The role of combination therapy in Hepatitis B

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Jorg Petersen
Liver Unit
IFI Institute for Interdisciplinary Medicine
Asklepios Klinik St. Georg
University of Hamburg

email: petersen@ifi-medizin.de

Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

www.easl.eu

Journal of Hepatology **2012** vol. 57 | 167–185

Is there a role for combination therapy ?

Partial virological response during NUC therapy

Check for **compliance**

In compliant patients with partial virological response under

- **LAM or LdT** at wk 24 or **ADV** at wk 48, **change (switch!) to a more potent drug** (ETV or TDF) preferentially without cross-resistance **(A1)**
- ETV or TDF at wk 48
  - If HBV DNA levels are declining, continue with the same agent (B1)
  - **If HBV DNA levels are not declining, add the other drug in order to prevent resistance in the long term (C2)**

Virological breakthrough during NUC therapy

- LAM resistance: **switch** to TDF (add ADV if TDF not yet available) (B1)
- ADV resistance: in NA naive patients before ADV, **switch** to ETV or TDF (B1);
  ETV may be preferred in such patients with high viraemia (C2)
  in patients with prior LAM-R, **switch** to TDF and add a nucleoside (C1)
- LdT resistance: **switch to or add** TDF (add ADV if TDF not yet available) (C1)
- ETV resistance: **switch to or add** TDF (add ADV if TDF not yet available) (C1)
- TDF resistance: genotyping and phenotyping by an expert laboratory.
  ETV, LdT, LAM or FTC **could be added** (C2);
  switch to ETV may be sufficient if the patient was NA naive before TDF (C2)

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AIDS. 2009 August 24; 23(13): 1707–1715. doi:10.1097/QAD.0b013e32832b43f2.

Combination HBV therapy is linked to gr… suppression in a cohort of la… infected individ…

Most patients with HIV do receive fixed combos such as Truvada

…[1], Joe …[2], Locarnini

…search, UNSW, Sydney, Australia

…g School of Public Health, John Hopkins University, MD,

…ious Diseases Reference Laboratory, Melbourne, Australia

…he Alfred Hospital, Melbourne, Australia

[5] Victorian Infectious Diseases Service, Melbourne, Australia

[6] Armed Forces Institute of Pathology. Washington DC, U.S.A.

[7] Department of Medicine, John Hopkins University, MD, U.S.A.

GASTROENTEROLOGY 2012;143:619–628

Efficacy of Entecavir With or Without Tenofovir Disoproxil Fumarate for Nucleos(t)ide-Naïve Patients With Chronic Hepatitis B

ANNA S. LOK,* HUY TRINH,‡ GIAMPIERO CAROSI,§ ULUS S. AKARCA,‖ ADRIAN GADANO,¶ FRANÇOIS HABERSETZER,# WILLIAM SIEVERT,** DAVID WONG,‡‡ MEGHAN LOVEGREN,§§ DAVID COHEN,§§ and CYRIL LLAMOSO§§

*Division of Gastroenterology, University of Michigan Health System, Ann Arbor, Michigan; ‡Pacific Health Foundation, San Jose, California; §Inst... Tropical Disease, University of Brescia, Brescia, Italy; ‖Department of Gastroenterology, Faculty of Medicine, Ege University, Izmir... Italiano de Buenos Aires-Argentina, Ciudad de Buenos Aires, Argentina; #Service d'Hépato-gastroentérologie... Strasbourg, Strasbourg, France; **Department of Medicine, Monash University, Monash Medical... Network, Toronto, Ontario, Canada; and §§Research and Development, Bristol...

Comparable efficacy in both arms, a TDF mono arm was missing !

...ive). The com-
...rovide an incremental ben-
...g-positive patients with baseline levels
of HBV DNA $\geq 10^8$ IU/mL. Clinical trial informa-
tion: ETV-110, the BE-LOW study; NCT00410072.

Tenofovir Disoproxil Fumarate (TDF), Emtricitabine/TDF, and Entecavir in Patients with Decompensated Chronic Hepatitis B Liver Disease

Yun-Fan Liaw,[1] I-Shyan Sheen,[1] Chuan-Mo Lee,[2]
Suet-Hing Wong,[5] Ting-Tsung
Martin Prieto,[11]

Concl: All treatments were well tolerated in patients with decompensated liver disease due to CHB with improvement in virologic, biochemical, and clinical parameters.

Research Article

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Entecavir plus tenofovir comb
pre-treated chroni

Combination therapy only for a very few patients that do show advanced liver disease and that have failed mono therapy mostly due to resistance to first line NUCs

patobiliary Surgery
Hepatology, University Leipzig,
ment of Microbiology, University Hospital

FROM ADD-ON TO TAKE-OFF IN TREATMENT EXPERIENCED CHRONIC HEPATITIS B PATIENTS WITH VIRAL RESISTANCE OR PARTIAL RESPONSES: FIRST RESULTS OF AN INTERNATIONAL MULTICENTER COHORT STUDY.

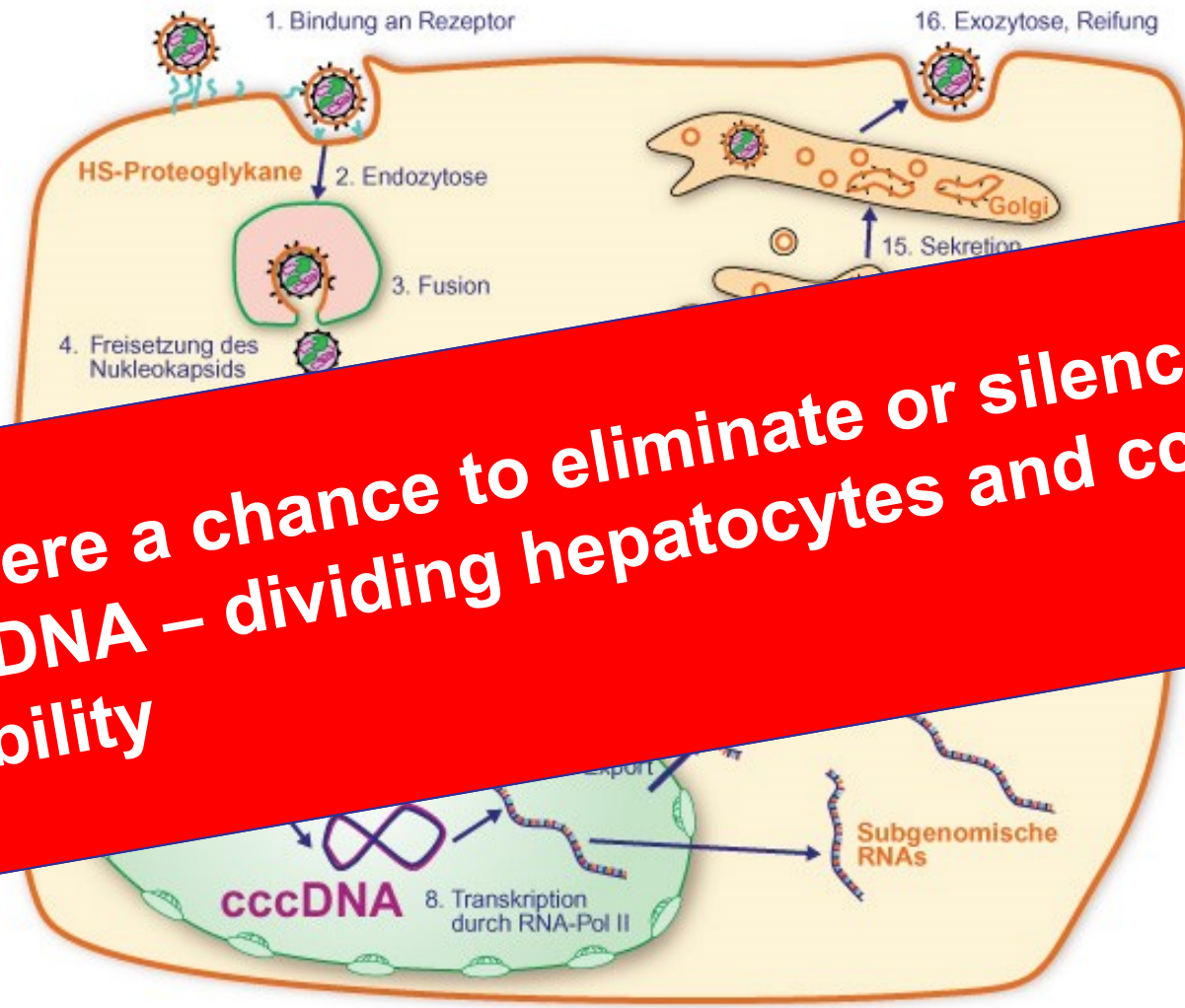
Jorg Petersen[1]*, Stefan Unger[1], Maria Buti[2], Marc Lutgehetmann[3], Pietro Lampertico[4], Christoph Sarrazin[5], Peter Buggisch[1]

Submitted for EASL 2013

- **Is combination therapy bringing us closer to eradication of HBV ?**

- Role of cccDNA ?
- Is combo better for higher rates of HBsAg loss?
- Novel combos?

Once HBV - always HBV ?!

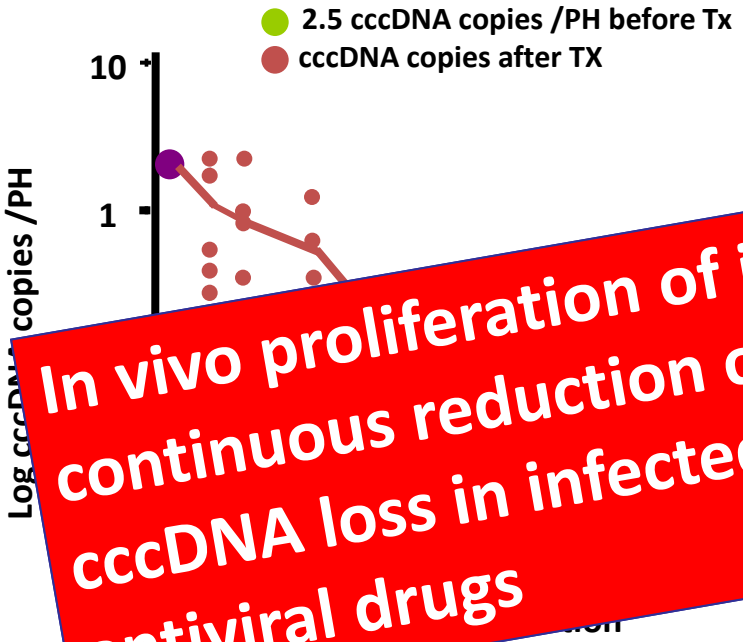


Is there a chance to eliminate or silence cccDNA – dividing hepatocytes and cccDNA stability

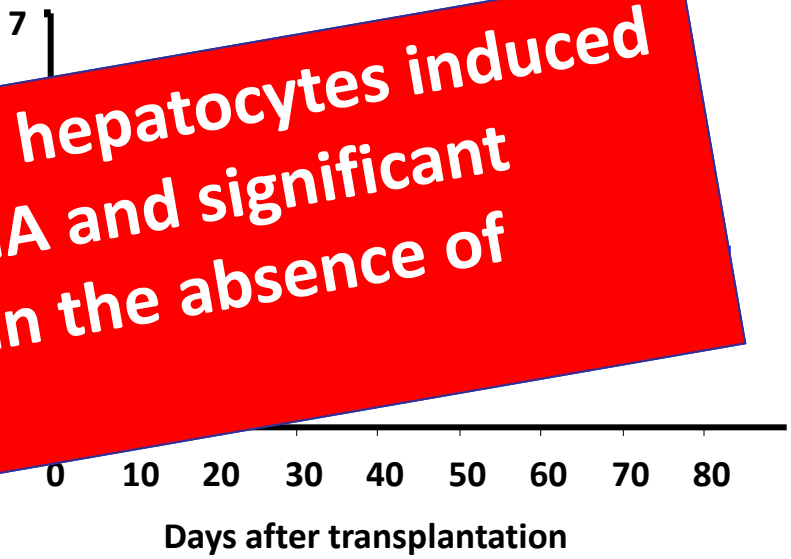
mod. from S Urban, J Petersen; J Hepatol 2010

Determination of intrahepatic cccDNA loads in proliferating hepatocytes in a mouse model (uPA/SCID mice)

cccDNA decline per infected cell



Intrahepatic cccDNA dilution or loss?



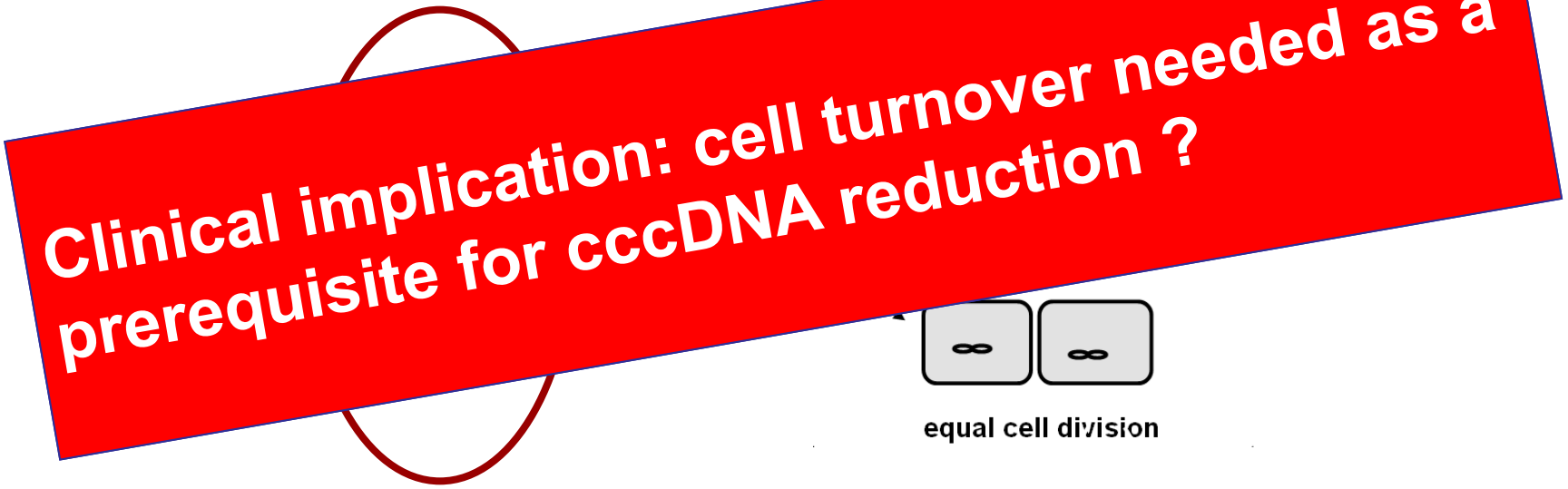
In vivo proliferation of infected hepatocytes induced continuous reduction of cccDNA and significant cccDNA loss in infected livers in the absence of antiviral drugs

Lutgehetmann, Petersen, Dandri, Hepatology 2010

Proposed model of cccDNA decline

cccDNA loss

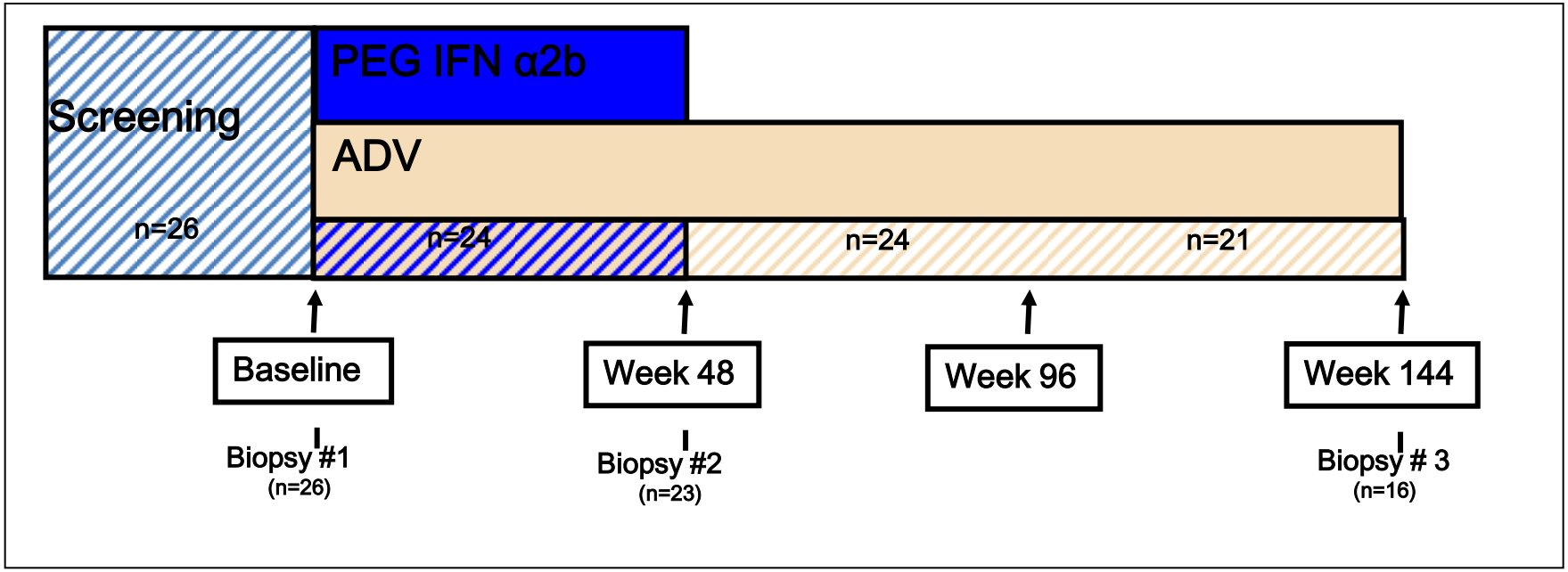
cccDNA dilution without loss



Clinical implication: cell turnover needed as a prerequisite for cccDNA reduction ?

Cell division in the setting of liver regeneration induces cccDNA destabilization and formation of cccDNA-free cells

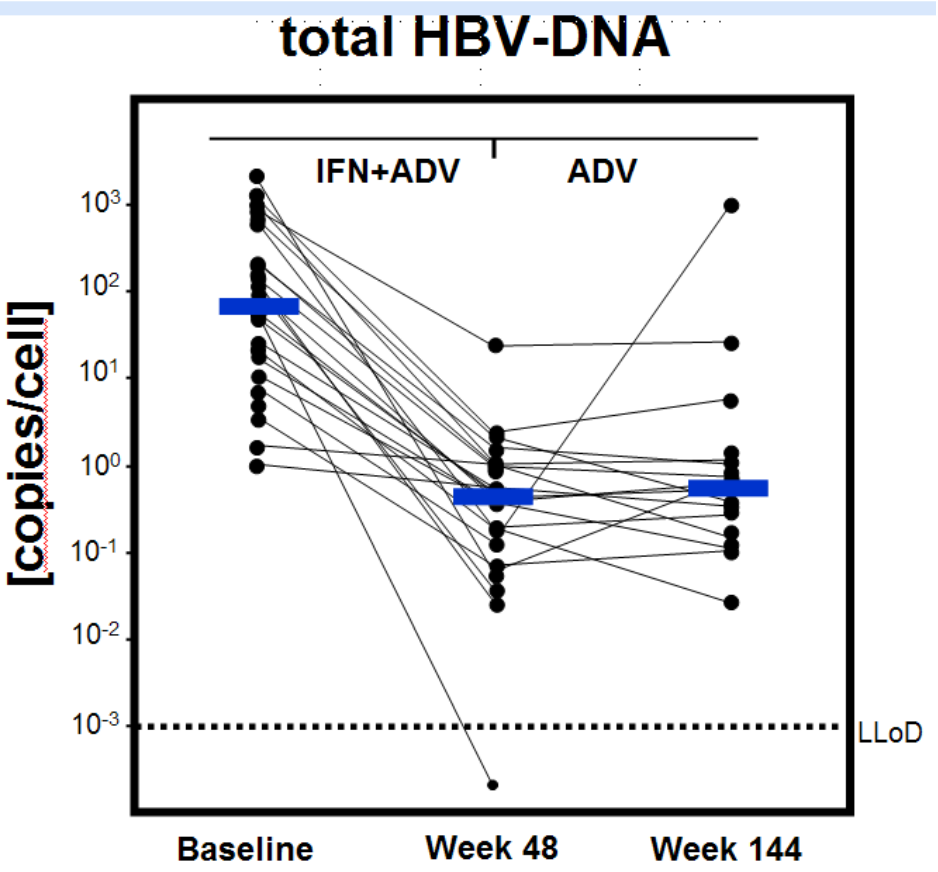
Study design: Monocenter open label, HBeAg+ and HBeAg- patients

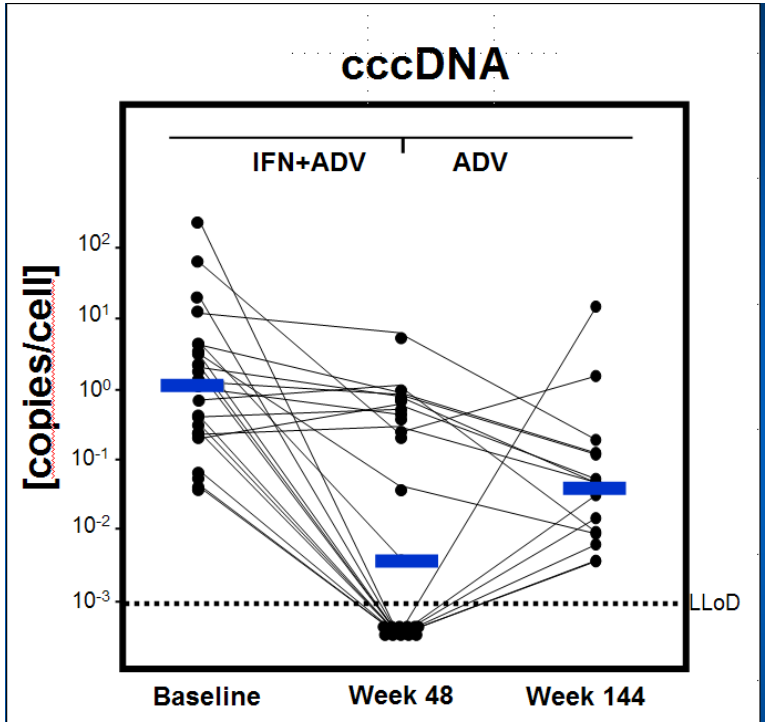


Triplet liver biopsies were obtained from 16 patients

Wursthorn, Petersen Hepatology 2006
Lütgehetmann, Petersen Antiviral Therapy 2008

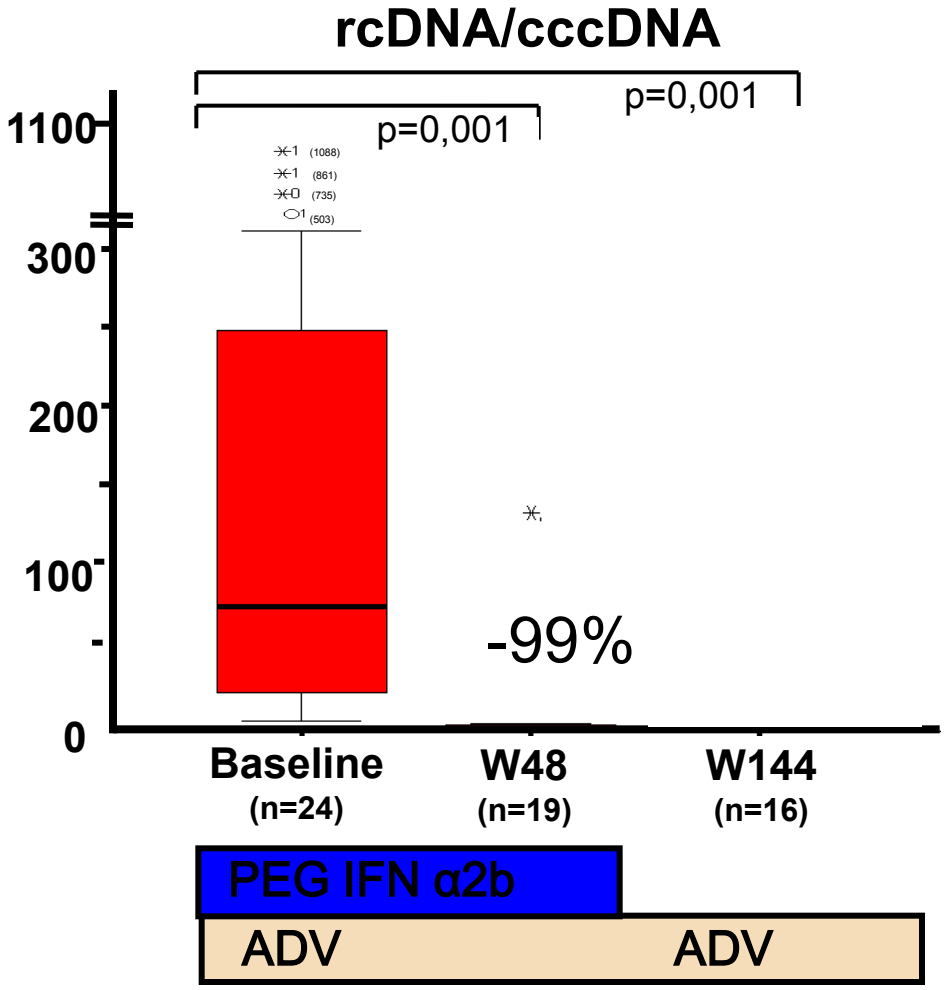
Combination therapy with PEG-IFNα + ADV induced strong intrahepatic HBV DNA reduction





Lütgehetmann Antiviral Therapy 2008

Inhibition of intrahepatic viral productivity by different antiviral regimens



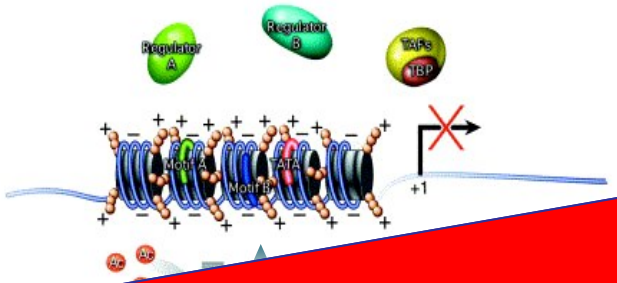
How about the more potent NUCs ETV and TDF ?

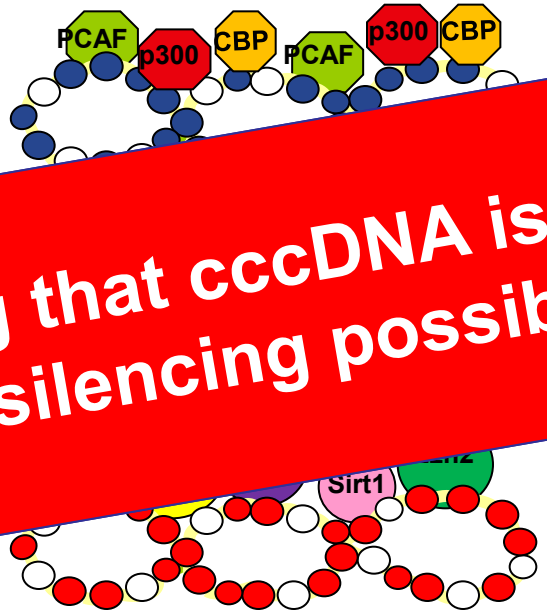
Silencing of cccDNA?

Regulation of cccDNA transcriptional activity?

Lütgehetmann Antiviral Therapy 2008

Transcription of the HBV cccDNA minichromosome can be regulated epigenetically





Beginning of understanding that cccDNA is controlled epigenetically – silencing possible?

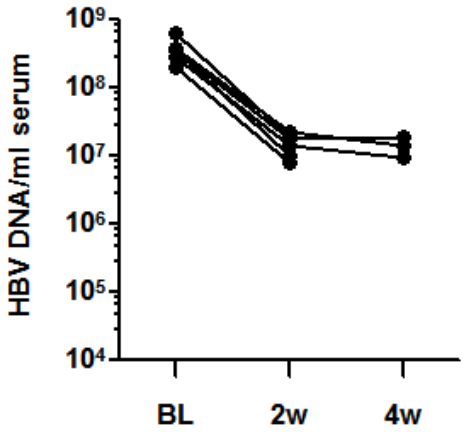
Histone acetylation/methylation affects the regulation of gene expression

IFNα treatment is accompanied by a decrease in the acetylation of cccDNA bound H4 histones in vitro

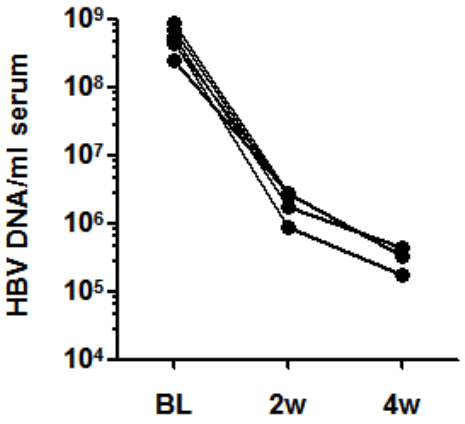
Pollicino et al. Gastroenteroplogy 2006; Levrero et al. J Hepatol, 2009; Belloni, PNAS 2009
Levrero, Dandri, Raimondo, Petersen J Hepatol 2009; Belloni, Levrero, Petersen, Dandri, Raimondo J Clin Inv 2012

Combo therapy in upa mice: viremia

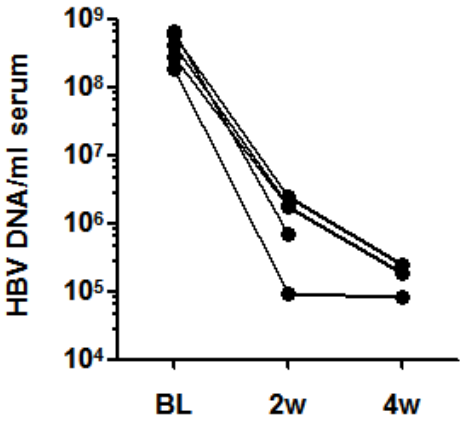
Viremia PEG-IFN



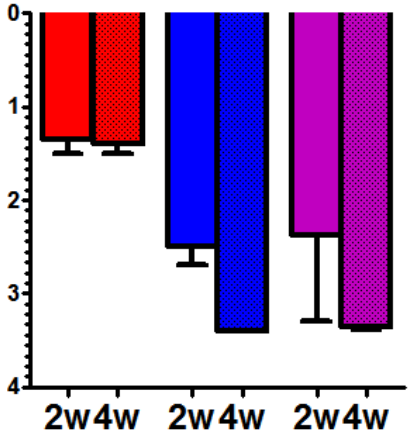
Viremia ETV



Viremia Combo



Viremia log reduction



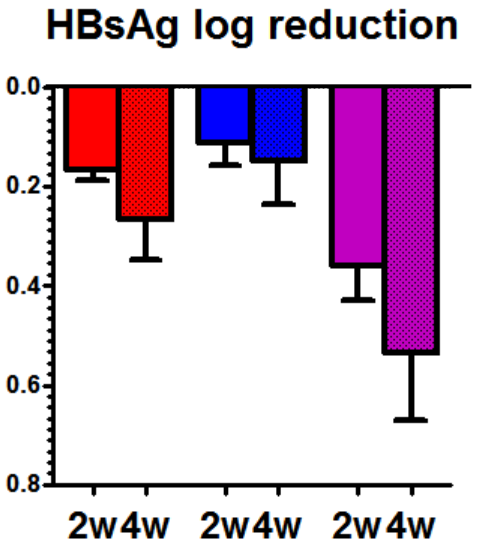
Median viremia reduction after 4 weeks of therapy:

- 1.4Log with Peg-IFN
- 3.4Log with ETV
- 3.3Log with the combination

Suppression in viremia was strongest in the presence of ETV

Allweiss et al EASL2012 submitted

Serological parameters: HBsAg & HBeAg changes



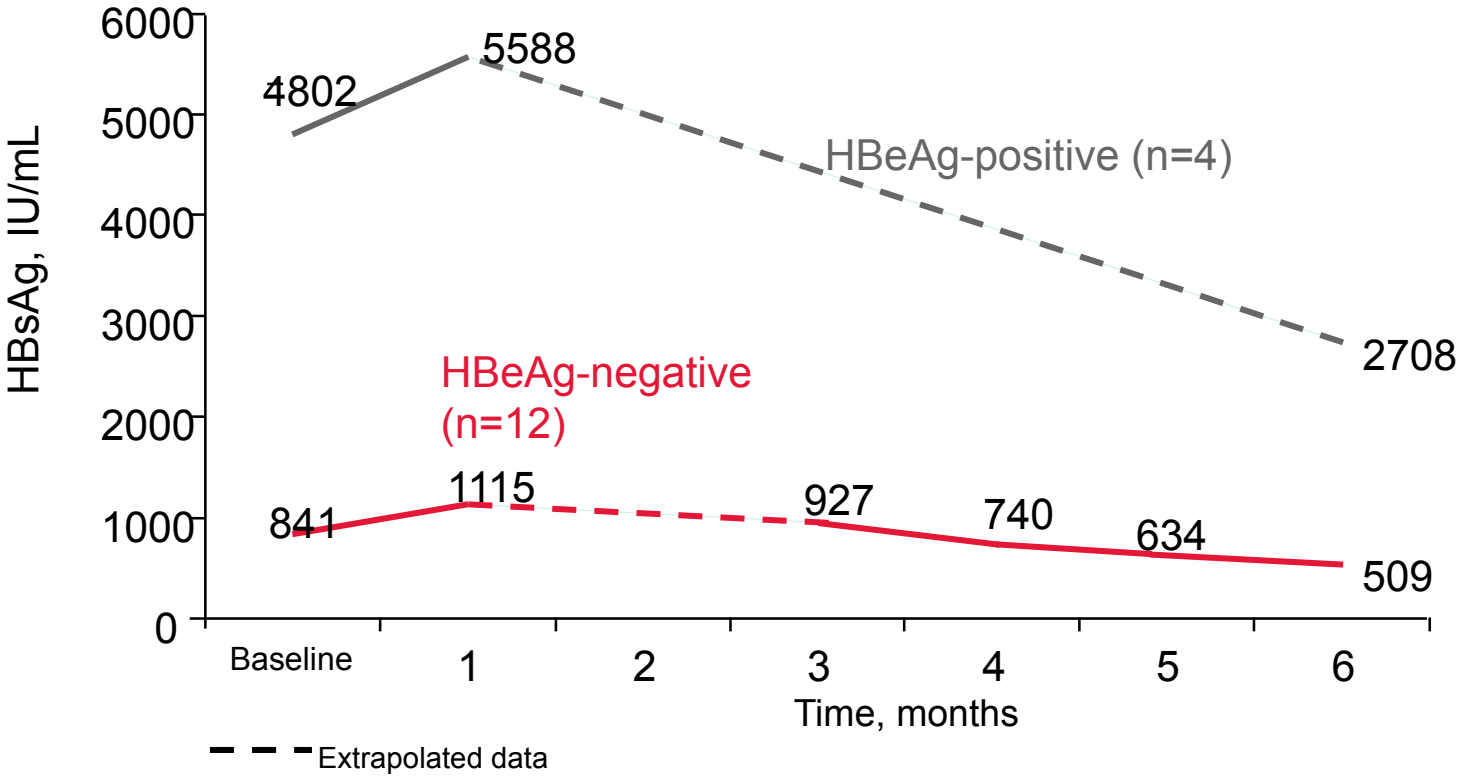
Median HBsAg reduction after 4 weeks of therapy:

- 0.21Log with Peg-IFN
- 0.13Log with ETV
- 0.5Log with combination

Suppression of HBsAg was strongest in the presence of Peg-IFN-α

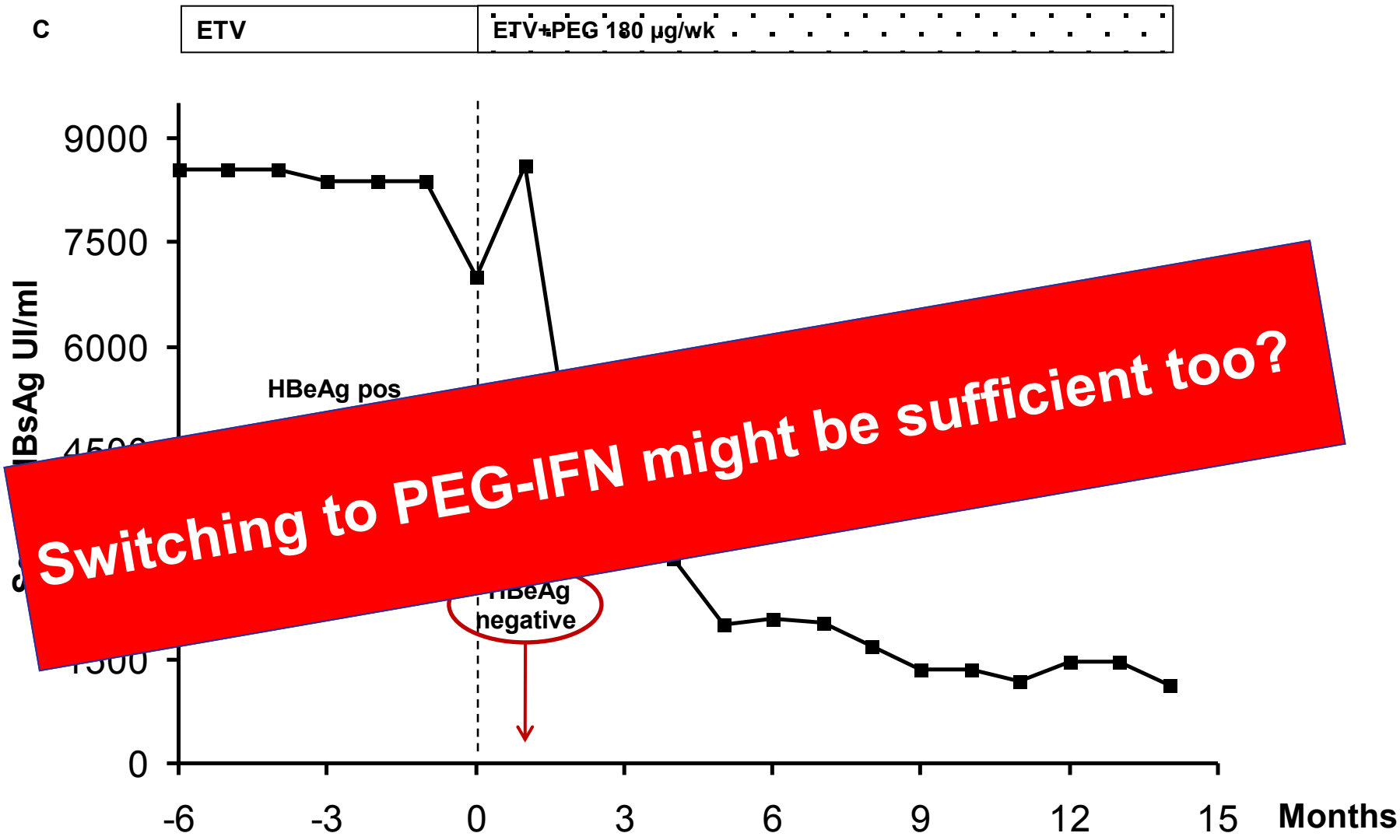
Allweiss et al EASL2012 submitted

Peg-IFN Add-On Strategy leads to more HBsAg reduction



- Seroconversion to anti-HBe in 2 patients (months 4 and 7)
- All patients remained HBV DNA negative
- 8 (50%) patients discontinued PEG-IFN, including
  5 (31%) for unchanged HBsAg levels at 24-week, and
  3 for IFN-related side effects

Lampertico P, et al. EASL 2012; Abstract 523



Lampertico et al EASL 2012, Abstract 523

Primary combo, add-on or switch ?
PEG-IFN plus NUCs

- Adding peginterferon to entecavir increases HBsAg decline and HBeAg clearance – first results from a global randomized trial (ARES-study) *Sonneveld et al, AASLD 2012, #19*

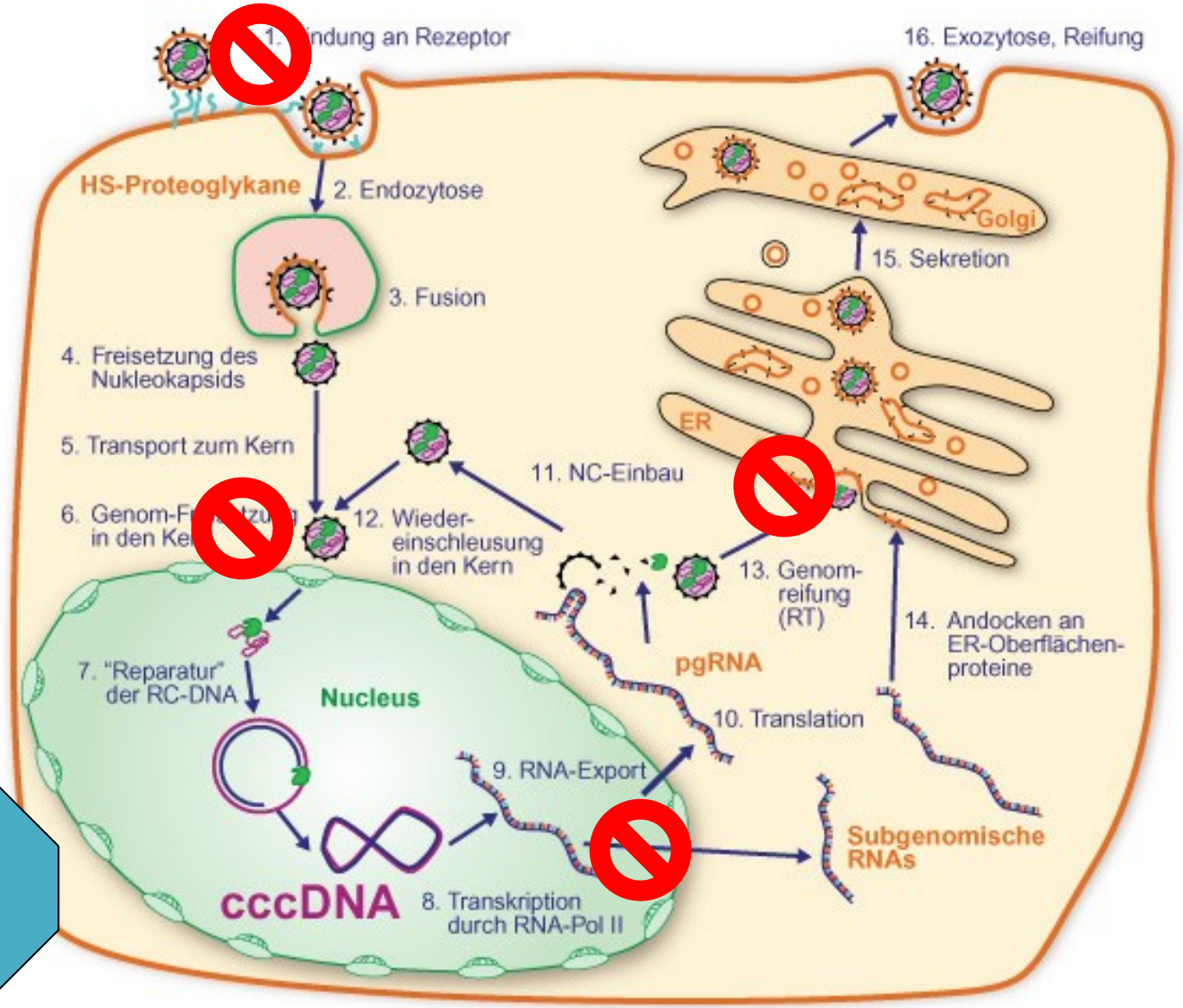
- Switching from long-term entecavir to peginterferon alfa-2a induces HBsAg seroconversion/HBsAg clearance in HBeAg positive patients *Qin Ning et al, AASLD 2012, #216*

- PADD-on study, multicenter Germany, main target: to dissect immunological responses, ongoing

- Improved efficacy by individualized combination of PEG IFN a 2a and ADV in HBeAg + chronic hepatitis B
  Wang et al, Hepatogastroenterology 2012

Towards new treatment targets

Innate responses



Adaptive Immune Responses

New HBV targets

Additional therapeutic strategies aiming at inhibiting different steps of the HBV life-cycle or mediating host factors are at early stages of development

TLR agonists (+)

Cyclophilin inhibitors (- ?)

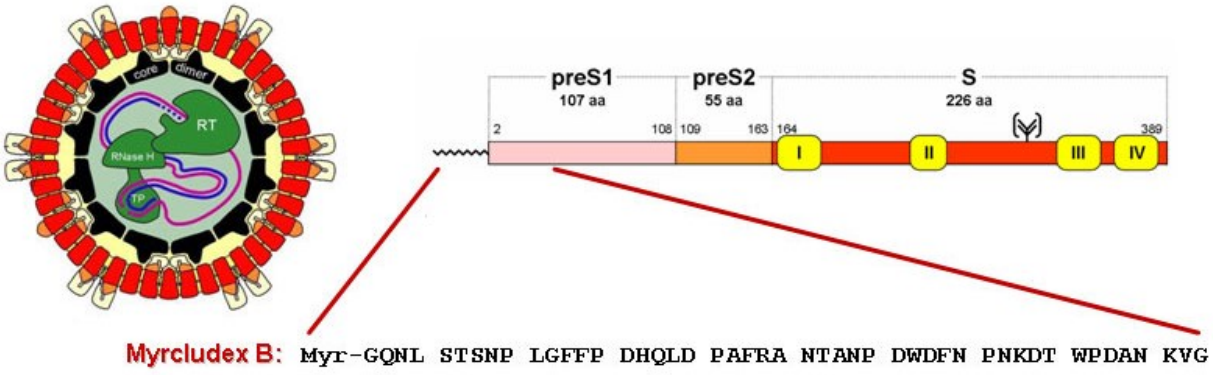
HBsAg release inhibitors (??)

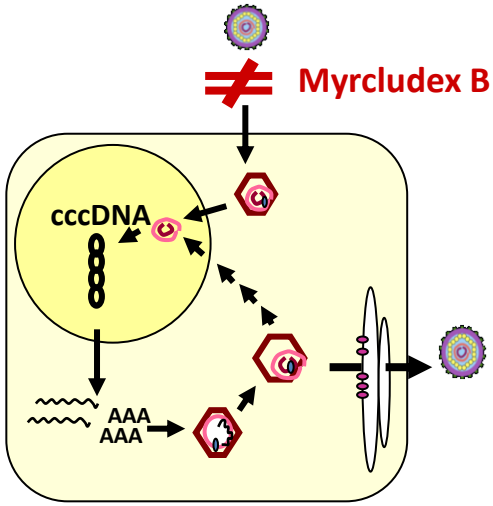
Entry inhibitors (HBV and HDV) (+)

Therapeutic vaccination (-)

Prenylation inhibition (HDV) (-?)

Acylated HBV preS1-derived peptides block HBV infection *in vitro* – *entry inhibitor*

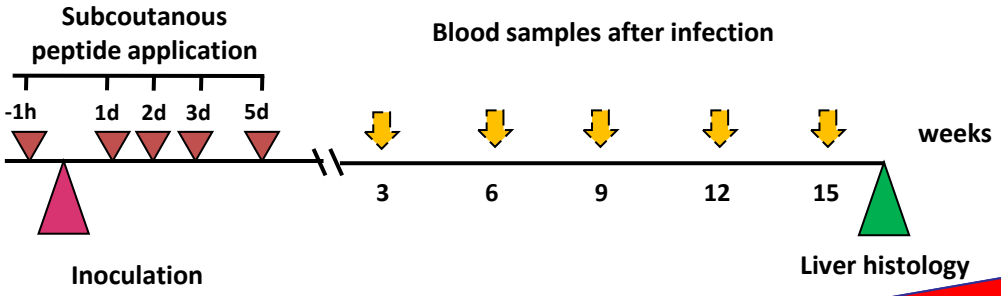




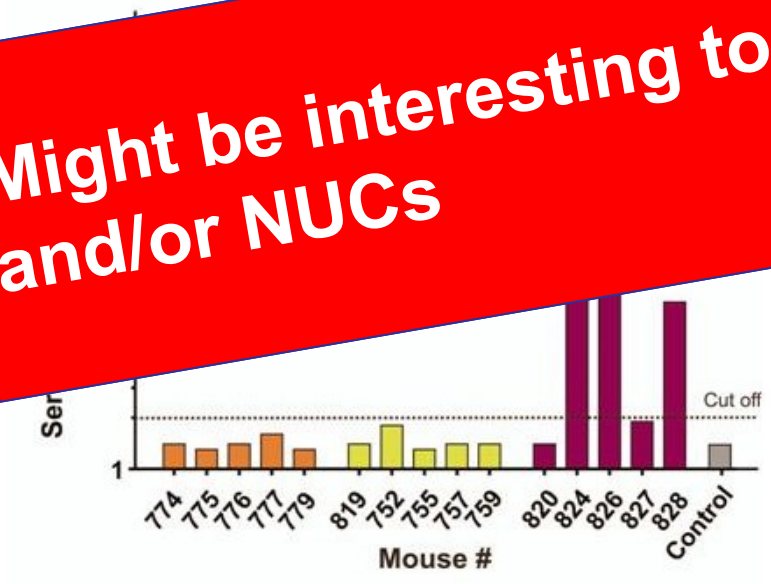
Chemically synthesized lipopeptides derived from the envelope of HBV block virus infection in cell culture (HepaRG & PTH, PHH)

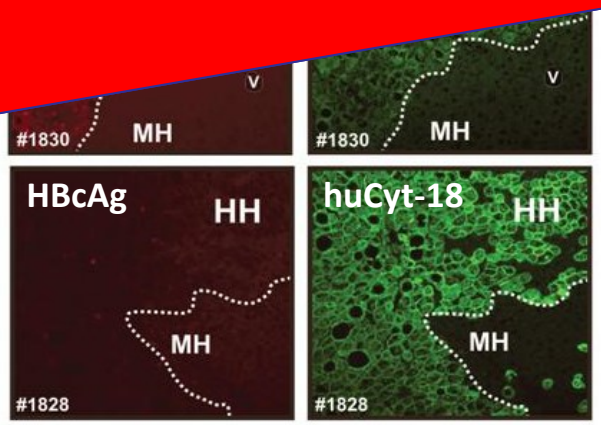
Gripon et al., PNAS, 99 (24) 2002
Urban et al., J. Virol, 79 (3), 2005
Glebe et al., Gastroenterology, 129, 2005
Engelke et al., Hepatology, 43, 2006
Schulze et al., Hepatology, 46, 2007

Administration of Myrcludex B prevents the establishment of de novo HBV infection in vivo; Phase I studies completed, IIa recruiting



Might be interesting to combine with PEG-IFN and/or NUCs





Petersen, Dandri et al. Nature Biotech. 2008

Conclusions

- Mono therapy either with NUCs or PEG IFN is the therapy of choice for the great majority of chronically infected HBV patients in 2012
- The combination of ETV plus TDF is only required in a very few clinical situations such as true drug resistance and advanced liver disease
- Combination therapy with NUCs and PEG IFN have shown to greater reduce the amount of cccDNA and HBsAg
- There might be room for combo therapy in the future for a higher chance of clinical cure (HBsAg loss)

Thank you for your attention

Jorg Petersen
Liver Unit
IFI Institute for Interdisciplinary Medicine
Asklepios Klinik St. Georg
University of Hamburg

email: petersen@ifi-medizin.de

Disclosures

My presentation includes off-label use of combination therapies (diiferent NUCs and NUCs plus PEG-IFN)

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