



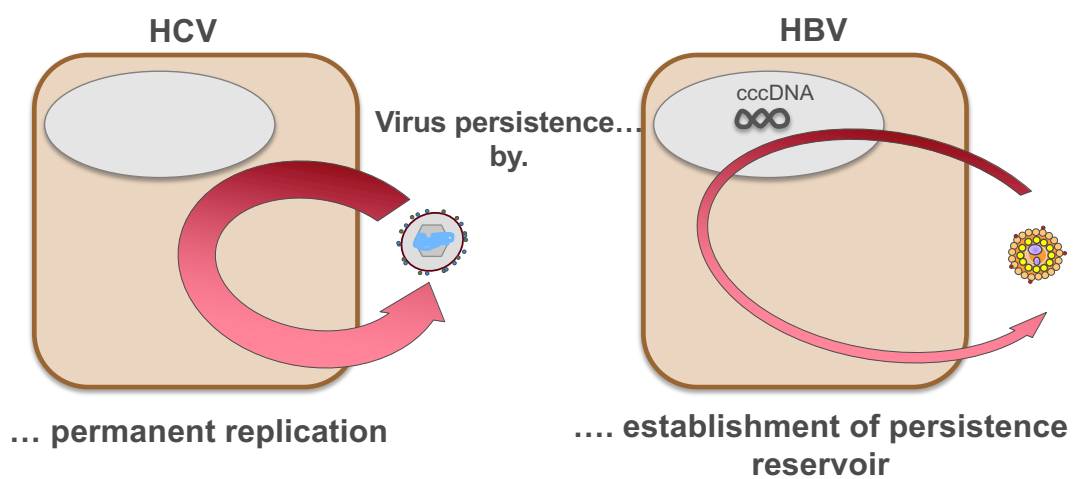
New insights into immunopathogenesis and management of hepatitis B virus infection

Robert Thimme
Department of Medicine II
University Hospital Freiburg

1

HCV vs. HBV

Why is HBV cure so difficult??



2

Management of hepatitis B virus infection



3

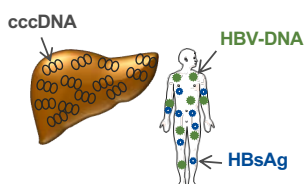
Stages of chronic HBV infection

viremic infection

HBV-DNA

HBsAg

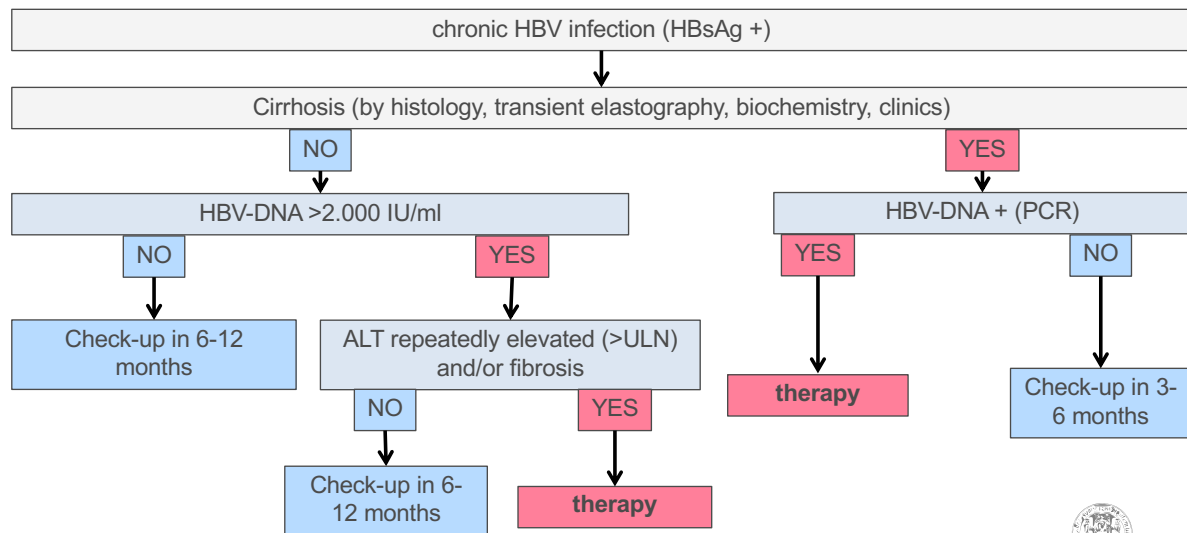
Anti-HBc



4

Therapeutic algorithm

chronic HBV infection – when to treat



5

chronic HBV infection

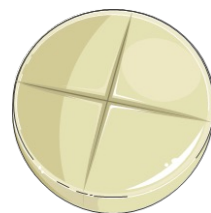
current treatment options

pegylated interferon-alpha



Nucleos(t)id analogues (NA)

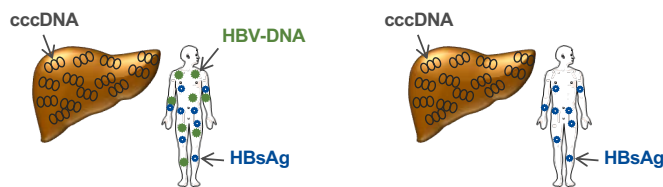
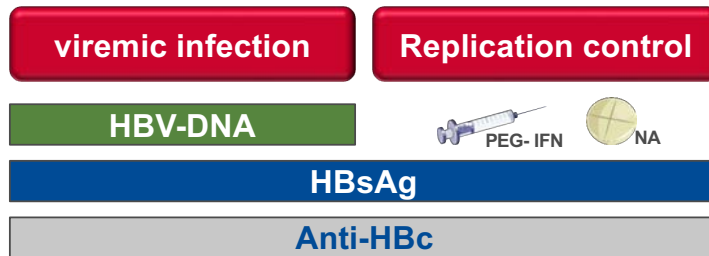
Entecavir



Tenofovir

6

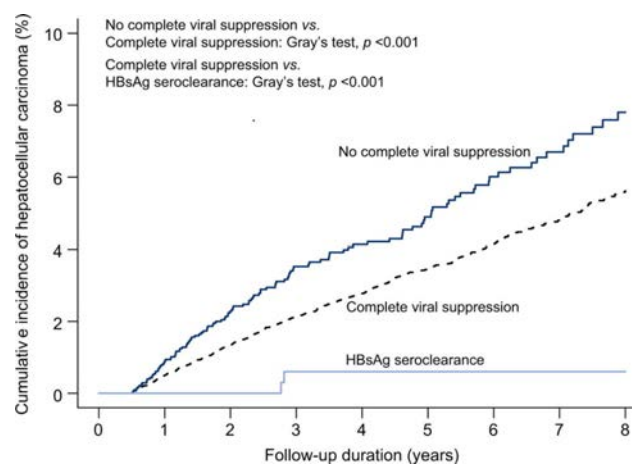
Stages of chronic HBV infection



7

Why functional cure

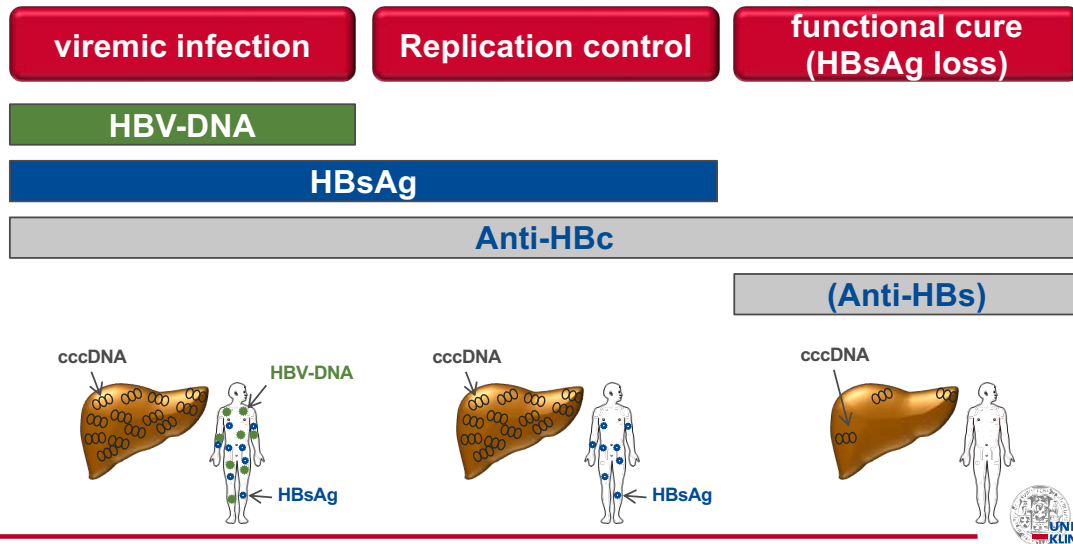
HCC risk in patients with viral suppression or HBsAg-loss



Yip et al., J Hepatol. 2019;70(3):361-370.

8

Stages of chronic HBV infection



9

HBV cure with current therapies

HBeAg+ patients:	48 weeks PEG-IFN: approx. 3-7% HBsAg-loss after 6 months
	48 weeks NA-therapy: ca. 0-3% HBsAg-loss after 6 months
HBeAg- patients:	48 weeks PEG-IFN: ca. 4% HBsAg-loss after 6 months
	48 weeks NA-therapy: 0% HBsAg-loss after 6 months

EASL Guidelines 2017



10

Chronic Hepatitis B –

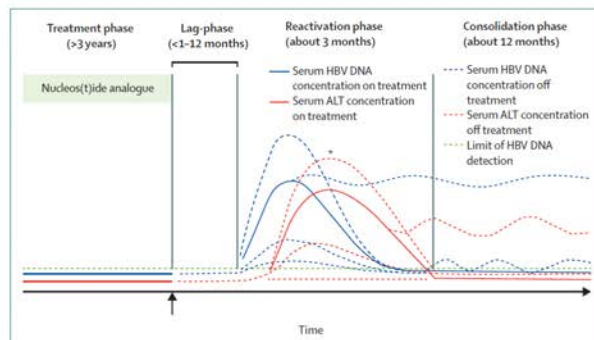
„functional cure“ with current therapeutic strategies

Stopping NAs?

Review

Serum alanine aminotransferase flares in chronic hepatitis B infection: the good and the bad

Marc G Ghany, Jordan J Field, Kyong Mi Chang, Henry L Y Chan, Anne S F Lok, Kumar Y Viswanathan, Harry I A Janssen



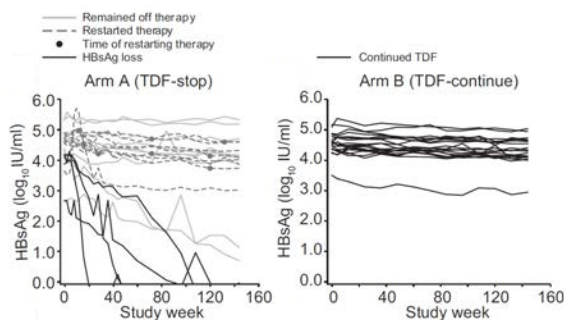
Ghany et al., Lancet Gastroenterol Hepatol, 2020



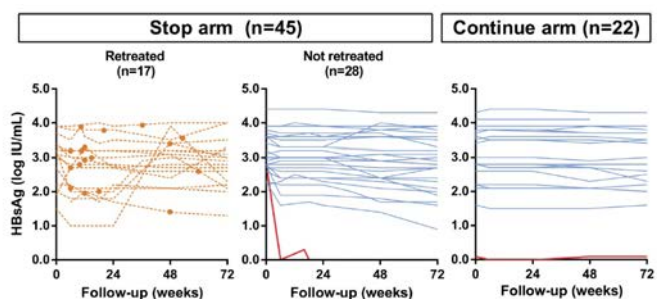
11

Stop NUC treatment?

Low rates of HBsAg loss after stop of NUC treatment



Berg et al. FINITE study. J Hepatol 2017; 67:918–24



Liem et al. TORONTO STOP study. GUT 2019; 68:2206–2213



12

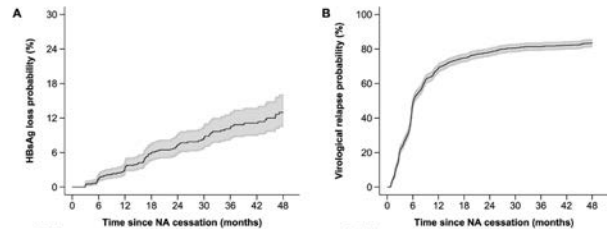
Retract-B Study?

Gastroenterology 2022;162:757-771

CLINICAL—LIVER

Off-Therapy Response After Nucleos(t)ide Analogue Withdrawal in Patients With Chronic Hepatitis B: An International, Multicenter, Multiethnic Cohort (RETRACT-B Study)

Grishma Hirode,^{1,2,3} Hannah S. J. Choi,^{1,2} Chien-Hung Chen,⁴ Tung-Hung Su,⁵ Wai-Kay Seto,⁶ Stijn Van Hees,⁷ Margarita Papatheodoridis,⁸ Sabela Lens,⁹ Grace Wong,¹⁰ Sylvia M. Brakenhoff,¹¹ Rong-Nan Chien,¹² Jordan Feld,^{1,2,3} Milan J. Sonneveld,¹¹ Henry L. Y. Chan,¹⁰ Xavier Forns,⁹ George V. Papatheodoridis,⁸ Thomas Vanwolleghem,⁷ Man-Fung Yuen,⁶ Yao-Chun Hsu,¹³ Jia-Hong Kao,⁹ Markus Cornberg,¹⁴ Bettina E. Hansen,^{1,3} Wen-Juei Jeng,¹² and Harry L. A. Janssen,^{1,2,3} on Behalf of the RETRACT-B Study Group



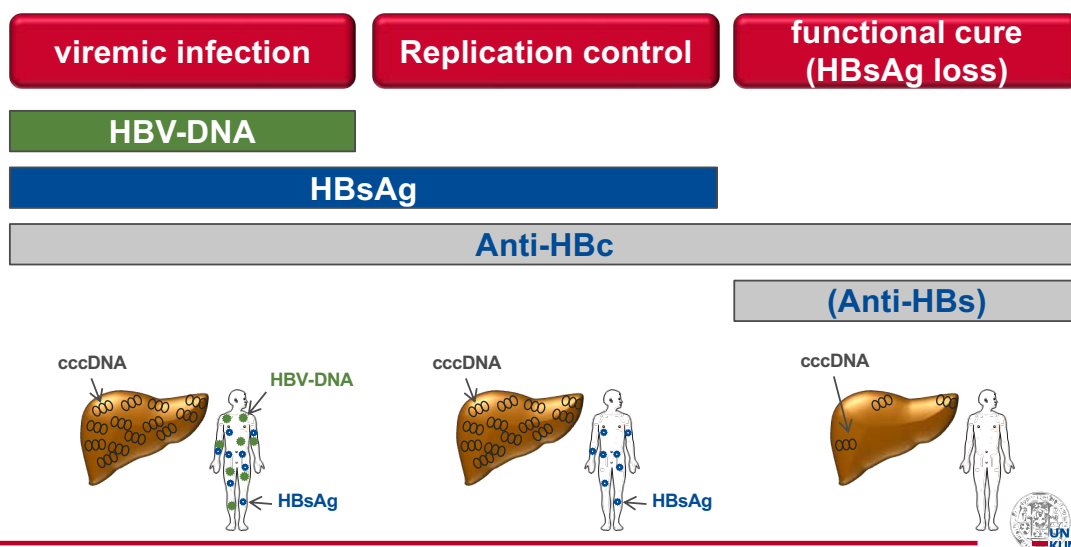
	Virally suppressed, HBeAg negative CHB patient on NA therapy			
Race/ethnicity	White		Asian	
End of therapy HBsAg levels	HBsAg <1000 IU/mL	HBsAg ≥1000 IU/mL	HBsAg <100 IU/mL	HBsAg ≥100 IU/mL
4-year off-therapy HBsAg loss probability	41%	5%	33%	2%
Clinical recommendations	Stop NA	Continue NA	Stop NA	Continue NA

Hirode et al. Gastroenterology 2022; 162:757-771



13

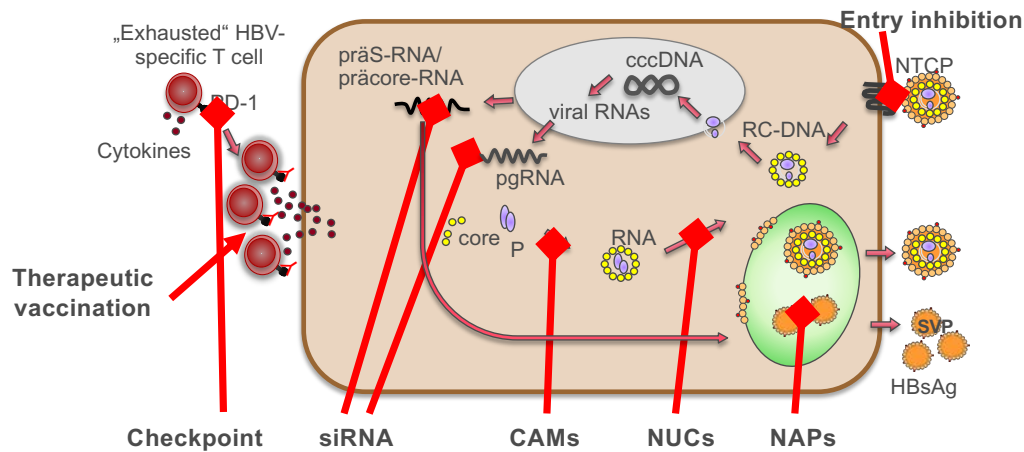
Stages of chronic HBV infection



14

Chronic Hepatitis B –

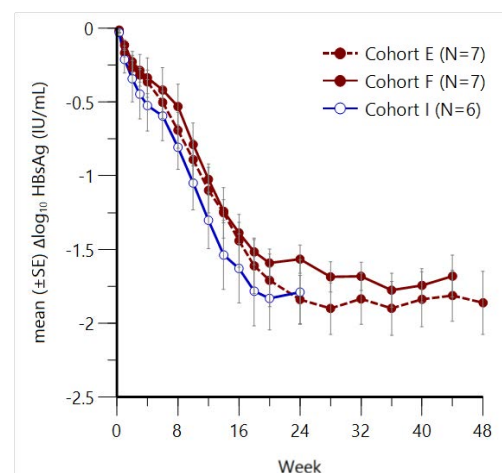
Aim of „functional cure“ with new therapeutic strategies



15

Hepatitis B: siRNA AB-729

- Blocks all HBV transcripts
- Injections each 4 / 8 weeks
- Duration 24 -> 48 weeks
- 15/20 patients reach HBsAg <100 IU/ml
- Reductions in total-HBV-RNA, pgRNA, L-HBsAg and M-HBsAg
- Activation of von HBV-spezifisch CD8+ T cells



Yuen MF et al., ILC 2021 (LBO-2764), Thi et al., ILC 2021 (PO-2822), Paratala et al., ILC 2021 (PO-2823)

16

Conclusion HBV management

- „functional cure“ = HBsAg-loss remains the exception with current therapies (NAs +/- PEG-IFN)
- Approx. 70% of patients experience virological relapse 4 years after NA withdrawal
- New treatments like entry inhibitors or interfering RNAs appear to be promising candidates for future therapeutic strategies

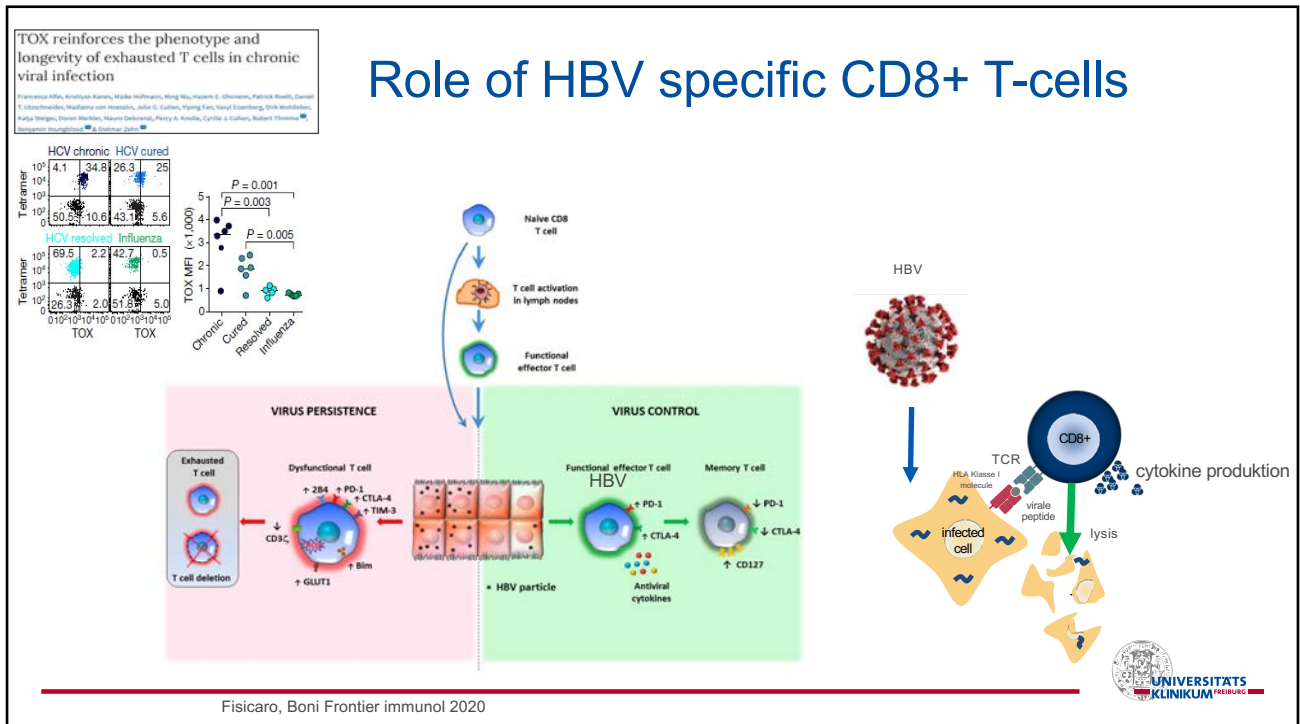


17

Immunopathogenesis of HBV

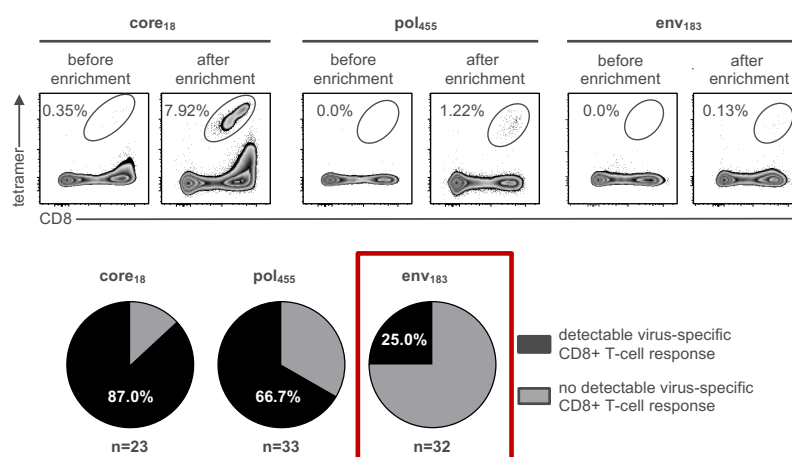


18



19

Differences in HBV specific CD8+ T-cell responses

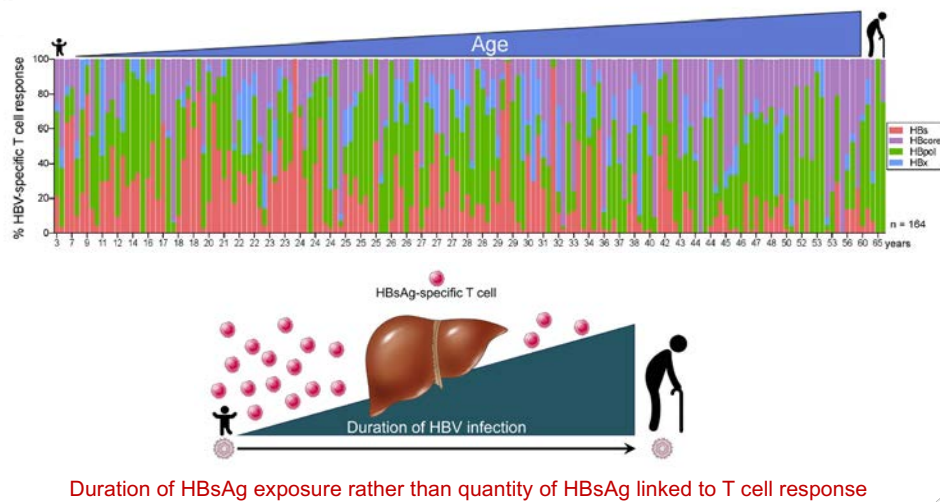


- Lack of HBsAg specific CD8+ T cell responses with increasing duration of infection
- Mechanism unknown

Schuch et al, *GUT* 2019

20

Effects of HBsAg on specific CD8+ T-cell

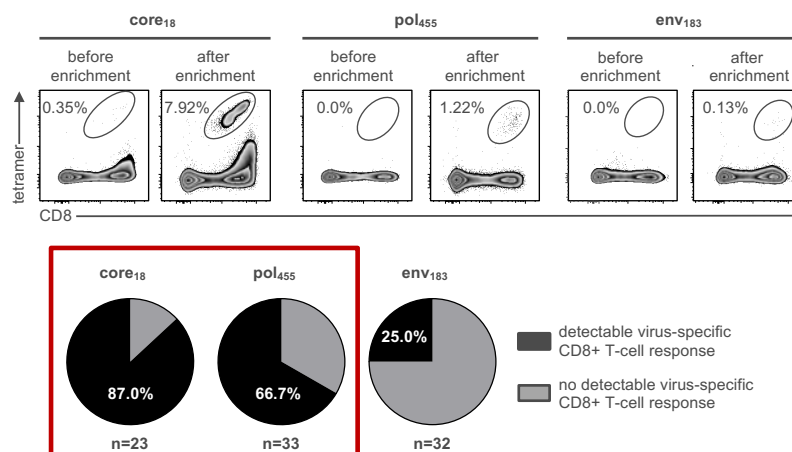


Le Bert, Gill, Hong et al Gastroenterology 2020



21

Differences in HBV specific CD8+ T-cell responses



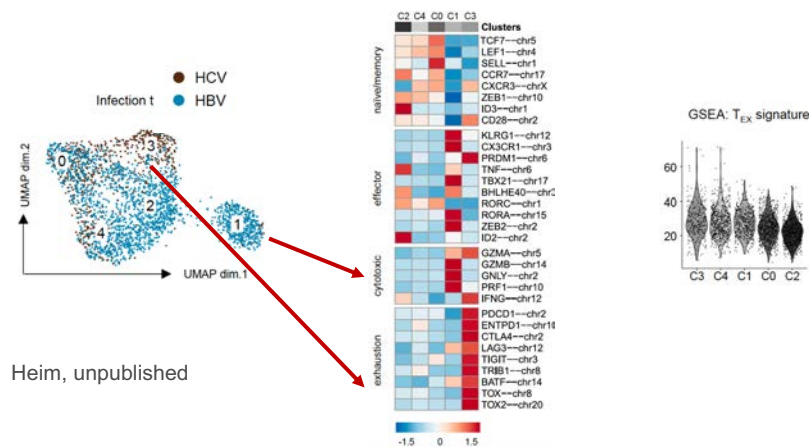
- Core and Pol specific CD8+ T cells detectable in majority of patients

Schuch et al, GUT 2019



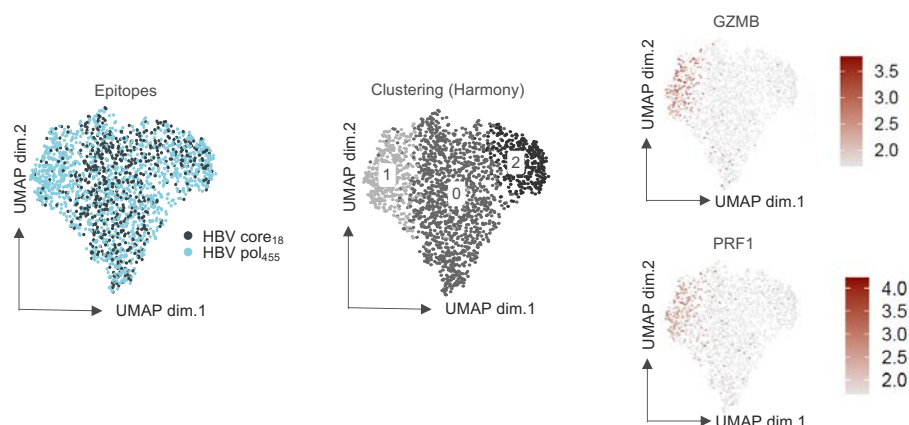
22

HBV specific CD8+ T cells are less exhausted compared to HCV



23

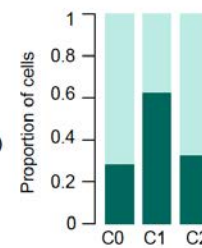
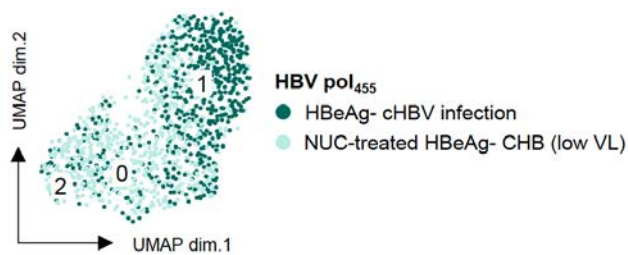
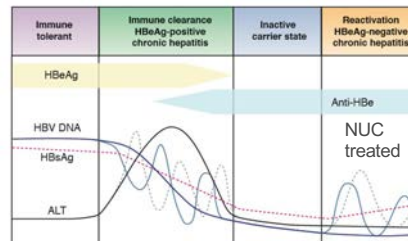
Does the molecular profile of HBV-specific CD8+ T cells targeting cor and pol differs?



Different subset diversification in HBV-specific CD8+ T cells with enforced cytotoxic signature in HBV pol₄₅₅-specific CD8+ T cells.

24

Cytolytic pol-specific CD8+ T cells are linked to endogeneous control of HBV Infection

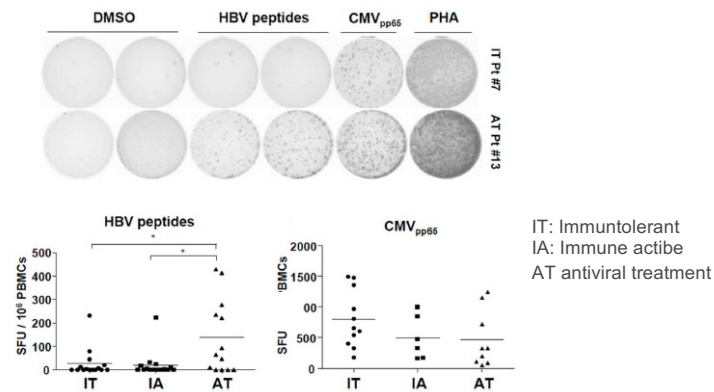


25

Can antiviral therapy restore HBV specific T cell dysfunction?

26

Therapy mediated restoration of HBV specific CD8+ T cells



At least partial restoration of HBV specific CD8+ T-cell function after therapy mediated antigen reduction

Sung et al Front Immunol 2020

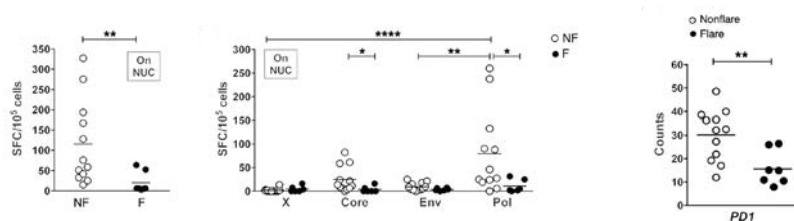


27

Functional relevance HBV specific CD8 T cells under NUC treatment

Hepatitis B virus-specific T cells associate with viral control upon nucleos(t)ide-analogue therapy discontinuation

Laura Rivino,¹ Nina Le Bert,^{1,2} Upkar S. Gill,^{1,2} Kamini Kunasegaran,¹ Yang Cheng,¹ Damien Z.M. Tan,¹ Etienne Becht,¹ Navjyot K. Hansi,¹ Graham R. Foster,¹ Tung-Hung Su,¹ Tai-Chung Tseng,¹ Seng Gee Lim,¹ Jia-Hong Kao,¹ Evan W. Newell,¹ Patrick T.F. Kennedy,¹ and Antonio Bertoletti^{1,4*}



Functional PD1+ cor and pol specific CD8+ T cells may predict absence of flare after discontinuation

JCI 2018

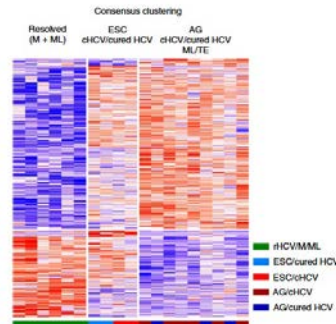


28

Lessons learned from HCV: CD8+ T-cell exhaustion reversible after antigen elimination?

Memory-like HCV-specific CD8+ T cells retain a molecular scar after cure of chronic HCV infection

Nina Hensel^{1,2,3,4,5}, Zhiqiang Gu^{1,2,3}, Sagar^{1,2,3}, Dominik Wieland^{1,2}, Katharina Jechow¹, Janine Kemming^{1,2,3}, Sian Llewellyn-Lacey¹, Emma Gostick¹, Özlem Sogukpinar^{1,2}, Florian Emmerich^{1,2}, David A. Price^{1,2,3}, Bertram Bengsch^{1,2,3}, Tobias Boettler^{1,2}, Christoph Neumann-Haefelin^{1,2}, Roland Ellis^{1,2}, Christian Conrad^{1,2}, Ralf Bartenschlager^{1,2,3,4,5}, Dominic Gröbe^{1,2,3}, Naveed Ishaque^{1,2}, Robert Thimme^{1,2,3,4,5} and Malke Hofmann^{1,2,3,4,5}



Maintenance of a molecular scar after antigen elimination

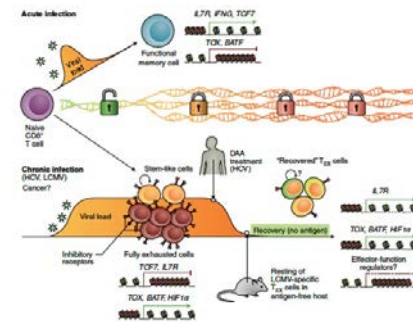
Hensel et al, Abdel-Hakeem et al, Yates et al, Tonnerre et al Nature Immunology 2021

IMMUNE EXHAUSTION

T cell exhaustion—a memory locked behind scars

Following clearance of chronic infections, virus-specific CD8+ T cells recover a subset of memory-related transcriptome features. Yet their unique open chromatin landscape largely reflects an exhausted or dysfunctional state, limiting their protective memory potential.

Amin Yousif and Hazem E. Ghoneim



29

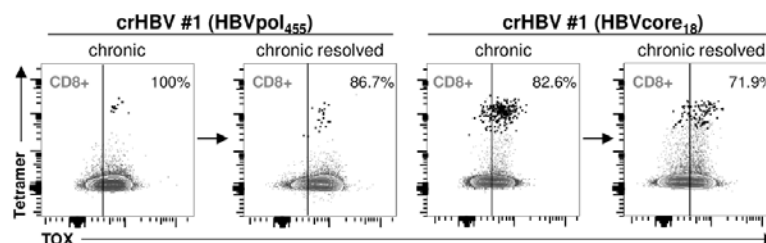
TOX expression maintained after antigen elimination

Original research

TOX defines the degree of CD8+ T cell dysfunction in distinct phases of chronic HBV infection

Kathrin Heim,^{1,2} Benedikt Binde¹, Sagar,¹ Dominik Wieland,¹ Nina Hensel,^{1,2} Sian Llewellyn-Lacey,¹ Emma Gostick,¹ David A. Price,^{1,2,3} Florian Emmerich,¹ Hildegard Vingerhoet,¹ Anke R M Kraft,^{1,2} Markus Cornberg,¹ Tobias Boettler,¹ Christoph Neumann-Haefelin,¹ Dietmar Zehn,^{1,2} Bertram Bengsch,^{1,2,3} Malke Hofmann,^{1,2} Robert Thimme,¹

GUT 2021

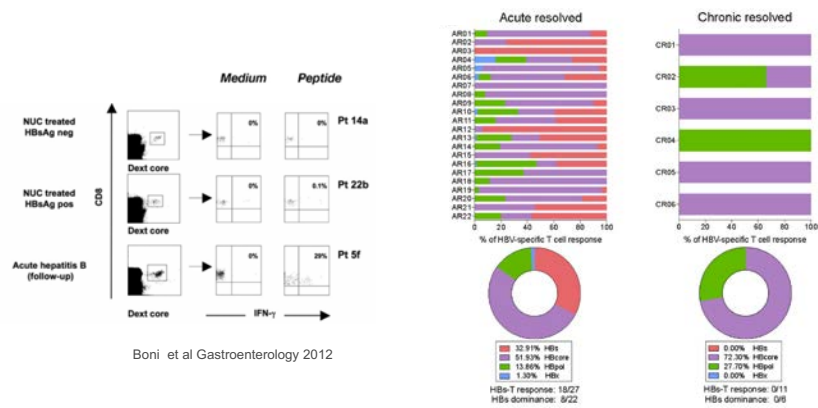


Transcriptional scar of HBV specific CD8+ T cell exhaustion after antigen elimination



30

Molecular scar in HBV specific CD8+ T cells after antigen elimination?



No complete recovery of HBV specific CD8+ T cells after resolution of chronic infection



31

Restoration of HBV specific T cell dysfunction by checkpoint inhibitors, vaccination?



32

Immunological cure of HBV infection

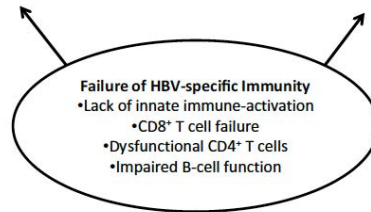
Julia Lang¹ · Christoph Neumann-Haefelin¹ · Robert Thimme¹

Restoring dysfunctional HBV-specific immune responses

- TLR agonist
- checkpoint inhibitors

Replacing dysfunctional HBV-specific T cell responses

- T cell engineering



Induction of novel HBV-specific immune responses

- therapeutic vaccination



Hepatology 2019

33

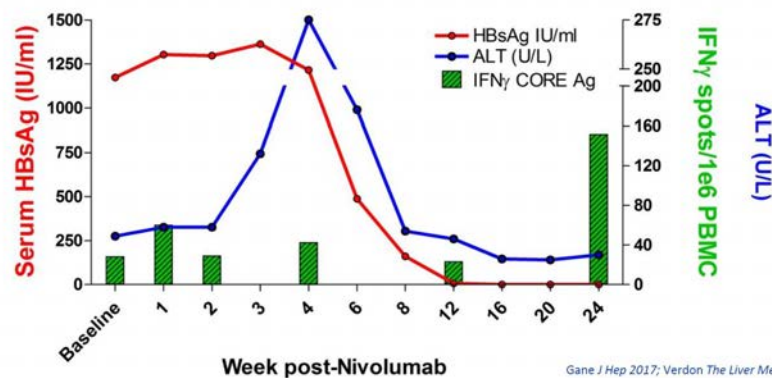
Anti-PD-1 blockade with nivolumab with and without therapeutic vaccination for virally suppressed chronic hepatitis B: A pilot study

Edward Gane^{1,*}, Daniel J. Verdon², Anna E. Brooks², Anuj Gaggar³, Anh Hoa Nguyen³, G. Mani Subramanian³, Christian Schwabe¹, P. Rod Dunbar²

Case Study: Clinical observations



SCIENCE



Gane J Hep 2017; Verdon The Liver Meeting 2017.

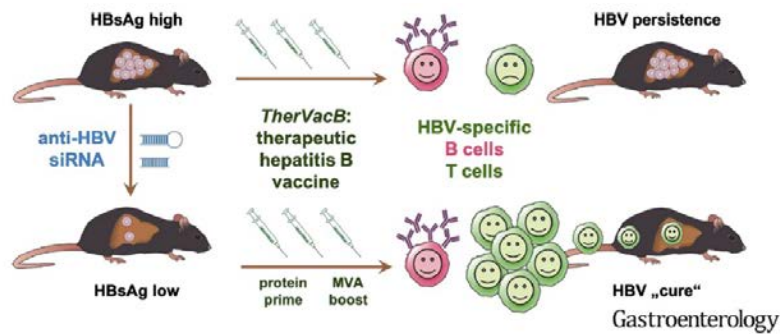


J Hepatol 2019

34

Knockdown of Virus Antigen Expression Increases Therapeutic Vaccine Efficacy in High-Titer Hepatitis B Virus Carrier Mice

Thomas Michler,^{1,2,*} Anna D. Kosinska,^{1,2,*} Julia Festag,¹ Till Bunse,^{1,2} Jinpeng Su,¹ Marc Ringelhan,^{1,3} Hortenzia Imhof,¹ Dirk Grimm,^{2,4} Katja Steiger,⁵ Carolin Mogler,⁵ Mathias Heikenwalder,⁶ Marie-Louise Michel,⁷ Carlos A. Guzman,^{2,8} Stuart Milstein,⁹ Laura Sepp-Lorenzino,⁹ Percy Knolle,^{2,10} and Ulrike Protzer^{1,2}



Gastroenterology 2020



35

Finally,
Lessons learned from SARS-CoV2?



36

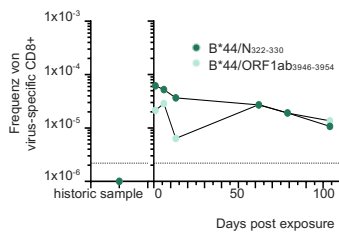
Lessons learned from SARS-CoV2

LETTERS

Characterization of pre-existing and induced SARS-CoV-2-specific CD8⁺ T cells

Isabel Schuster^{1,2}, Janina Krenning^{1,2}, Valeria Oberhardt^{1,2}, Katharina Wild^{1,2}, Lea M. Seidel^{1,2}, Saskia Kilmer^{1,2}, Sagar, Franziska Döhl^{1,2}, Mariya Solov'eva^{1,2}, Annette Decker^{1,2}, Hendrik Lusenberger^{1,2}, Benedikt Bräuer^{1,2}, Dominik Böttlinger^{1,2}, Oriton Teggebar^{1,2}, Saphir Bhat^{1,2}, Marissa Pöschel^{1,2}, Daniela Hübner^{1,2}, Martin Schwaninger^{1,2}, Georg Kocher^{1,2}, Cornelius F. Waller^{1,2}, Alexandra Nierke^{1,2}, David Dornschneider^{1,2}, Florian Emmertich^{1,2}, Henrik E. Maier^{1,2}, Axel Ronald Schmid^{1,2}, Sonja Liewert-Lucy^{1,2}, David A. Price^{1,2}, Tobias Boettler^{1,2}, Bertram Bengsch^{1,2}, Robert Thiemann^{1,2}, Malika Hufnagel^{1,2} and Christoph Neumann-Haefelin^{1,2}

Nature Medicine (2021)



Immediate induction of cross-reactive SARS-CoV2-specific CD8⁺ T cells

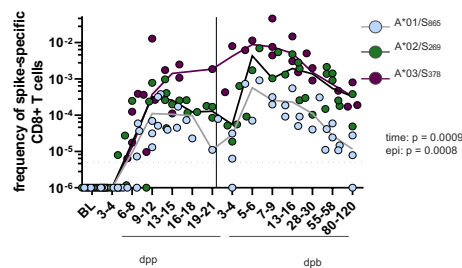
Article

Nature | Vol 597 | 9 September 2021

Rapid and stable mobilization of CD8⁺ T cells by SARS-CoV-2 mRNA vaccine

Valeria Oberhardt^{1,2}, Hendrik Lusenberger^{1,2}, Janina Krenning^{1,2}, Isabel Schuster^{1,2}, Lea M. Seidel^{1,2}, Saskia Kilmer^{1,2}, Sagar, Franziska Döhl^{1,2}, Mariya Solov'eva^{1,2}, Annette Decker^{1,2}, Hendrik Lusenberger^{1,2}, Benedikt Bräuer^{1,2}, Dominik Böttlinger^{1,2}, Oriton Teggebar^{1,2}, Saphir Bhat^{1,2}, Marissa Pöschel^{1,2}, Daniela Hübner^{1,2}, Martin Schwaninger^{1,2}, Georg Kocher^{1,2}, Cornelius F. Waller^{1,2}, Alexandra Nierke^{1,2}, David Dornschneider^{1,2}, Florian Emmertich^{1,2}, Henrik E. Maier^{1,2}, Axel Ronald Schmid^{1,2}, Sonja Liewert-Lucy^{1,2}, David A. Price^{1,2}, Tobias Boettler^{1,2}, Bertram Bengsch^{1,2}, Robert Thiemann^{1,2}, Malika Hufnagel^{1,2} and Christoph Neumann-Haefelin^{1,2}

Nature (2021)

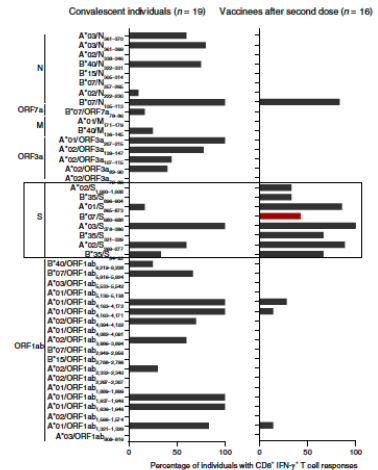


OPEN

SARS-CoV-2-specific T-cell epitope repertoire in convalescent and mRNA-vaccinated individuals

Julia Lang-Med^{1,2}, Hendrik Lusenberger^{1,2}, Katharina Wild^{1,2}, Vivien Karl^{1,2}, Valeria Oberhardt^{1,2}, Eike Salzer-Alzner^{1,2}, Anne Grasser^{1,2}, Matthias Reinschopf^{1,2}, Natarscha Ruckelshausen^{1,2}, David B. Reag^{1,2}, Sebastian Giese^{1,2}, Kevin Ciesinski^{1,2}, Veronika Götze^{1,2}, Dietrich Augustin^{1,2}, Sighart Kling^{1,2}, Cornelius F. Waller^{1,2}, Tobias Wengenmayr^{1,2}, David Staudacher^{1,2}, Daniela Hübner^{1,2}, Bertram Bengsch^{1,2}, Georg Kocher^{1,2}, Martin Schwaninger^{1,2}, Florian Emmertich^{1,2}, Tobias Boettler^{1,2}, Robert Thiemann^{1,2}, Malika Hufnagel^{1,2} and Christoph Neumann-Haefelin^{1,2}

Nature Microbiology (2022)



37

Conclusion HBV immunopathogenesis

- Virus-specific CD8⁺ T cells are heterogeneous with respect to function and transcriptional profile depending of antigen
- Cytolytic pol-specific CD8⁺ T cells are linked to endogenous control
- Virus-specific CD8⁺ T cells remain a molecular scar after chronic antigen stimulation
- Partial reversion with checkpoint inhibitors/ vaccination

38

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Sagar

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Lena Mayer

Jonas Szentandrasei
Nadine Reuter



All patients and volunteers!



39

Thank you very much for your attention!



40