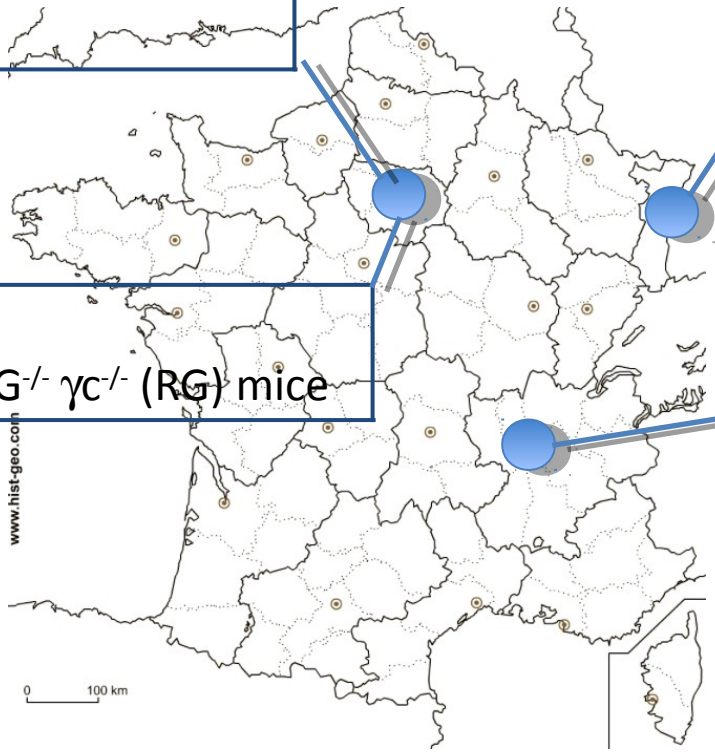
« Humanized mouse models for studying viral hepatitis »

Partner 1:
BALB/c Rag2$^{-/-}$ IL$_2$Rγc$^{-/-}$ NOD.*sirpa* uPA mice (BRGSuPA)

Partner 3:
uPA/SCID-bg mice

Partner 4:
Humanized HLA transgenic RAG$^{-/-}$ γc$^{-/-}$ (RG) mice

Partner 2:
Fah$^{-/-}$ Rag2$^{-/-}$ Rγc$^{-/-}$ mice (FRG)



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Agence autonome de l'Inserm

ANRS consortium

« Humanized mouse models for studying viral hepatitis »

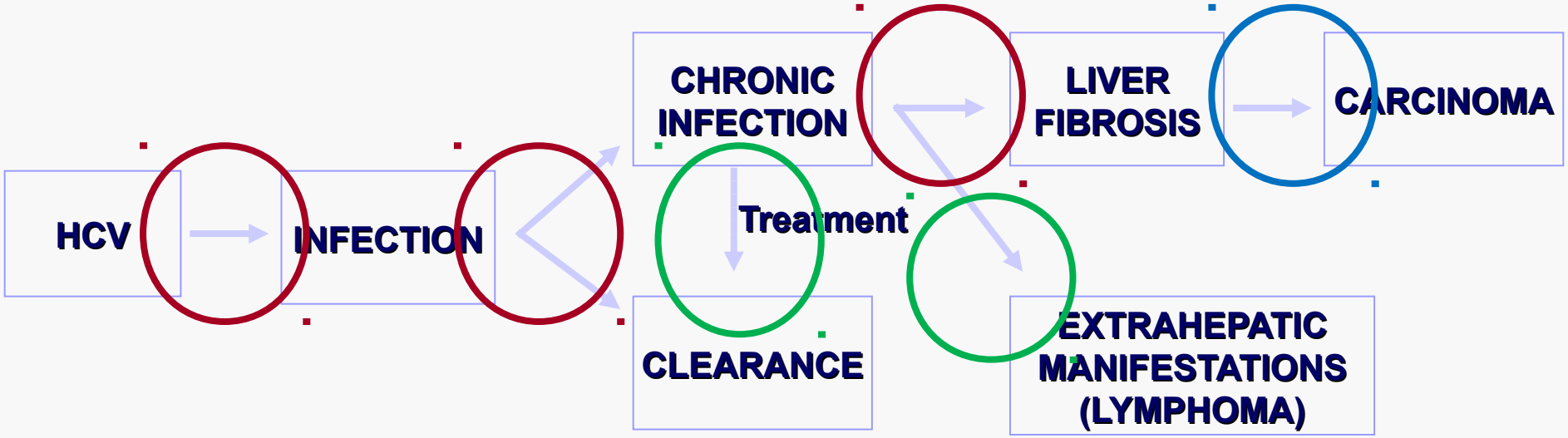
Ongoing

- Comparison of primary human hepatocytes (PHH) engraftment and liver repopulation in the different HUHEP mice models.
- Comparison of immune response to HBsAg immunization in the different HIS mice models.
- Comparison of permissivity to HBV and HCV infection of the different HUHEP mice models using selected common virus stocks.

Financial support

700,000 € on a 3-year basis, starting on January 2013.

Human Genetics of HCV-related phenotypes:The ANRS studies
Investigated phenotypes: Genome-wide association studies



Investigated phenotypes

- Completed and ongoing: Liver fibrosis, spontaneous clearance, and infection
- Accepted and started in 2013: Lymphoma and response to treatment by triple therapy including protease inhibitors
- To be submitted: Hepatocarcinoma

L. Abel et al.

Liver fibrosis

GWAS completed:

- **467 French patients genotyped with Illumina array HumanCNV370 and follow-up studies with 192 SNPs genotyped in 320 patients**
- **Combined with Swiss and other cohorts (total of > 2000 patients)**
- **Identification of 3 SNPs related to apoptosis pathway**

Genome-Wide Association Study Identifies Variants Associated With Progression of Liver Fibrosis From HCV Infection

ETIENNE PATIN,[*,‡] ZOLTÁN KUTALIK,[§,‖] JULIEN GUERGNON,[¶] STÉPHANIE BIBERT,[#] BERTRAND NALPAS,[‡,**] EMMANUELLE JOUANGUY,[*,‡,‡‡] MONA MUNTEANU,[§§] LAURENCE BOUSQUET,[‡,**] LAURENT ARGIRO,[‖‖] PHILIPPE HALFON,[¶¶] ANNE BOLAND,[##] BEAT MÜLLHAUPT,[***] DAVID SEMELA,[‡‡‡] JEAN-FRANÇOIS DUFOUR,[§§§] MARKUS H. HEIM,[‖‖‖] DARIUS MORADPOUR,[¶¶¶] ANDREAS CERNY,[###] RAFFAELE MALINVERNI,[****] HANS HIRSCH,[‡‡‡] GLADYS MARTINETTI,[§§§§] VIJAYAPRAKASH SUPPIAH,[‖‖‖‖,¶¶¶¶] GRAEME STEWART,[¶¶¶¶] DAVID R. BOOTH,[¶¶¶¶] JACOB GEORGE,[‖‖‖‖] JEAN-LAURENT CASANOVA,[*,‡,‡‡] CHRISTIAN BRÉCHOT,[####] CHARLES M. RICE,[*****] ANDREW H. TALAL,[‡‡‡‡] IRA M. JACOBSON,[‡‡‡‡] MARC BOURLIÈRE,[§§§§§] IOANNIS THEODOROU,[¶] THIERRY POYNARD,[‖‖‖‖‖] FRANCESCO NEGRO,[¶¶¶¶¶] STANISLAS POL,[‡,**] PIERRE-YVES BOCHUD,[#] and LAURENT ABEL,[*,‡,‡‡] on behalf of the Swiss Hepatitis C Cohort Study Group, the International Hepatitis C Genetics Consortium, and the French ANRS HC EP 26 Genoscan Study Group

GASTROENTEROLOGY 2012;143:1244–1252

Ongoing projects:

To investigate the role of rare variants by exome sequencing of a subsample of 100 French patients with extreme phenotypes: 50 with fast progression to severe liver fibrosis and 50 without liver fibrosis after a long time of chronic HCV infection (>20 years)

To investigate the main signals found in the first study in monoinfected patients in patients co-infected with HIV (the HEPAVIH cohort)

L. Abel et al.

Spontaneous clearance and Infection (Egypt and Europe)

Candidate gene study in 380 Egyptian subjects (with chronic infection, spontaneous clearance, or non infected) Confirmation of the role of IL28B variants in Egypt, and reduction of the IL28B chromosomal region of interest. - PLoS One . 2012. 143(5):1244-52.

Analysis of *IL28B* Variants in an Egyptian Population Defines the 20 Kilobases Minimal Region Involved in Spontaneous Clearance of Hepatitis C Virus

Vincent Pedergnana[1,2], Mohamed Abdel-Hamid[3,4], Julien Guergnon[5], Amira Mohsen[6], Lénaïg Le Fouler[7], Ioannis Theodorou[5], Mostafa Kamal Mohamed[6], Arnaud Fontanet[7,8], Sabine Plancoulaine[1,2], Laurent Abel[1,2,9]*

PLoS one June 2012 | Volume 7 | Issue 6 | e38578

Projects:

1) To search for the role of common variants in HCV infection (HCV non infected vs. HCV infected subjects) both in Egypt and in available European cohorts who have GWAS data;
2) to investigate the role of rare variants in spontaneous clearance by exome sequencing of a subsample of 40 subjects with spontaneous clearance and 40 with chronic infection

L. Abel et al.

HCV-related lymphoma

Ongoing project (with O. Hermine): GWAS in 65 HCV patients who developed a lymphoma. Use as controls the HCV patients previously genotyped in the liver fibrosis study.

Response to treatment by new protease inhibitors

Ongoing project in the context of the CUPIC cohort: Subjects with available DNA (~350 patients) treated by triple therapy including new protease inhibitors (boceprevir or telaprevir). Phenotypes of interest: 1) response to treatment; 2) adverse effects (anemia). Ongoing projects:

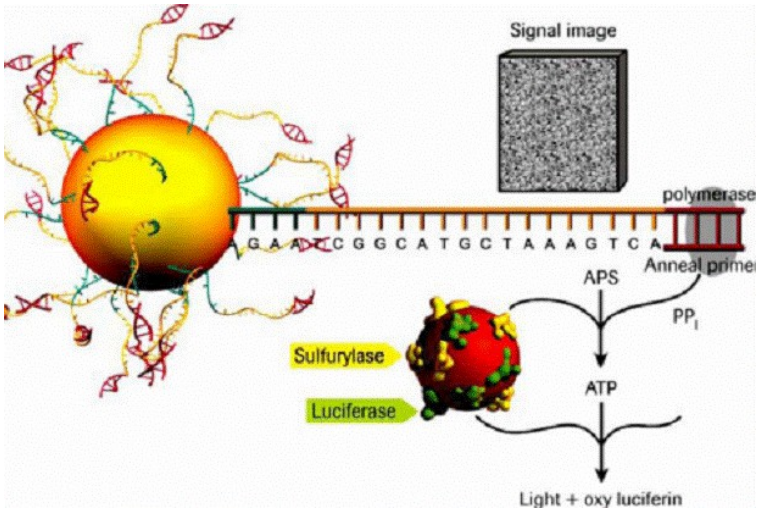
-Role of IL28B and ITPA variants (analysis is ongoing)

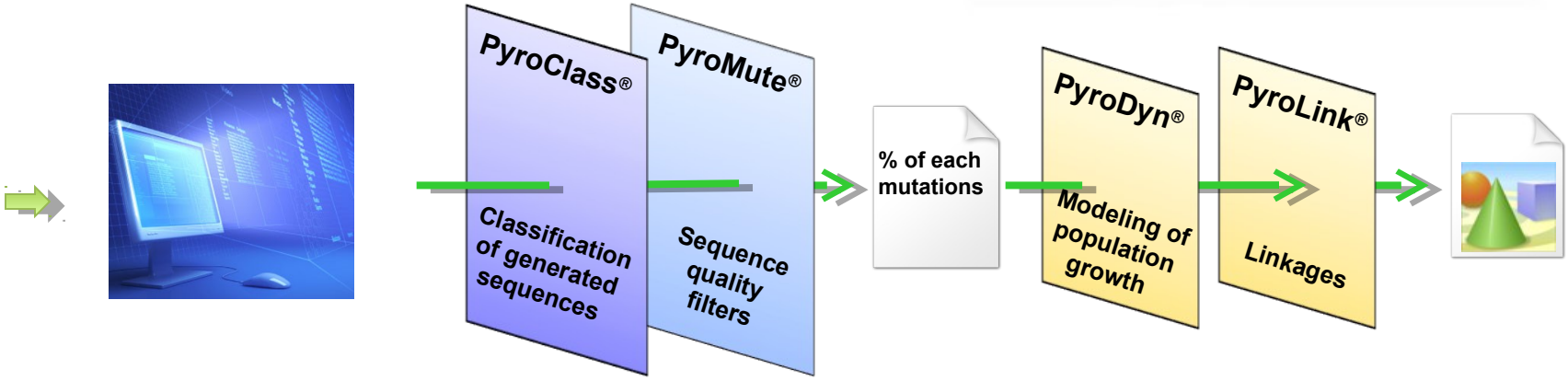
-Genome-wide investigation by exome sequencing of the most extreme phenotypes (those who have not cleared despite favorable IL28B genotype vs those who have cleared despite unfavorable IL28B genotype)

HCV Hepatocarcinoma

Project to be submitted: to investigate the role of rare variants by exome sequencing of a in a sample of ~ 50 patients with fast development of hepatocarcinoma. Exomes that will be done in project on liver fibrosis could be used as controls. Samples from France (CIRVIR cohort) and Egypt.

Assessment of Antiviral Drug Resistance by Ultra-Deep Pyrosequencing (UDPS)

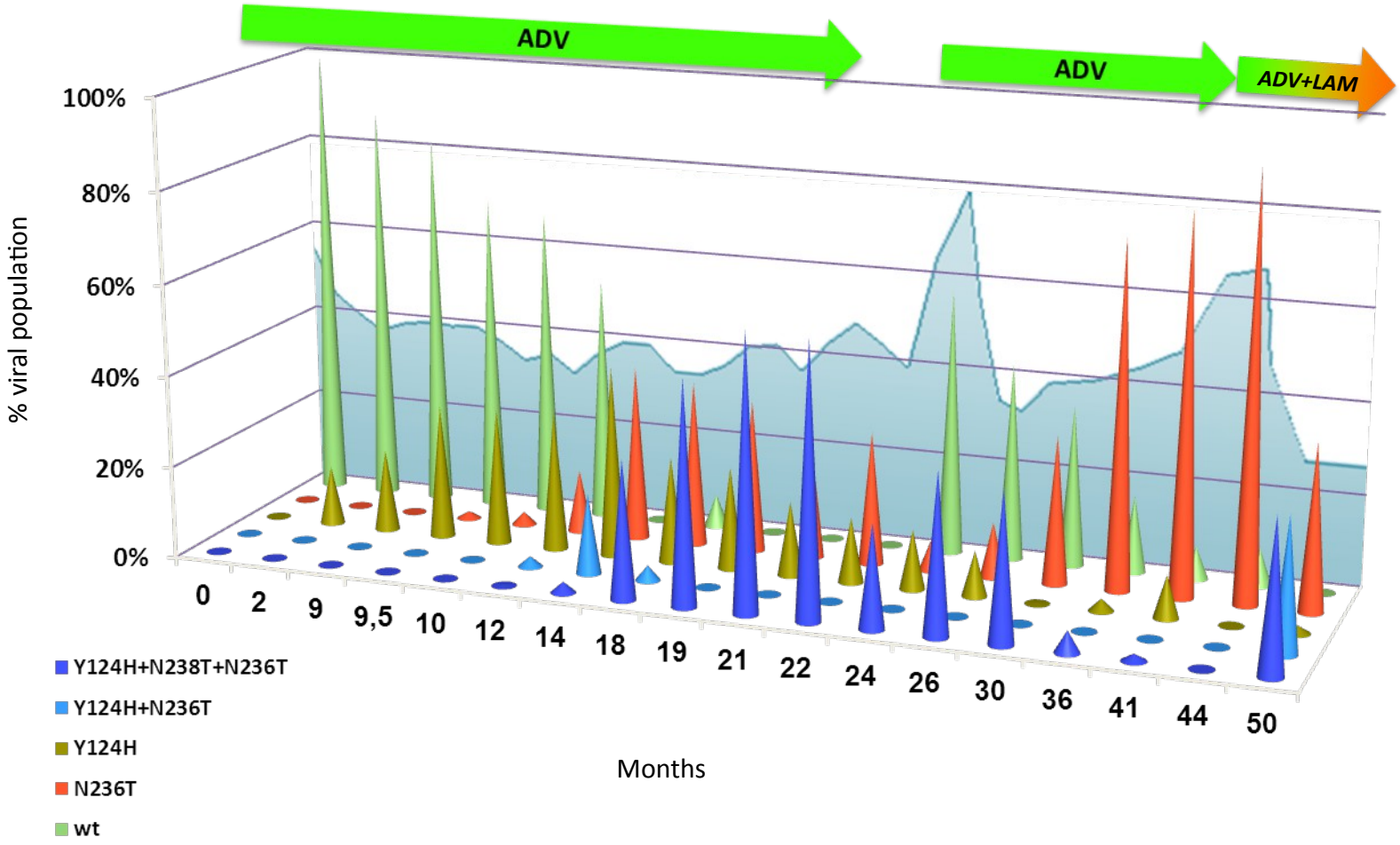




Pyropack® software

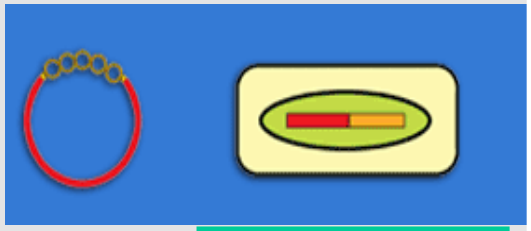
Rodriguez C, Chevaliez S, et al., Hepatology 2013;58(3):890-901.

Dynamics of HBV resistance to adefovir by UDPS (ANRS funded)



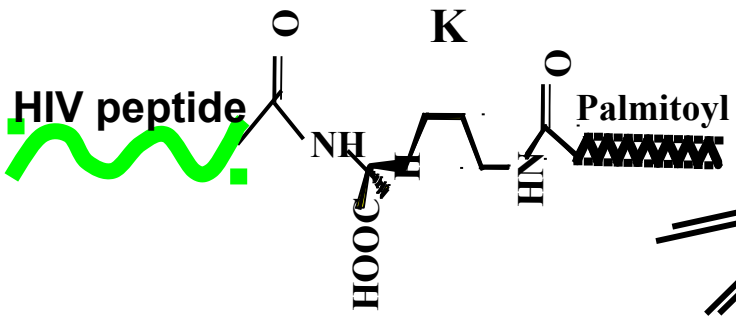
Rodriguez C, Chevaliez S, et al., Hepatology 2013;58(3):890-901.

Development of an epitope-based vaccine approach that could be employed in prime-boost strategy combined with recombinant viruses aimed to elicit strong, long lasting, polyepitopic T-cell responses focused on highly conserved epitopes

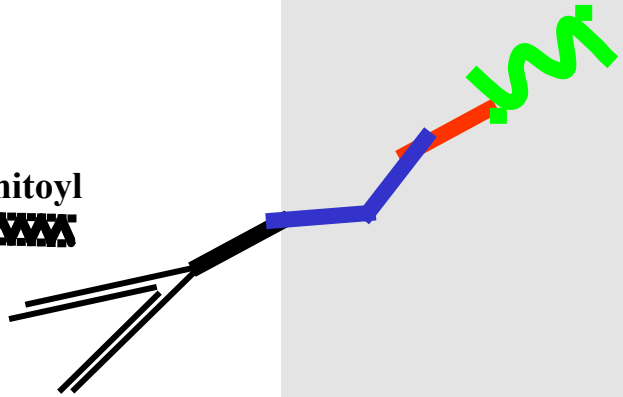


ADN

NYVAC (B/C)
MVA (B)



LIPO5



Peptide-anti-DC

Early 2014 : Translational Research / Clinical Trials

Mono Infection:

HVB Mono Infection (180 patients)

ANRS HB 06 PEGAN

HCV Mono Infection (1690 patients)

ANRS HC 06 LIPIOCIS
ANRS HC 13 LYMPHO-C
ANRS HC 15 NRFI
ANRS HC 19 FIBROSAR
ANRS HC 23 COAT
ANRS HC 29 BOCEPRETRANSPLANT
ANRS HC 32 QUATTRO
ANRS HC EP 26 GENOSCAN, ANRS HC EP 28
ANRS HC EP 29 AIXPLORER
ANRS ELASTIQUE

HIV Co-Infection

HBV-HIV (856 patients)

ANRS HB01 EMVIPEG
ANRS HB03 VIHVAC-B
ANRS HB04 B-BOOST
ANRS HB EP 03 CISOVAC

HCV-HIV (381 patients)

ANRS HC20 ETOC,
ANRS HC 26 TELAPREVIH
ANRS HC 27 BOCEPREVIH
ANRS HC 30 QUADRIH
ANRS HC 31 SOFTRIH

SAFETY OF TELAPREVIR OR BOCEPREVIR IN COMBINATION WITH PEGINTERFERON ALFA/RIBAVIRIN, IN CIRRHOTIC NON RESPONDERS FIRST RESULTS OF THE FRENCH EARLY ACCESS PROGRAM (ANRS CO20-CUPIC)

C Hézode[1], C Dorival[2], F Zoulim[3], T Poynard[4], P Mathurin[5], S Pol[6], D Larrey[7], P Cacoub[4], V de Ledinghen[8], M Bourlière[9], PH Bernard[10], G Riachi[11], Y Barthe[2], H Fontaine[6], F Carrat[2], JP Bronowicki[12] for the CUPIC study group (ANRS CO 20)

Hôpital Henri Mondor, Créteil[1], UMR-S 707, Paris[2], INSERM U871, Lyon[3], Hôpital de la Pitié-Salpêtrière, Paris[4], Hôpital Claude Huriez, Lille[5], Hôpital Cochin, Paris[6], Hôpital Saint-Eloi, Montpellier[7], Hôpital Haut-Lévèque, Pessac[8], Fondation Hôpital Saint Joseph, Marseille[9], Hôpital Saint André, Bordeaux[10], Hôpital Charles Nicolle, Rouen[11], Hôpital de Brabois, Nancy[12], France

CUPIC: Major conclusions

- In this large cohort of compensated cirrhotic patients, the safety profile of TVR or BOC in triple combination was poor as compared with phase III trials (Increased rates of SAEs and more difficult management of anemia) but associated with high rates of on-treatment virologic response
- Risk / benefit ratio should be assessed in cirrhotic experienced patients with platelets count <100,000/mm^3 and albumin level <35 g/L. These patients should be treated on a case by case basis due to high risk to develop severe complications
- However, cirrhotic experienced patients without predictors of severe complications should be treated but cautiously and carefully monitored

ANRS CO 20 CUPIC : Translational Research

Study	Title
Mod-CUPIC	Modelling of initial viral kinetics of HCV infected patients treated with novel association of antiretrovirals including PEG interferon/ribavirin and telaprevir or boceprevir
Late viral escape	Characterization of HCV resistance to specific protease inhibitors of HCV in treatment failure within the CUPIC cohort.
Ultra- deep pyrosequencing	Study of the dynamics of HCV viral variants resistant to protease inhibitors during therapy by associating ultra deep pyrosequencing and mathematical modelling
GWAS	Identification of genetic polymorphisms and plasma biomarkers predictif of the response and secondary effects of the tritherapy PEG-IFN/RBV + NS3
ApoH (sub-study of GWAS)	Identification of genetic polymorphisms and plasma biomarkers predictif of the response and secondary effects of the tritherapy PEG-IFN/RBV + NS3
GenoFibroTest-CUPIC /CUPIC-3D	Establishment of a 3B biomarker of the response to HCV therapy

French Early Access Program

ATU

The Temporary Authorization for Use (ATU) is an early access program for medicinal products which have undergone full clinical development and are waiting for marketing authorization by the French Health Products Safety Agency (Afssaps)

CUPIC / or X ?

Compassionate Use of Protease Inhibitors in viral C Cirrhosis

National multicenter observatory in the setting of the ATU

Promoter: ANRS

Aim: to prospectively collect clinical data and biological specimen

Cohorte ANRS CO22 HEPATHER

Therapeutic option for hepatitis B/or C: a French nationwide cohort study

Unique French national cohort (F. Carrat, S. Pol)

- ***25 000 patients (10 000 HBV-infected*** and ***15 000 HCV-infected patients)*** from the French Hepatology centers.
- ***a structured network of expert clinical centers*** and ***labs*** associated with ***multidisciplinary experts***.
- To provide a ***research platform*** to address key questions (disease progression and complications) and ***to evaluate safety and efficacy of antiviral treatments in the real-life, post marketing experience, French compassionate use program(ATU)***
- a ***public/private partnership from the inception of the project.***

End 2013 : 23 Clinical Centers - 7300 patients included

anRS Agence nationale de recherches sur le sida et les hépatites virales | Agence autonome de l'Inserm |

Instituts thématiques Inserm Institut national de la santé et de la recherche médicale

AFEF Association Française pour l'Etude du Foie UPMC Paris Universitas

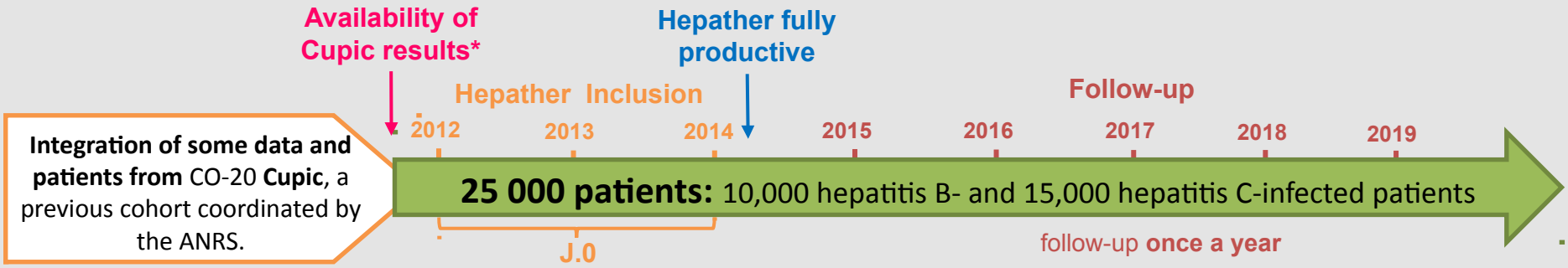
Investissements d'avenir

Cupic → Hepather project (ANRS CO22)

✓Main scientific objective of Hepather (ANRS CO 22)

To improve quality and effectiveness of medical cares in taking into account the new treatment options and host characteristics by integrating genetic, pharmacogenomics, clinical, environmental and behavioral data in a large number of patients.

✓Data collection and Hepather timeline:



- ***Database:*** **Clinical, biological, treatment, environmental** and **social** data integrated through **clinician and self-reporting** (80% of historical patient data would be imported from existing medical files)

- ***Biobank:*** **Blood, serum and urine sampling.**

- ***Database:*** **Combination of systematic follow-up visit by using the various different national administrative databases** and sources to ascertain death and other health-related information (RNIPP, CépiDc, SNIIR-AM, Plastico).

- ***Biobank:*** **Sampling follow-up is not systematic** but will be **motivated by a specific research project or a medical event** such as disease progression or the initiation of a new treatment.

Challenges of Viral Hepatitis Research

PAST

- Epidemiology of hepatitis virus infections
- Description of the diseases
- Development of cell culture and animal models
- Unraveling of the HCV lifecycle
- Identification of therapeutic targets

PRESENT

- Prevalence and incidence of viral hepatitis well established
- Clinical manifestations and natural history well understood
- Therapeutic revolution
  - HBV: most patient can control infection
  - HCV: therapeutic revolution with >90% cure rates (DAA)

Challenges of Viral Hepatitis Research
Remaining key questions

- Development of new methods and strategies for broad screening and access to care (North and South)
- Post-approval clinical research on new antiviral drugs
  - Care practices
  - Long-term safety
  - Treatment failures and resistance++
- Unraveling and preventing the mechanisms of liver carcinogenesis in viral hepatitis patients with active, controlled or cured infection
- New curative approaches for HBV infection
- Vaccine development in HCV
  - Prophylactic?
  - Protective ++ (resolution of infection when it occurs)
- Treatment for prevention in HCV ?
- Clinical description, epidemiology and therapy of Hepatitis E infections.

HBV CURE
Why a need for new antiviral targets for hepatitis B ?

- Current antivirals achieve viral suppression in the majority of patients (in western countries)
- Issues with antiviral drug resistance in developing countries (use of low barrier to resistance antivirals)
- The rate of cccDNA / HBsAg loss remains very low
- Life-long therapy is needed in the majority of the cases
- HBsAg clearance is associated with a lower risk of HCC development
- Treatment with finite duration if:
  - cccDNA control or loss
  - HBsAg loss

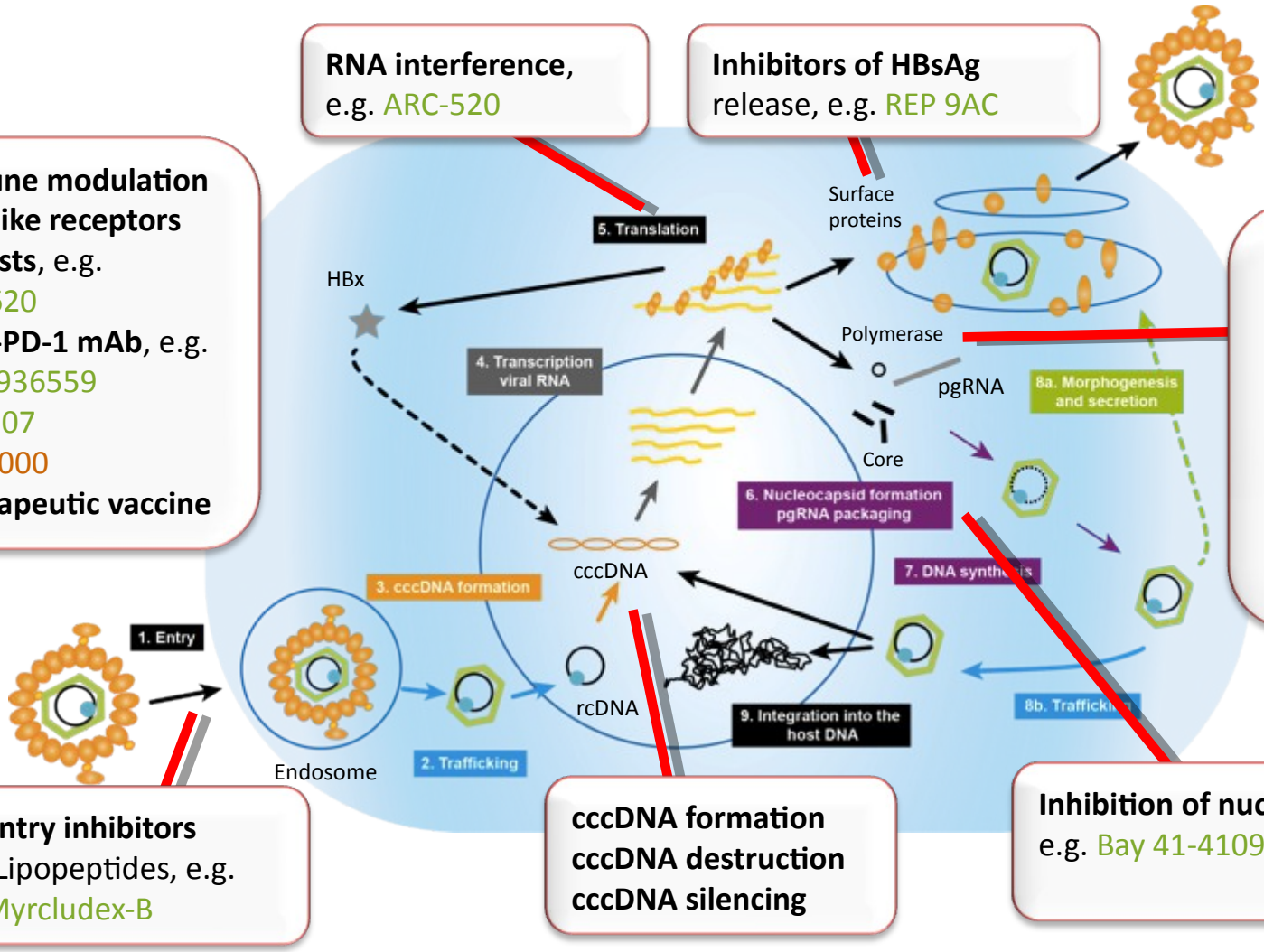
Zoulim, Antiviral Research 2012

HBV : Future directions: new targets

RNA interference, e.g. ARC-520

Inhibitors of HBsAg release, e.g. REP 9AC

Immune modulation
- **Toll-like receptors agonists**, e.g. GS-9620
- **Anti-PD-1 mAb**, e.g. BMS-936559
- CYT107
- GI13000
- **Therapeutic vaccine**



Polymerase inhibitors
- Nucleoside analogues, e.g. emtricitabine, amdoxovir, MIV-210
- Non-nucleoside, e.g. LB80380

Entry inhibitors
- Lipopeptides, e.g. Myrcludex-B

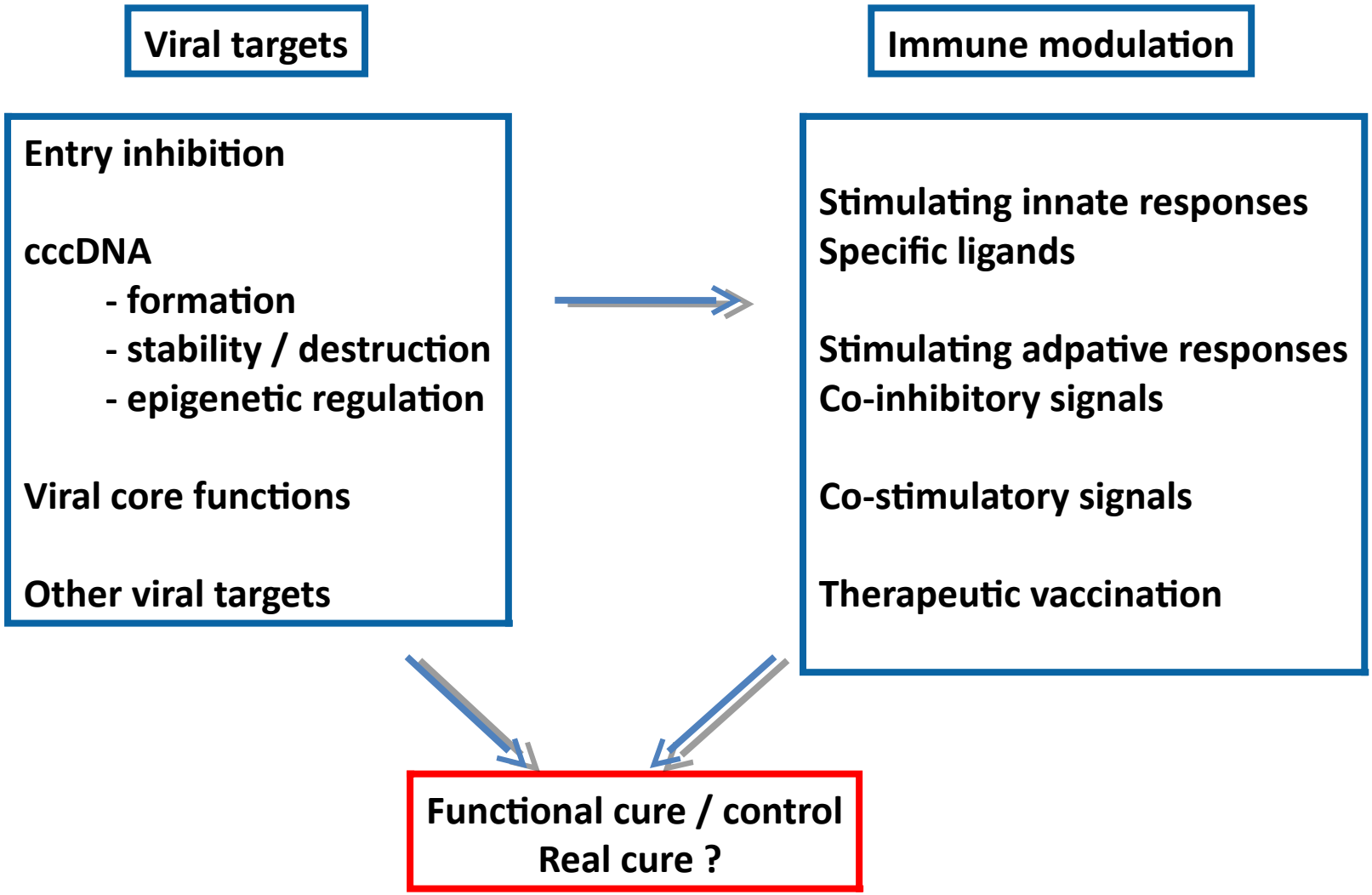
cccDNA formation
cccDNA destruction
cccDNA silencing

Inhibition of nucleocapsid assembly, e.g. Bay 41-4109, NVR1221

Development stage: **preclinical**, **clinical**

Zoulim F, et al. Antiviral Res 2012;96(2):256–9; HBF Drug Watch, Available at: http://www.hepb.org/professionals/hbf_drug_watch.htm. Accessed 15 Aug 2013. Zoulim F, et al. Gastroenterology 2013;144:1342–4.

HBV CURE :The concept of combination therapy



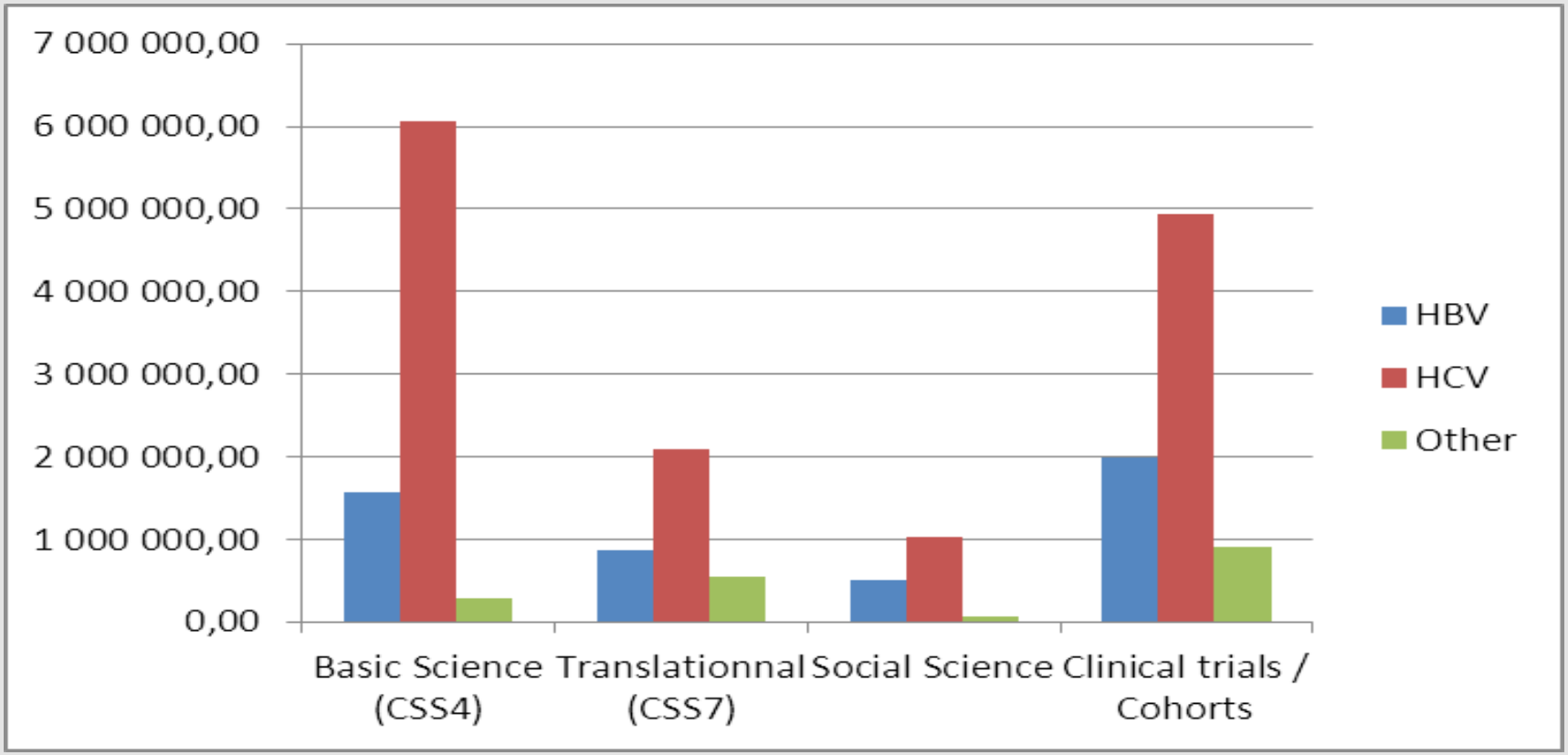
HBV CURE / ANRS : 2014 and…

- **Right time to promote HBV research**
  - Clinical need for new treatment concepts
  - Better understanding of the viral life cycle
  - New study models and expertise to evaluate new approaches

- **ANRS assets**
  - Longstanding experience in basic, translational and clinical research (HIV, HCV, HBV)
  - Support of basic science projects and animal models
  - Clinical cohorts for translational research (HEPATHER)
  - Support of clinical trials
  - Partnership with pharma industry

- **Expected clinical benefits of an HBV cure**
  - Shorter treatment duration / Decreased treatment cost
  - Possibility to consider earlier treatment intervention
  - Improvement of clinical outcome / Prevention of hepatocellular carcinoma

ANRS Funding 2010 -2011-2012
HCV+++ > HBV



HCV : Where we are: limitations

Insufficient screening

Undiagnosed Pool
2.5 million

Diagnosed Pool
0.9 million

Undiagnosed Pool
1.8 million

Diagnosed Pool
1.6 million

P. Marcellin 2013

Strategies to improve:
- Screening
- Linkage to care

The proportion of patients aware of their HCV infection

-In France = 57%

-In Italy = 45%

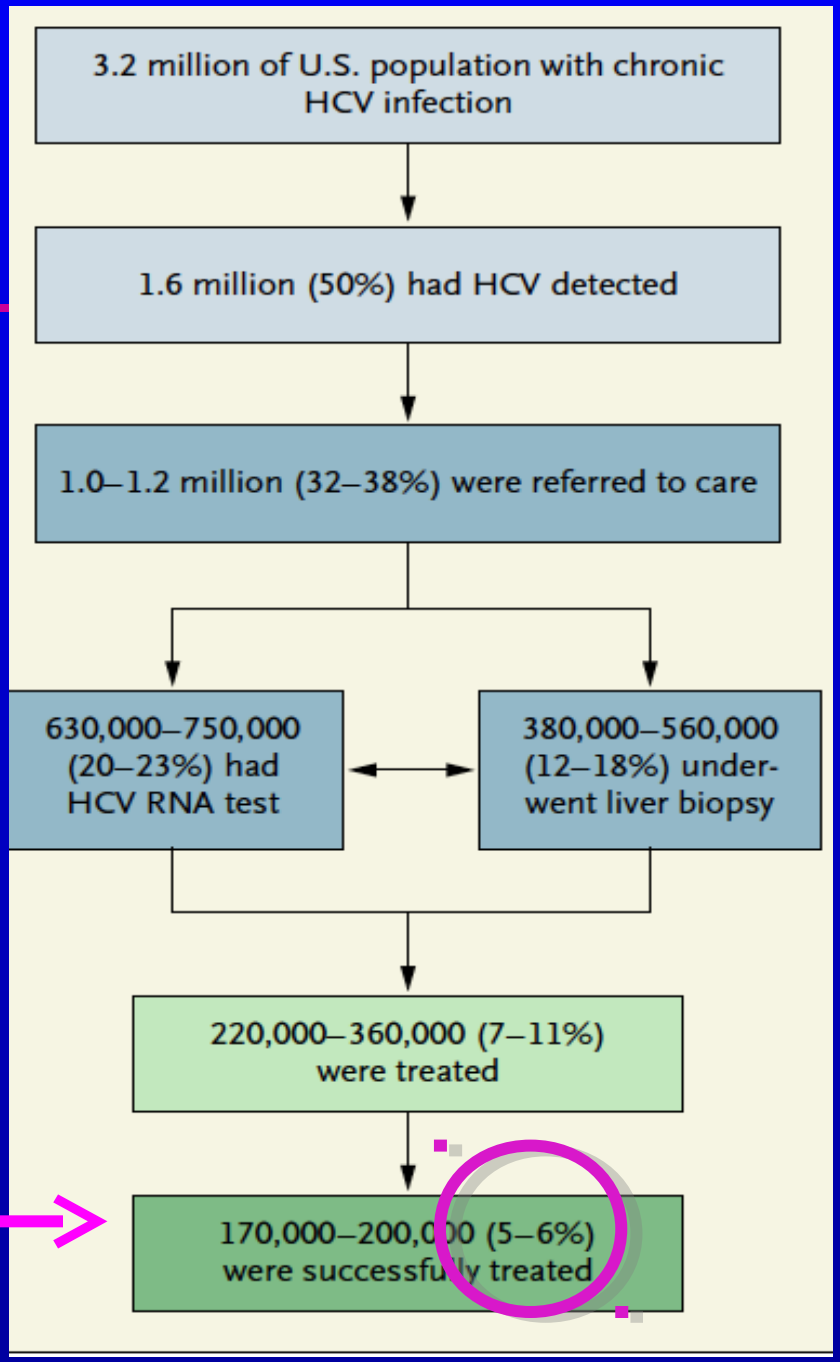
-In Spain = 35%

Meffre J Med Virol 2010

Varela Med Clin 2010

Mariano Dig Liver Dis 2009

The proportion of patients successfuly treated in the US



Holmberg SD, et al. NEJM 2013;368(20):1859-61.

Two key questions

1- How research data can contribute to political decisions ?

2- How best to utilize the resources that are available ?

- In low-income countries
- In high-income countries

Resource constraints
in particular in the time of crisis;

The Cost-effectiveness Research Agenda

- Earlier versus deferred initiation of Trt (ANRS)
  - Delaying treatment until the arrival of new DAAs (at least for mild and moderate fibrosis stages)?
- Strategies to monitor efficacy
- TasP in high risk populations (IDUs)(ANRS)
- Treatment in special populations

- HCV testing (patients unaware of their status)(ANRS)
- Linkage to care interventions
- Loss to follow-up interventions
- Adherence interventions

In high-income countries
&
In low-income countries

Effectiveness and cost-effectiveness of immediate vs. delayed treatment of HCV-infected patients in a country with limited resources: the case of Egypt (ANRS 12215)

- In Egypt, treating HCV-infected patients with Peg-Inf and ribavirin* at fibrosis stages F2 to F4 is effective and cost-effective.
- If we consider that affordable triple therapies with new DAAs will be available in three years, treatment for patients at stage F1 should be delayed.

*Peg-Inf and ribavirin cost for 48 weeks= 2000 US$ US

Obach et al. Clin Infect Dis 2014 (In press)

25th Anniversary of ANRS – November 26, 2013

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

25 anrs

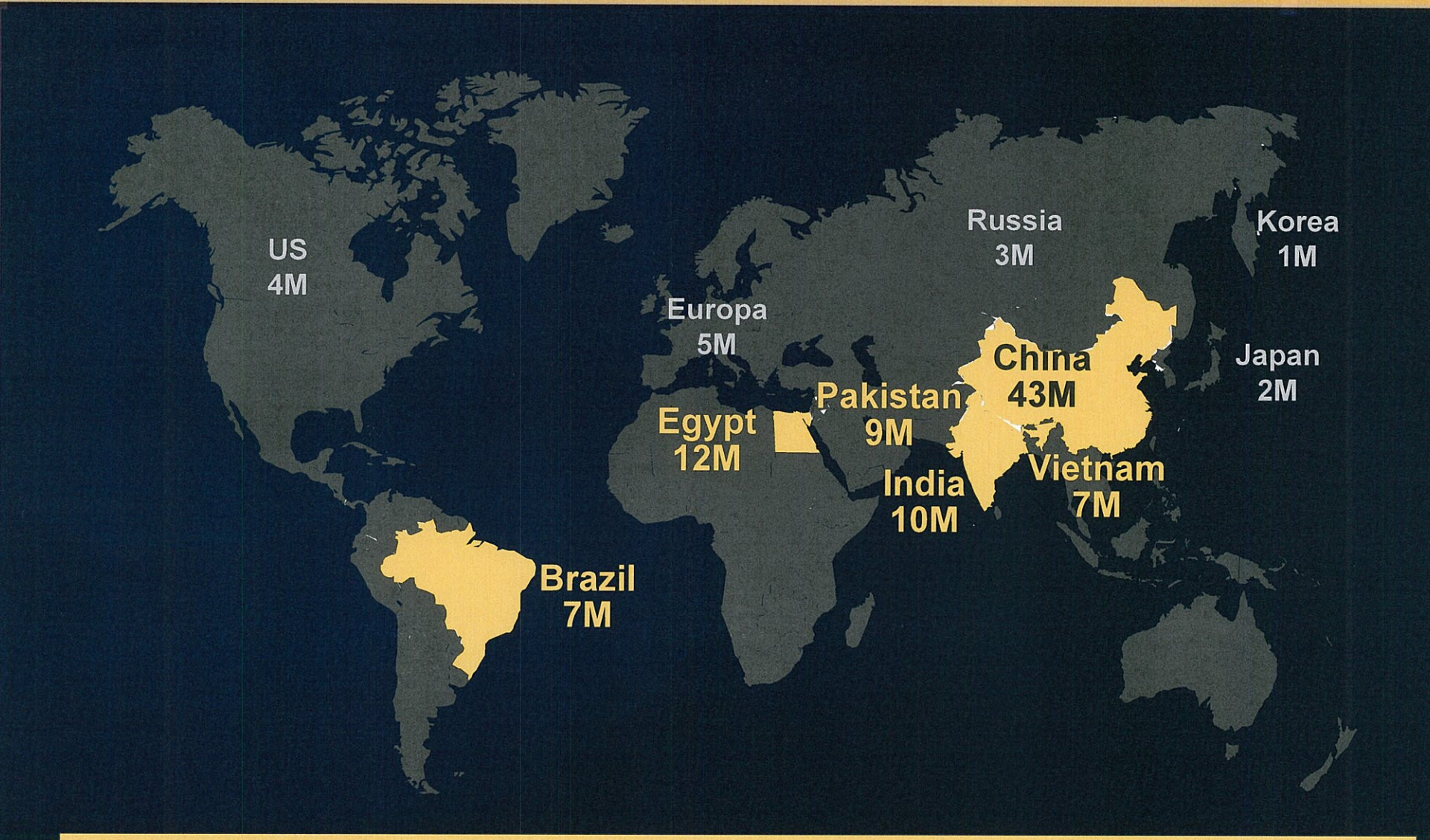
ACKNOWLEDGMENTS

- Clinical and research teams, AFEF
- Chairs of Coordinated working groups
- ANRS staff
- Patients NGOs, more specifically CHV, SOS Hépatites, TRT5
- INSERM, Institut Pasteur, IRD, CNRS, Universities
- Pharmaceutical Industry
- INCA, ANSM, HAS
- Patients

Research priorities (SHS)

- Hepatitis B and C among drug users and inmates,
- Strategies to improve the uptake of hepatitis B vaccination in France,
- Screening strategies of HCV and HBV chronic infection, including rapid tests,
- Modeling of HCV transmission among drug users.

Where we are: limitations



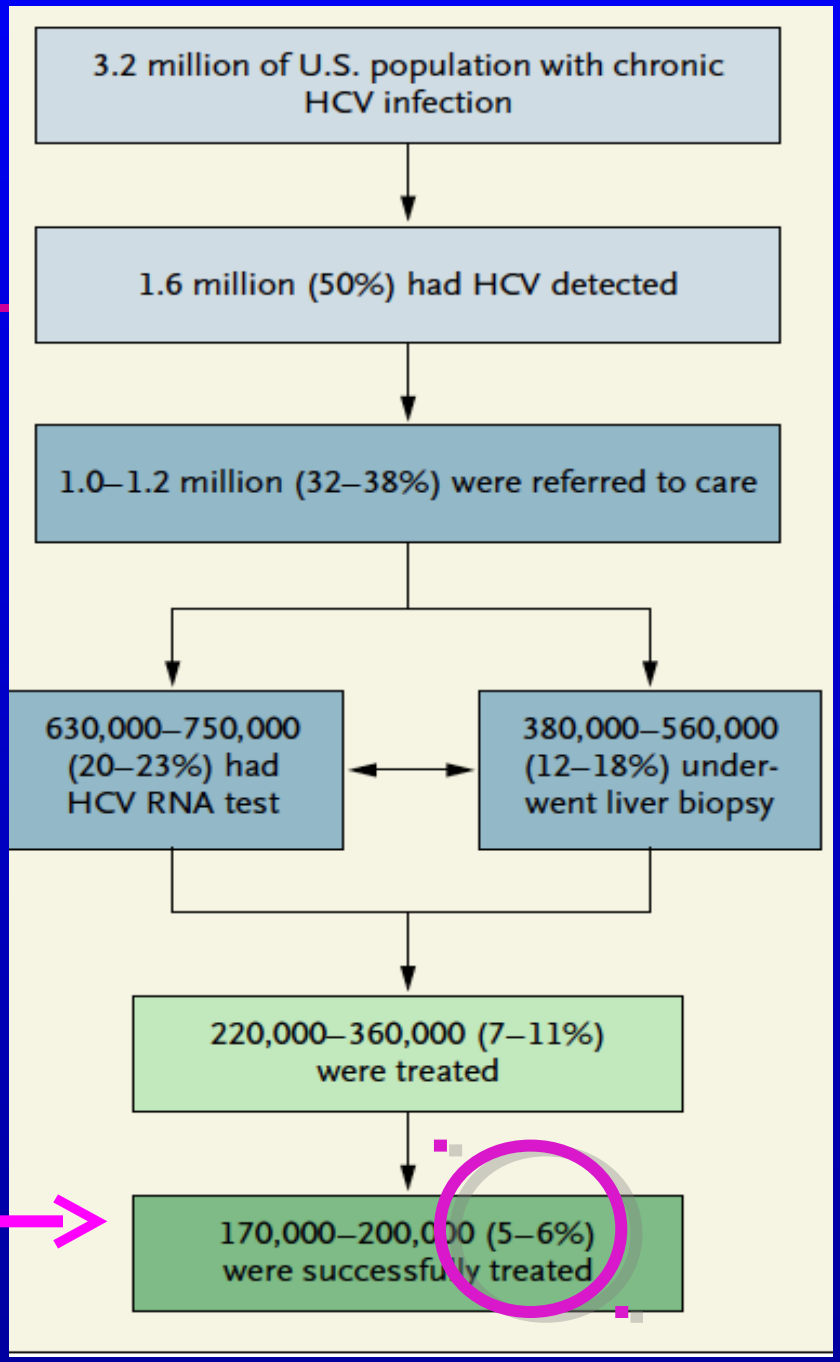
170 million people HCV infected worldwide

- New and more effective treatments with a better tolerance

- Screening guidelines require reconsideration
  - US guidelines may not extrapolated to Europe

But also strategies targeting

- Linkage to care
- Retention to care
- Adherence to treatment



Holmberg SD, et al. NEJM 2013;368(20):1859-61.

- New and more effective treatments with a better tolerance

However….

Treatment costs may limit scaleup, and should be addressed

- “Cost-effectiveness analysis”: understanding, prioritizing and optimizing the use of health care services (cost-effective doesn’t mean cheap)
- “Budget impact analysis”: The financial consequences of introducing a new technology in a specific setting over the short to medium term (*affordability)*

CUPIC: SVR12 and risk of occurrence of severe complications

		Platelets count ≤ 100,000/mm³	Platelets count > 100,000/mm³
Albumin < 35 g/L	N	37	31
	Complications, n (%)	19 (51.4%)	5 (16.1%)
	SVR12, n (%)	10 (27.0%)	9 (29.0%)
Albumin 35 g/L	N	74	305
	Complications, n (%)	9 (12.2%)	19 (6.2%)
	SVR12, n (%)	27 (36.5%)	168 (54.9%)

Hézode C, et al. J Hepatol 2013;59:434-441

Fontaine H et al. AFEF 2013

VHC et VHB en France (données 2004)

- Prévalence
  - Ac anti-VHC = 0,84 %
  - AgHBs = 0,65 %

- Proportion de sujets ne connaissant pas leur séropositivité
  - VHC : 43 % (2004)
    - **100 868 personnes** (IC 95 % : 58 534-143 202).
  - VHB : 55 % (2004)
    - **154 956 personnes** (IC 95 % : 87 988-221 923)

La proportion des patients porteurs de VHC traités avec succès aux EU

Holmberg SD, et al. NEJM 2013;368(20):1859-61.

3,2 millions d'américains sont porteurs d'une infection chronique à VHC

↓

1,6 millions (50 %) sont diagnostiqués

↓

1,0 à 1,2 millions (32–38 %) ont été adressés à un spécialiste

220,000–360,000 (7–11 %) ont été traités

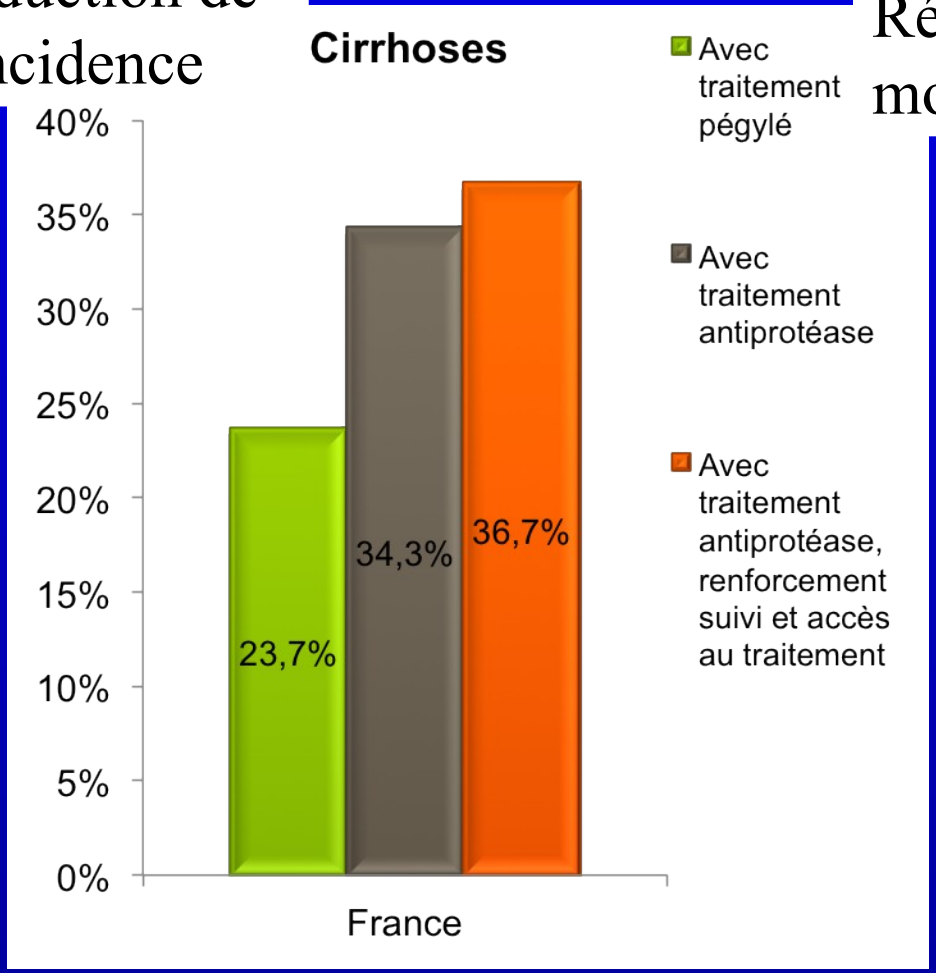
↓

170,000–200,000 (**5–6 %**) ont été traités avec succès

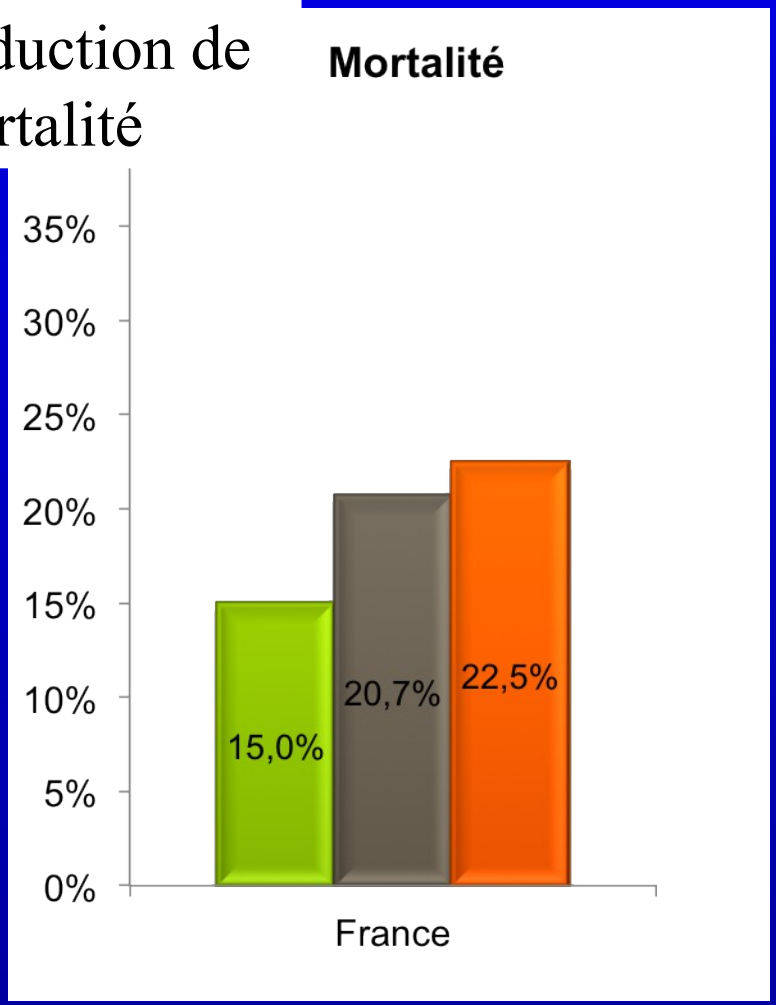
Impact du traitement sur l'incidence des cirrhose et sur la mortalité en France 2012 à 2021

Deuffic-Burban S, et al. Gastroenterology 2012

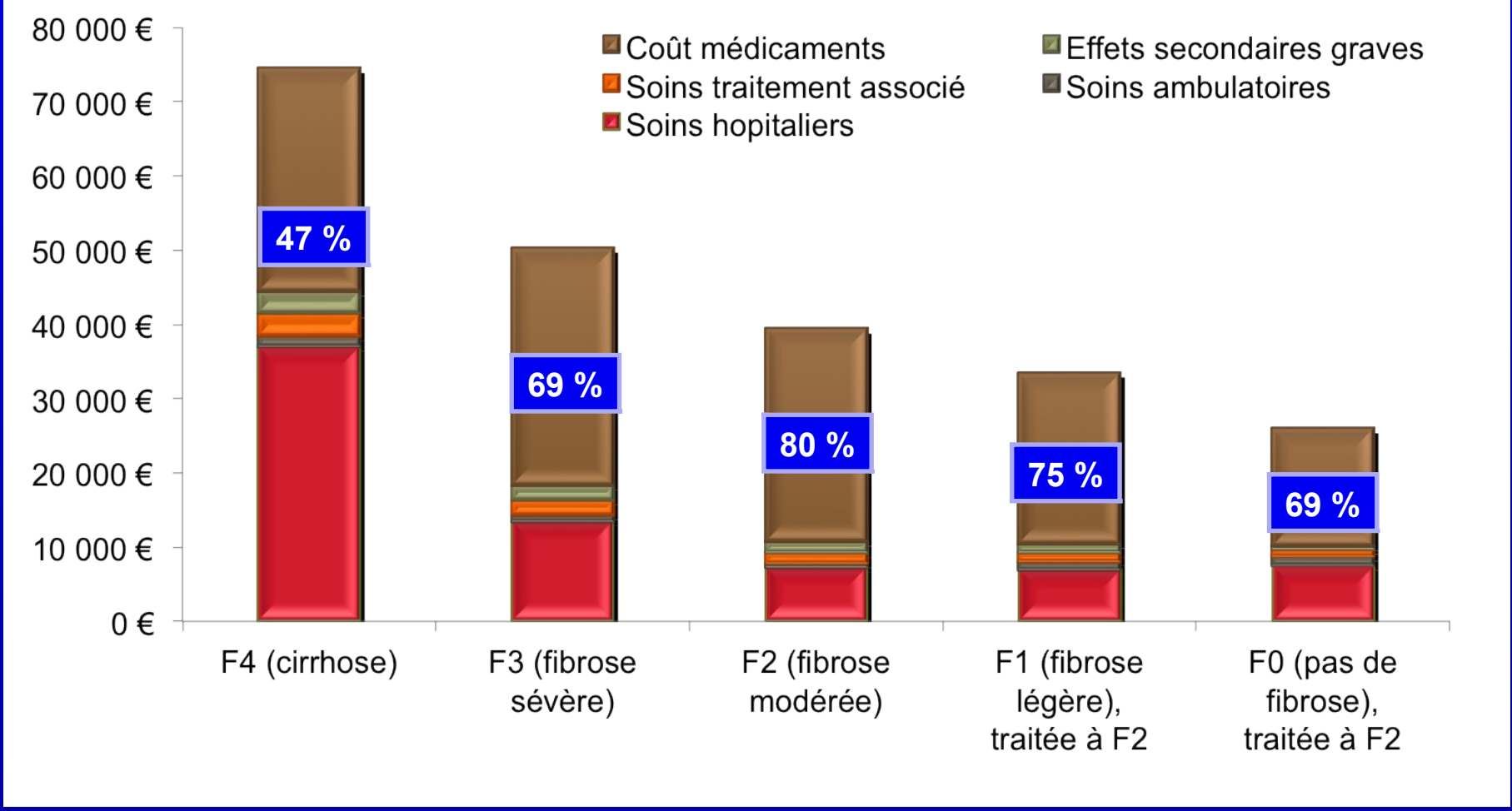
Réduction de l'incidence



Réduction de mortalité



Coût de la prise en charge de l'hépatite C selon le stade de la fibrose au moment du diagnostic en France (Trt = Telaprevir + PegInf-Riba)



M Schwartzinger, et al. Journal of Hepatology 2013;58:S1–S24.

- **Le rapport bénéfice-risque de la mise en place d'un traitement a fortement évolué vers le traitement**
  - les nouveaux traitements sont plus efficaces et sont très bien tolérés.

Mais quel est le coût, le coût-efficacité, l'impact budgétaires?

Questions de Recherche prenant en compte des critères économiques

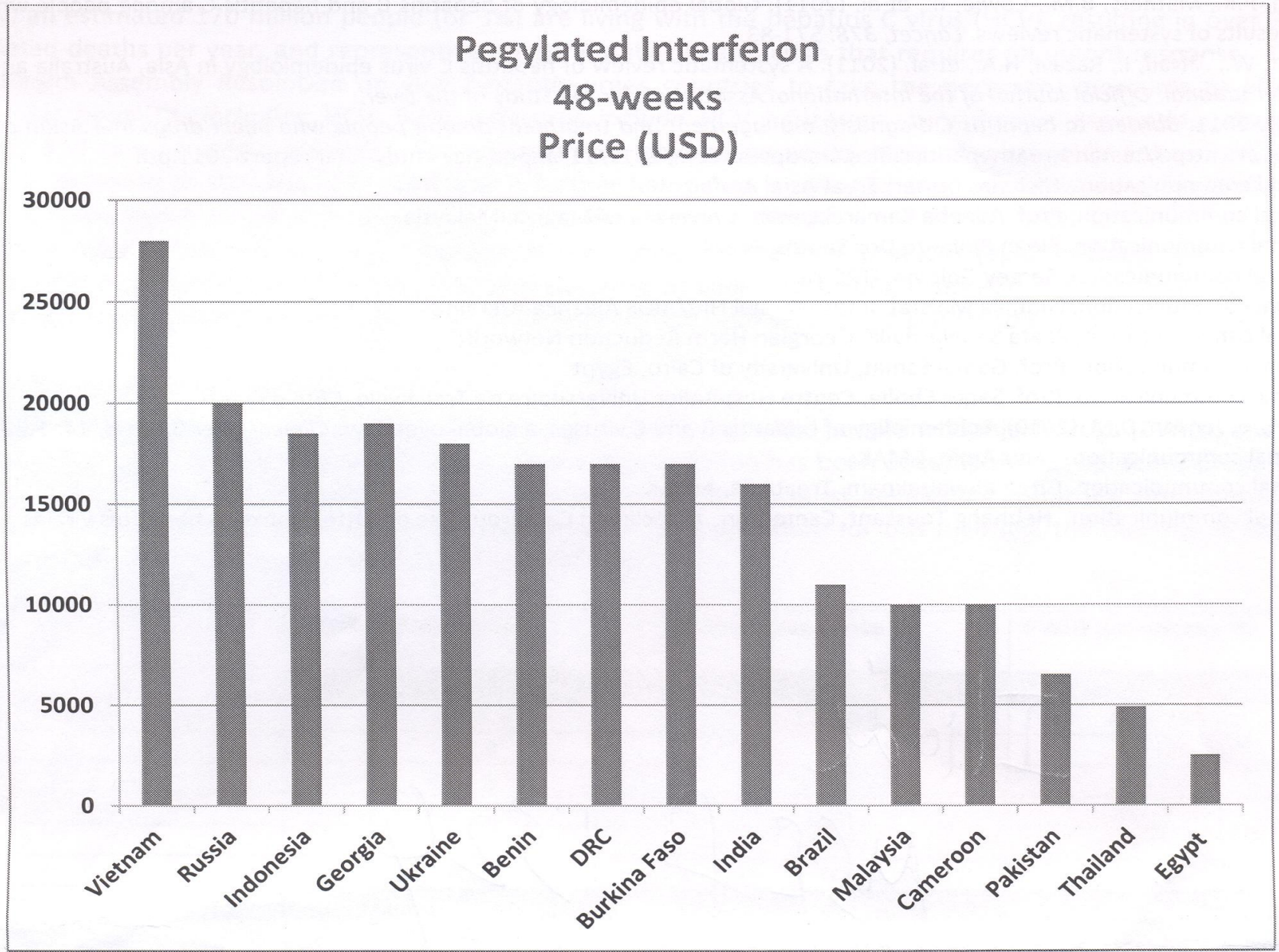
- Quelle stratégie de dépistage?
- Quand commencer le traitement (F0-F1; >F2)?
- Retarder le traitement jusqu'à l'arrivée des nouveaux traitements (les DAAs)?
- Traitement comme outil de prévention dans les groupes à risque : UDI?

VHC dans le monde

- 130 à 170 millions de personnes sont infectées par le virus de l'hépatite C (VHC)[1,2]

1-Lavanchy D. Clin Microbiol Infect 2011;17:107-15.
2. Averhoff FM, et al. Clin Infect Dis. 2012;55(S1):S10-S15.

Slide, adapted from Pr Gamal Esmat



Questions de Recherche prenant en compte des critères économiques dans les pays du Sud

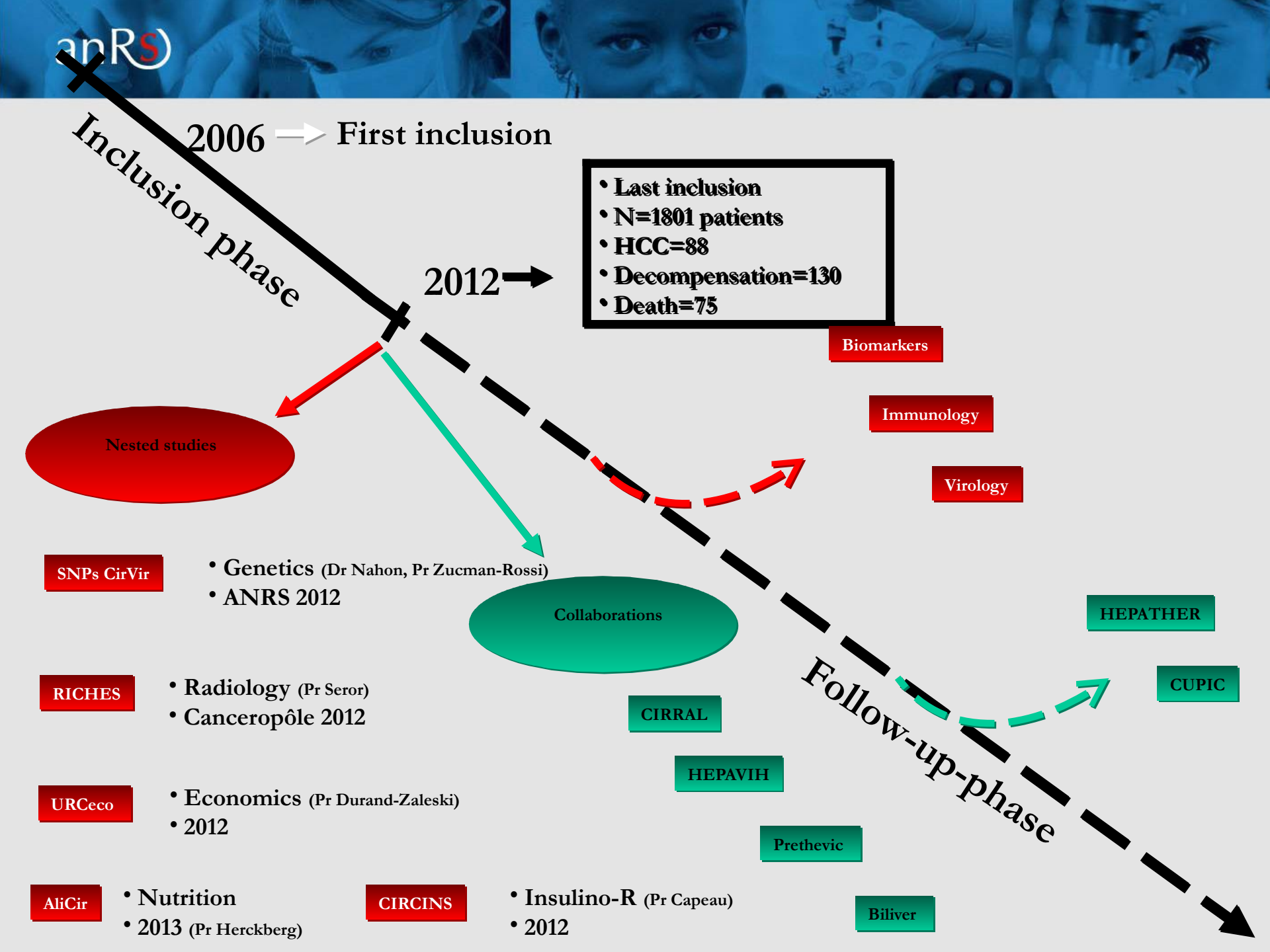
- Le traitement est-il cout-efficace? À quel prix?
- Quand commencer le traitement (F0-F1; >F2)?
- Comment évaluer la fibrose?
- Comment suivre l'efficacité de Trt?

CLINICAL RESEARCH
IN VIRAL HEPATITIS /ANRS AGENDA

ANRS CO12 CIRVIR

multicenter French cohort: backbone for the study of viral cirrhosis and hepatocellular carcinoma.

- Multicenter study (39 french hospitals)
- Number of included patients: 1801 (15/06/12)
- Visits: every 6 months (HCC screening)
- Biobanks: at inclusion and every year


2006 First inclusion
Inclusion phase
2012
• Last inclusion
• N=1801 patients
• HCC=88
• Decompensation=130
• Death=75
Biomarkers
Immunology
Virology
Nested studies
SNPs CirVir
• Genetics (Dr Nahon, Pr Zucman-Rossi)
• ANRS 2012
Collaborations
HEPATHER
CUPIC
RICHES
• Radiology (Pr Seror)
• Canceropôle 2012
CIRRAL
HEPAVIH
URCeco
• Economics (Pr Durand-Zaleski)
• 2012
Prethevic
Follow-up-phase
AliCir
• Nutrition
• 2013 (Pr Herckberg)
CIRCINS
• Insulino-R (Pr Capeau)
• 2012
Biliver

ANRS CO20-CUPIC

SAFETY OF TELAPREVIR OR BOCEPREVIR IN COMBINATION WITH PEGINTERFERON ALFA/RIBAVIRIN, IN CIRRHOTIC NON RESPONDERS FIRST RESULTS OF THE FRENCH EARLY ACCESS PROGRAM

AFEF
ASSOCIATION FRANÇAISE POUR L'ETUDE DU FOIE
CUPIC
AnrS CO20
Instituts thématiques
UPMC
PARIS UNIVERSITAS
Inserm
Institut national de la santé et de la recherche médicale

French early access program

ATU

The use of medicinal products not benefiting from Marketing Authorization in France and not used in clinical trials is conditioned by first obtaining a Temporary Authorization for Use (ATU) by the French Health Products Safety Agency (Afssaps)

Two types of ATU:
–Nominative ATU
–Cohort ATU

CUPIC

Compassionate Use of Protease Inhibitors in viral C Cirrhosis
National multicenter observatory in the setting of ATU cohort.
Promoter: ANRS

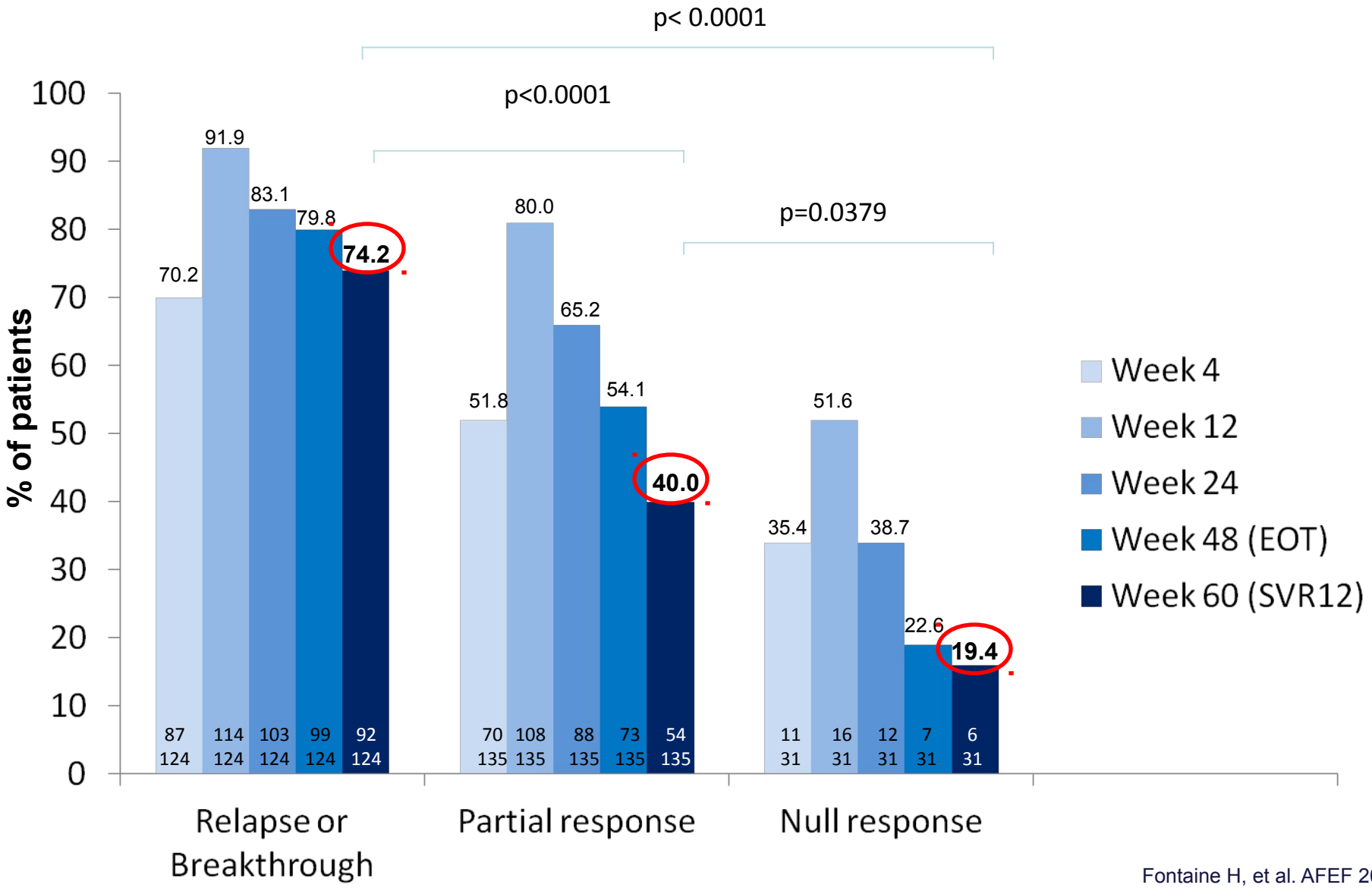
Aim: to prospectively collect data and biological specimen
Number of investigators: 197

HEPATITIS/ANRS
in resource-limited countries

HIV cure: 2-models

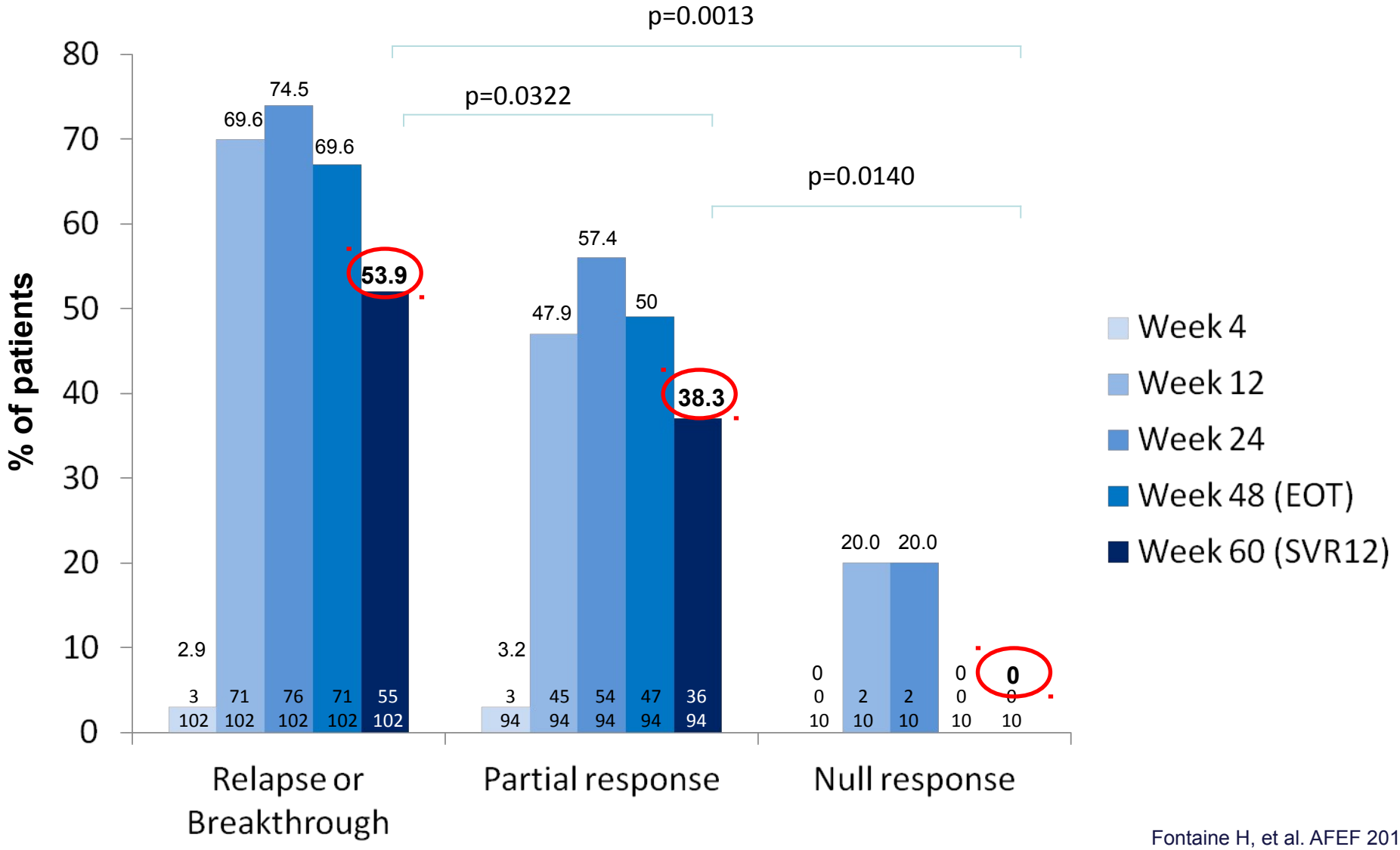
Eradication	Remission
Sterilizing cure	Functional cure
Elimination of all HIV-infected cells	Long-term health without cART
HIV RNA < 1 cop/mL	HIV RNA <50 cop/mL
Berlin Patient post-BMT	Elite controllers Post-cART controllers

Telaprevir: SVR12 by prior treatment response



Fontaine H, et al. AFEF 2013

Boceprevir: SVR12 by prior treatment response



Fontaine H, et al. AFEF 2013

Current treatment: sustained disease control achieved with NUCs/IFN in majority of patients

	Entecavir[1,2]	Tenofovir[3]	PEG-IFN α-2a[4,5]
HBeAg positive	n = 354	n = 176	n = 271
HBV DNA undetectable	67%	76%	25%[a]
HBeAg seroconversion	21%	21%	27%
ALT normalisation	68%	68%	39%
HBsAg loss	2%	3.2%	2.9%[b]
HBeAg negative	n = 325	n = 250	n = 177
HBV DNA undetectable	90%	93%	63%[a]
ALT normalisation	78%	76%	38%
HBsAg loss	0.3%	0%	0.6%[b]

Results at 48 weeks

[a] HBV DNA < 400 copies/mL; [b] At 72 weeks

1. Chang T-T, et al. N Engl J Med 2006;354:1001–10.
2. Lai C-L, et al. N Engl J Med 2006;354:1011–20.
3. Marcellin P, et al. N Engl J Med 2008;359:2442–55.
4. Lau GKK, et al. N Engl J Med 2005;352:2682–95.
5. Marcellin P, et al. N Engl J Med 2004;351:1206–17.

Slow kinetics of HBV clearance

- Rate of cccDNA decline (liver)

  < 1 log10 copie/cell at year one

  Estimated time for clearance (in the absence of hepatocyte turnover) > 15 years

Werle et al, Gastroenterology 2004; Wong et al Clin Gastroenterol and Hepatol 2013

- HBsAg decline (serum)

  - Rate of decline: 0.007 ± 0.007 Log UI/mL/month

  -Median time to negativation 52,2 years (IQR: 30,8-142,7)

Borgniet et al, J Med Virol 2009, Chevaliez et al J Hepatol 2013

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

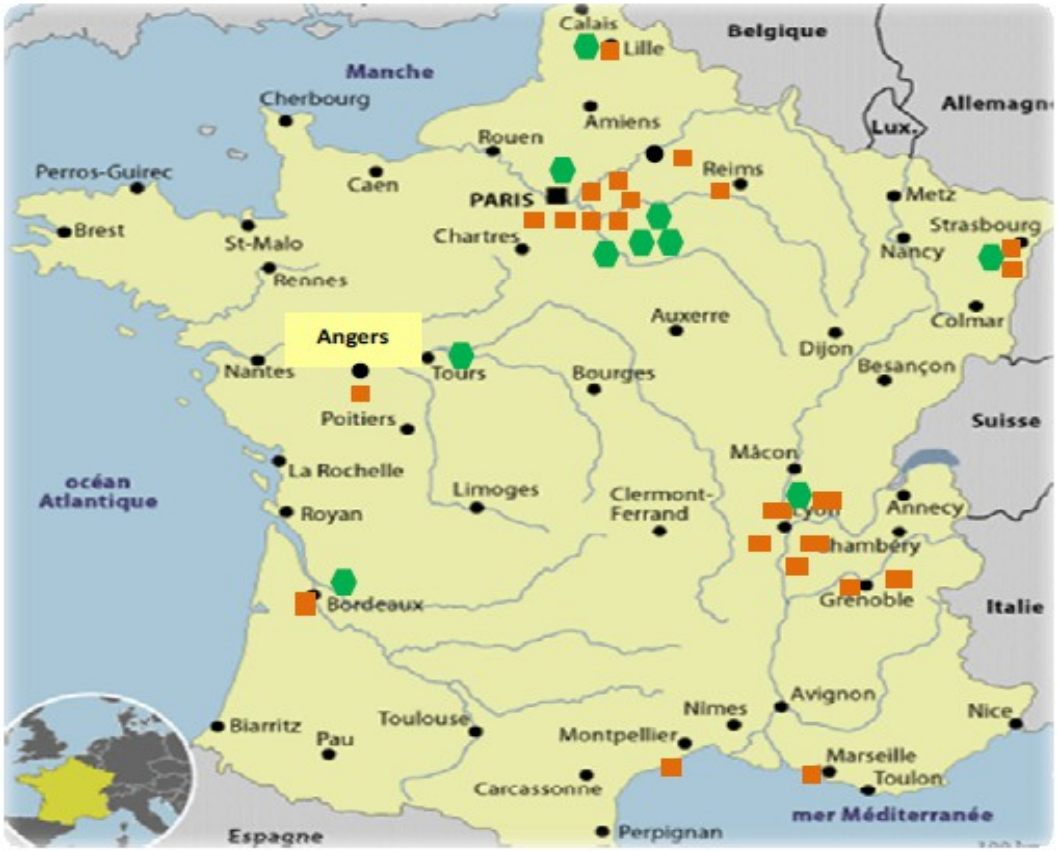
ANRS consortium

« Humanized mouse models for studying viral hepatitis »

Rationale

- Current humanized liver (HUHEP) mice models are generated in immunodeficient mice, a limitation for the study of virus-host interactions, viral evasion, pathogenesis of virus-induced liver disease, novel immunotherapies and vaccine candidates.
- The development of mouse models harboring both human immune cells (HIS) and human hepatocytes (HUHEP) is an urgent need for the research community.

INSERM, CNRS, UNITS, INVESTIGATED IN HEPATITIS FIELD RESEARCH



CNRS, INSERM, UMR

INSERM

LabEx HEPSYS Coordinator: Thomas Baumert, MD

UMR_S748, Institut de Virologie, Université de Strasbourg

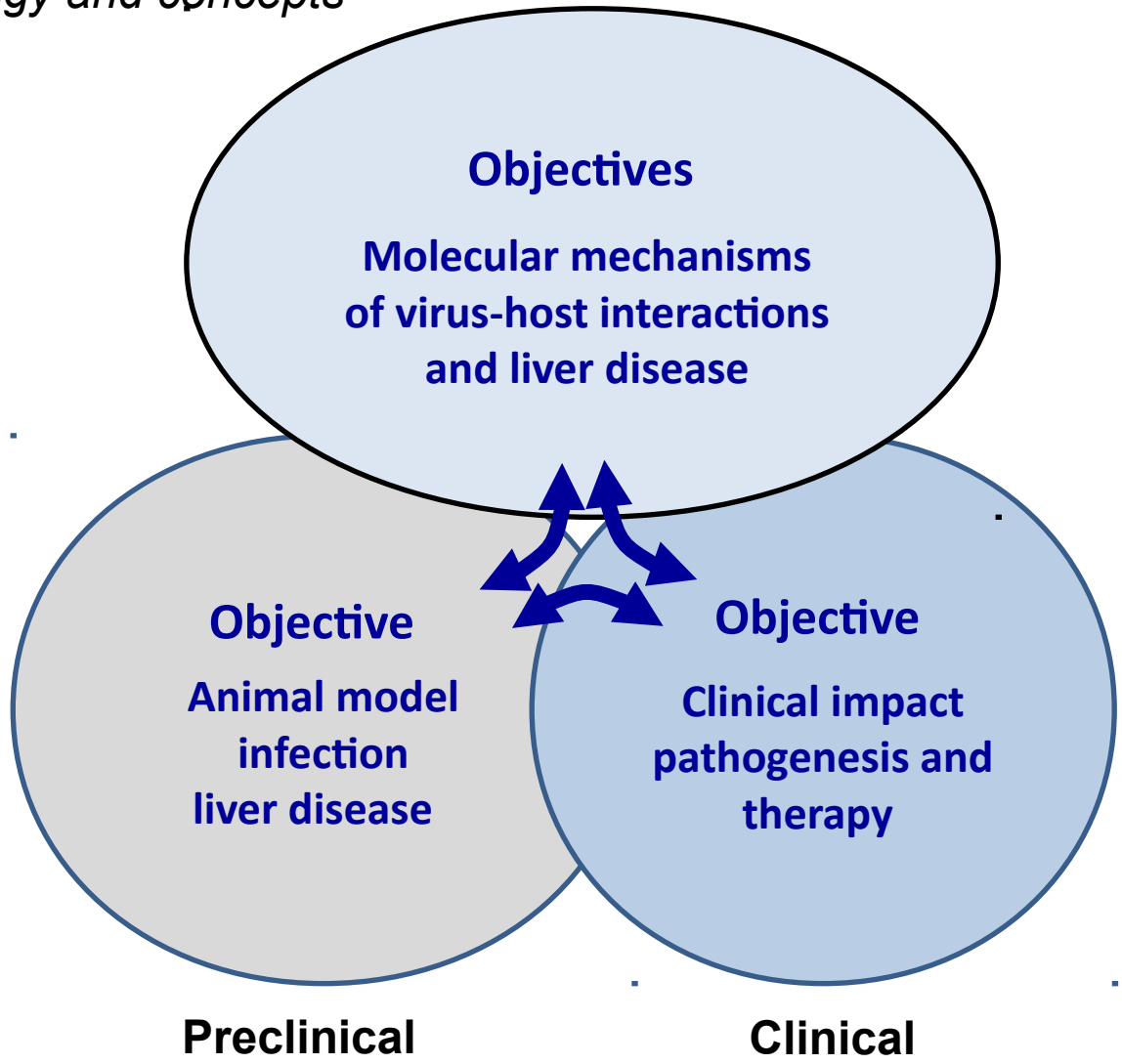
Functional genomics of viral hepatitis and liver disease

Scientific program - Strategy and concepts

Cell-based models

Molecular virology program

Translational program



ADDITIONAL ANRS ANIMATION EVENTS IN THE HEPATITIS FIELD

- **Annual Meeting Of The National Hepatitis Network Of Basic Hepatitis Research (Paris):**
  - About 200 attendees
  - Discussion of the last French advances in basic and translational research
  - Opportunity to give the floor to young researchers

- **ANRS Symposium During The Annual AFEF Meeting (France)**

- **ANRS Annual Research Seminary (Institut Pasteur, Paris):**
  - Opportunity to discuss common topics to hepatitis and HIV infection (such as prevention, eradication and cure)

- **Annual Clinical Leaflet of ANRS Hepatitis Department : Lists Of The On-going / Including Clinical Trial For Hospital Clinicians To Increase Inclusions In ANRS Trials**

The NEW ENGLAND JOURNAL of MEDICINE

Regulatory T-Cell Responses to Low-Dose Interleukin-2 in HCV-Induced Vasculitis

David Saadoun, M.D., Ph.D., Michelle Rosenzwajg, M.D., Ph.D., Florence Joly, Ph.D., Adrien Six, Ph.D., Fabrice Carrat, M.D., Ph.D., Vincent Thibault, Pharm.D., Damien Sene, M.D., Ph.D., Patrice Cacoub, M.D., and David Klatzmann, M.D., Ph.D.

N Engl J Med 2011;365:2067-77.

JCI The Journal of Clinical Investigation

Evidence for an antagonist form of the chemokine CXCL10 in patients chronically infected with HCV

Armanda Casrouge,[1,2] Jérémie Decalf,[1,2] Mina Ahloulay,[3,4,5] Cyril Lababidi,[6] Hala Mansour,[1] Anaïs Vallet-Pichard,[3,4,5] Vincent Mallet,[3,4,5] Estelle Mottez,[6] James Mapes,[7] Arnaud Fontanet,[8] Stanislas Pol,[3,4,5] and Matthew L. Albert[1,2]

The Journal of Clinical Investigation http://www.jci.org Volume 121 Number 1 January 2011

Science Translational Medicine AAAS

A Prime-Boost Strategy Using Virus-Like Particles Pseudotyped for HCV Proteins Triggers Broadly Neutralizing Antibodies in Macaques

Sci Transl Med 3, 94ra71 (2011);
DOI: 10.1126/scitranslmed.3002330

Pierre Garrone,[1*†] Anne-Catherine Fluckiger,[1†] Philippe E. Mangeot,[1] Emmanuel Gauthier,[2] Pia Dupeyrot-Lacas,[1] Jimmy Mancip,[1] Arnaud Cangialosi,[1] Isaure Du Chéné,[1] Roger LeGrand,[3] Isabelle Mangeot,[3] Dimitri Lavillette,[2] Bertrand Bellier,[4,5,6] François-Loic Cosset,[2‡] Frederic Tangy,[7‡] David Klatzmann,[4,5,6,8‡§] Charlotte Dalba[1,9‡§]

nature International weekly journal of science

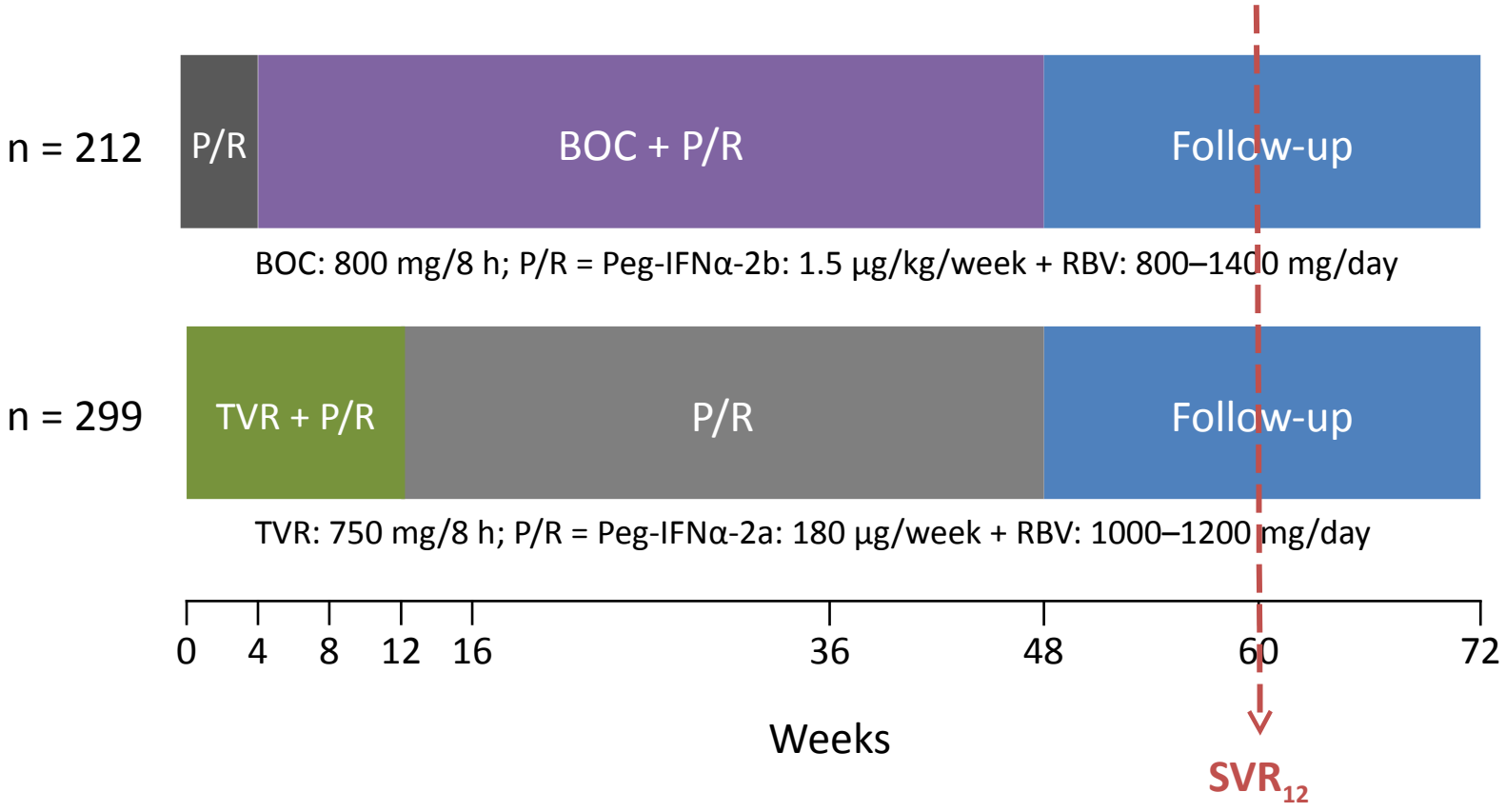
EGFR and EphA2 are host factors for hepatitis C virus entry and possible targets for antiviral therapy

Joachim Lupberger[1,2,13], Mirjam B Zeisel[1,2,13], Fei Xiao[1,2], Christine Thumann[1,2], Isabel Fofana[1,2], Laetitia Zona[1,2], Christopher Davis[3], Christopher J Mee[3], Marine Turek[1,2], Sebastian Gorke[4], Cathy Royer[1,2], Benoit Fischer[5], Muhammad N Zahid[1,2], Dimitri Lavillette[6], Judith Fresquet[6], François-Loïc Cosset[6], S Michael Rothenberg[7], Thomas Pietschmann[8], Arvind H Patel[9], Patrick Pessaux[10], Michel Doffoël[11], Wolfgang Raffelsberger[12], Olivier Poch[12], Jane A McKeating[3], Laurent Brino[5] & Thomas F Baumert[1,2,11]

NATURE MEDICINE VOLUME 17 | NUMBER 5 | MAY 2011

CUPIC: G1 treatment-experienced cirrhotics

- Triple therapy including boceprevir or telaprevir was examined in 511 cirrhotic patients



Hézode C et al. AASLD 2013, Abstract 1845

Plasma apolipoprotein H (apoH) limits HCV replication and is associated with successful response to NS3 protease inhibitors-based therapy

(ANRS CO20-CUPIC)

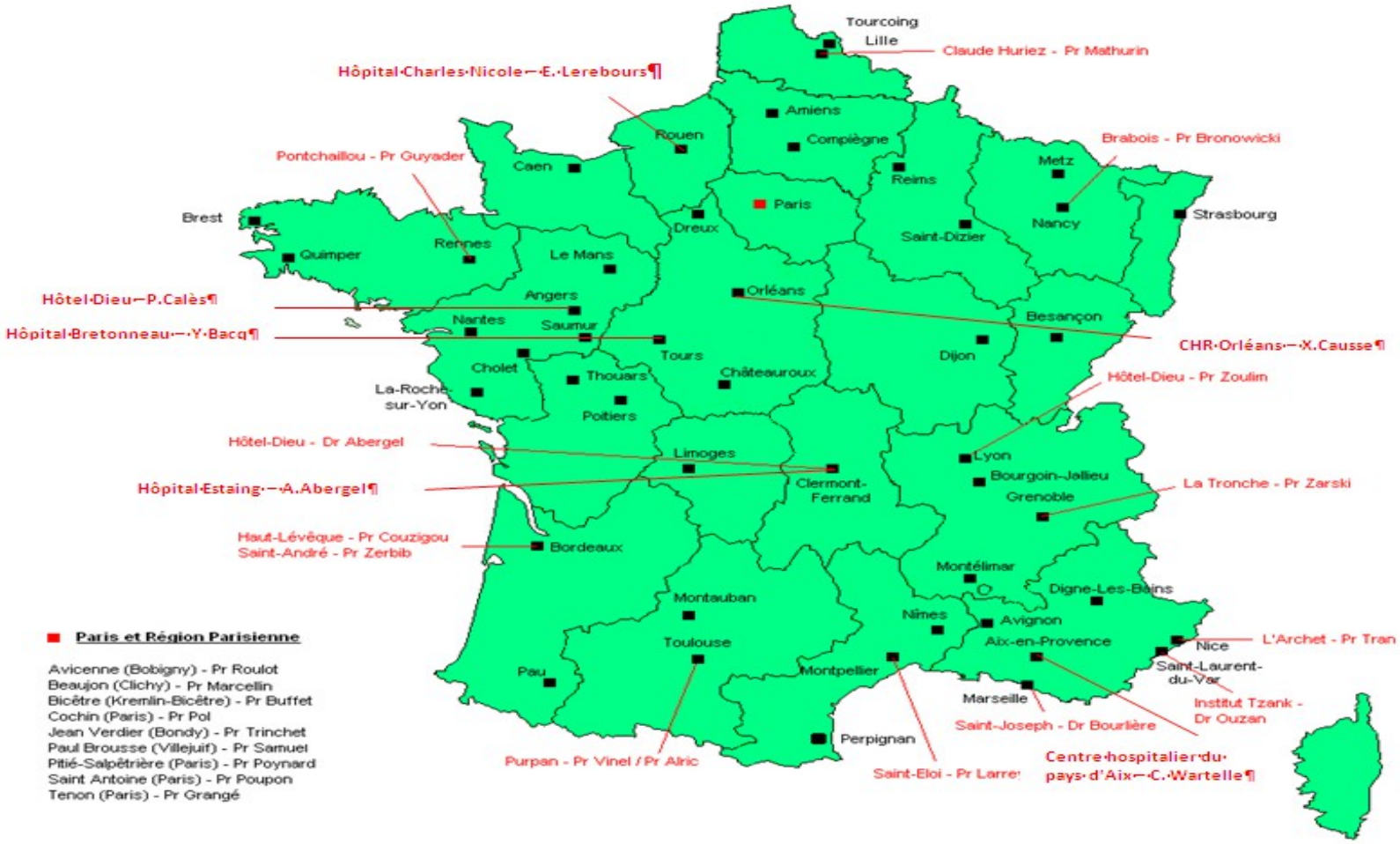
P. Sultanik[1,2],*, V. Mallet [1,2,*] , S. Lagaye[2], A. Casrouge[3], C. Dorival[4], Y. Barthe[4] , H. Fontaine[1,2], C. Hézode[5], E. Mottez[6], J-P. Bronowicki[7], F. Carrat [4,8], I. Theodorou[9], L. Abel [10,11,12], E. Gayat [13, 14], A Fontanet [15], S. Pol [1,2],M.L. Albert [3,6]

on behalf of ANRS CO20-CUPIC

VIRAL HEPATITIS

ANRS Staff support in hepatitis clinical sites

28 Clinical Centers
> 65000 patients



AC24, AC 5/24, AC7

Clinical Trials, physiopathological studies and Cohorts

Number of completed trials since 2005 n=17 # 2000 patients

Ongoing clinical studies n = 25 # 3500 patients

Clinical trials 17

- mono and : 9

- co infection : 8

- Physiopathological studies: 8

Ongoing Cohorts n= 5 # 10 000 patients

- ANRS CO 13 HEPAVIH

- ANRS CO 12 CIRVIR,

- ANRS CO 20 CUPIC,

- ANRS CO 22 HEPATHER

- ANRS CO 23 CUPILT

HEPATITIS CO-INFECTION - NEW DRUGS PILOT STUDIES

ANRS HC26 TELAPREVIH : Pilot Study of PegInterferon-Ribavirin-Telaprevir Efficacy and Tolerability in HIV-HCV Coinfected Patients Who Had Previously Failed a PegInterferon-Ribavirin Regimen n=70 CROI 2013 ORAL / AASLD 2013 POSTER

ANRS HC27 BOCEPREVIH : A pilot study to assess the efficacy and the safety of Boceprevir in combination with PegInterferon alfa and Ribavirin, in subjects with HCV/HIV coinfection, in failure to a previous therapy of Peginterferon/Ribavirin n=69 CROI 2013 ORAL / AASLD 2013 POSTER

ANRS HC30 QUADRIH : Pilot study to assess the efficacy and safety of a Quadruple therapy with Asunaprevir, Daclatasvir, Ribavirin and pegylated Interferon alpha2a, in HIV and HCV genotype 1 or 4 co-infected patients, previously null responders to a standard Pegylated interferon – Ribavirin regimen n=75 On going

ANRS HC 31 SOFTRIH Pilot study assessing efficacy and toleranceoral Tritherapy oral with Sofosbuvir plus GS-5885 fixed dose an ribavirine in co-infected VIH-VHC de génotype 1 patients, relapsers to a tritherapy with NS3/4A protéase inhibitor - Start January 2014

HEPATITIS MONO INFECTION - NEW DRUGS PILOT STUDIES

ANRS HC29 BOCEPRETRANSPLANT :

Pilot Study on the Efficacy of Pegylated Interferon-Ribavirin-Boceprevir Triple Therapy in Patients Infected With Genotype 1 HCV With Cirrhosis and Awaiting Liver Transplantation (n=58) Ongoing

ANRS HC 32 QUATTRO :

Pilot study of Quadri therapy with Asunaprevir and Daclatasvir in Hepatitis C virus Genotype 4 Infected Null/ Partial responders and relapsers to Peginterferon Alfa and Ribavirin– BMS / ANRS Partnership (n=60) Start November 2013

ANRS research programme on HCV in Egypt

HCV risk factors
-Iatrogenic
-Intra-familial

Public Health

Factors associated with HCV clearance
-epidemiology
-lipids
-virology
-immunology

Treatment efficacy
- Acute phase
- Chronic infection

Mathematical modeling
-Prediction
-cost-effectiveness

Principal Investigators
Arnaud FONTANET - Institut Pasteur – Paris
Gamal ESMAT – Cairo

2020 A DREAM !

- **HCV CURE**
- **HIV CURE ?**
- **HBV CURE ?**

Coordinated action 29 (AC29) « Mechanisms of entry and assembly of hepatitis viruses »

Characterization of the role of HCV cellular entry factors

- **EGF receptor and HRas signaling play a major role in HCV entry**

  Lupberger et al., Nat Med, 2011; Zona et al., Cell Host Microbe, 2013

- **The LDL receptor is involved in a non-productive entry pathway**

  Albecka et al., Hepatology, 2012

- **Only highly mobile CD81 molecules are involved in HCV entry**

  Potel et al., Cell Microbiol, 2013

- **SRB1 receptor plays a role at different steps of HCV entry**

  Dao Thi et al., JBC, 2012; Zahid et al., Hepatology, 2013

Characterization of HCV envelope glycoproteins

- **Identification of crosstalks between HCV envelope glycoproteins**

  Albecka et al., J Virol, 2011; Maurin et al., JBC, 2012; Wahid et al., J Virol, 2013

- **HCV envelope glycoproteins form large oligomers on the virion**

  Vieyres et al., J Virol, 2010

Coordinated action 29 (AC29) « Mechanisms of entry and assembly of hepatitis viruses »
Neutralizing antibodies & escape from neutralization

- **Structure of HCV neutralizing epitope in interaction with a Mab**

  Krey et al., PLoS Pathog, 2013

- **A « glycan shield » protects neutralizing epitopes in HCV**

  Helle et al., J Virol 2010; Anjum et al., JID, 2013

- **Escape from antibody neutralization by altering interaction with HCV entry factors**

  Fafi-Kremer et al., J Exp Med, 2010; Fofana et al., Gastroenterology, 2012

Vaccines inducing neutralizing antibodies

- **Chimeric subviral HBV particles containing HCV envelope proteins**

  Beaumont et al., Hepatology, 2013

- **Retroviral pseudotypes containing HCV envelope proteins**

  Garrone et al., Sc Transl Med, 2011

Animal Model Working Group

- **Goal**: merge several French projects of development of an animal model for HCV and HBV infection into one single project
- Creation of the **ANRS Consortium "Humanized mouse models for the study of viral hepatitis"**
- **Composition**
  - James Di Santo, Hélène Strick-Marchand, Dina Kremsdorf
  - François-Loïc Cosset, Els Verhoeyen
  - Thomas Baumert, Eric Robinet
  - Sylvie Garcia, Marie-Louise Michel
  - Cyrille Feray, Herve Lerat
  - Fabien Zoulim, David Durantel
- ANRS SAB expressed caution on relevance
- Assessment by internationally recognized researcher: relevance, usefulness , priority)
- **ANRS funding: 700 000 € (late 2012, 2013, 2014)**
- First scientific report received end of 2Q 2013

France REcherche Nord & sud Sida-hiv Hépatites

Agence autonome de l'Inserm

ANRS consortium

« Humanized mouse models for studying viral hepatitis »

Aim

- To improve human hepatocyte (HUHEP) repopulation in the different HUHEP mouse models and make side by side comparison of HUHEP models for HBV and HCV infection.
- To create new models or to optimize mouse models that harbor both human immune cells (HIS) and human hepatocytes: HIS/HUHEP mice.
- To investigate HBV and HCV infection in HIS/HUHEP models using standardized protocols, viral stocks and biomarker detection methods.
- To select and share the best model(s) to investigate immune responses and virus-induced and immune mediated liver disease in HIS/HUHEP mice infected with human hepatotropic viruses.