实现慢乙肝临床治愈

NUC经治患者干扰素联合治疗新策略

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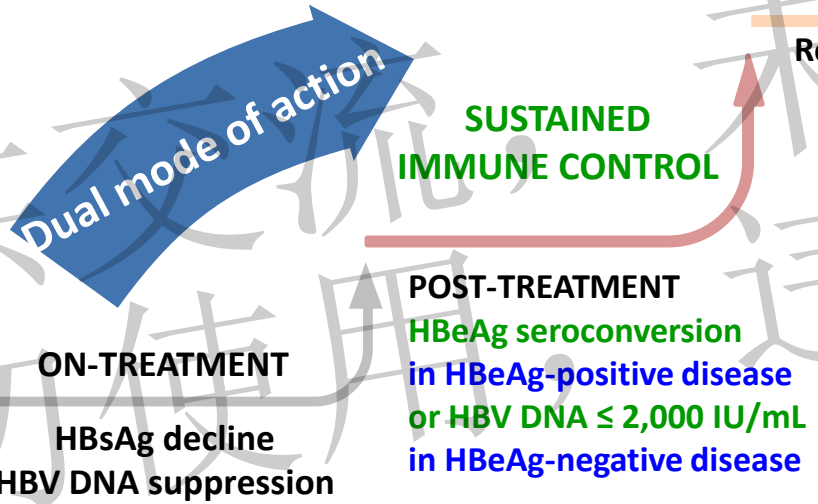
概论

- 慢乙肝患者疾病谱及临床重大需求
- 序贯/联合治疗和临床治愈
- 序贯/联合治疗重塑机体抗病毒免疫效能，实现HBsAg阴转

持续的免疫控制是慢乙肝治疗的终极目标

- Sustained immune control is associated with sustained off-therapy response, and the critical step towards HBsAg seroclearance



E抗原阳性或阴性慢乙肝患者，其理想的抗病毒治疗治疗终点均为：出现持续的HBsAg消失，伴或不伴HBsAg血清学转换

EASL Clinical Practice Guidelines: Management of chronic hepatitis B, 2009

慢乙肝“治愈”的定义

绝对或完全治愈

- cccDNA清除
- 血清和肝脏HBV DNA检测不到
- 持续HBsAg转阴

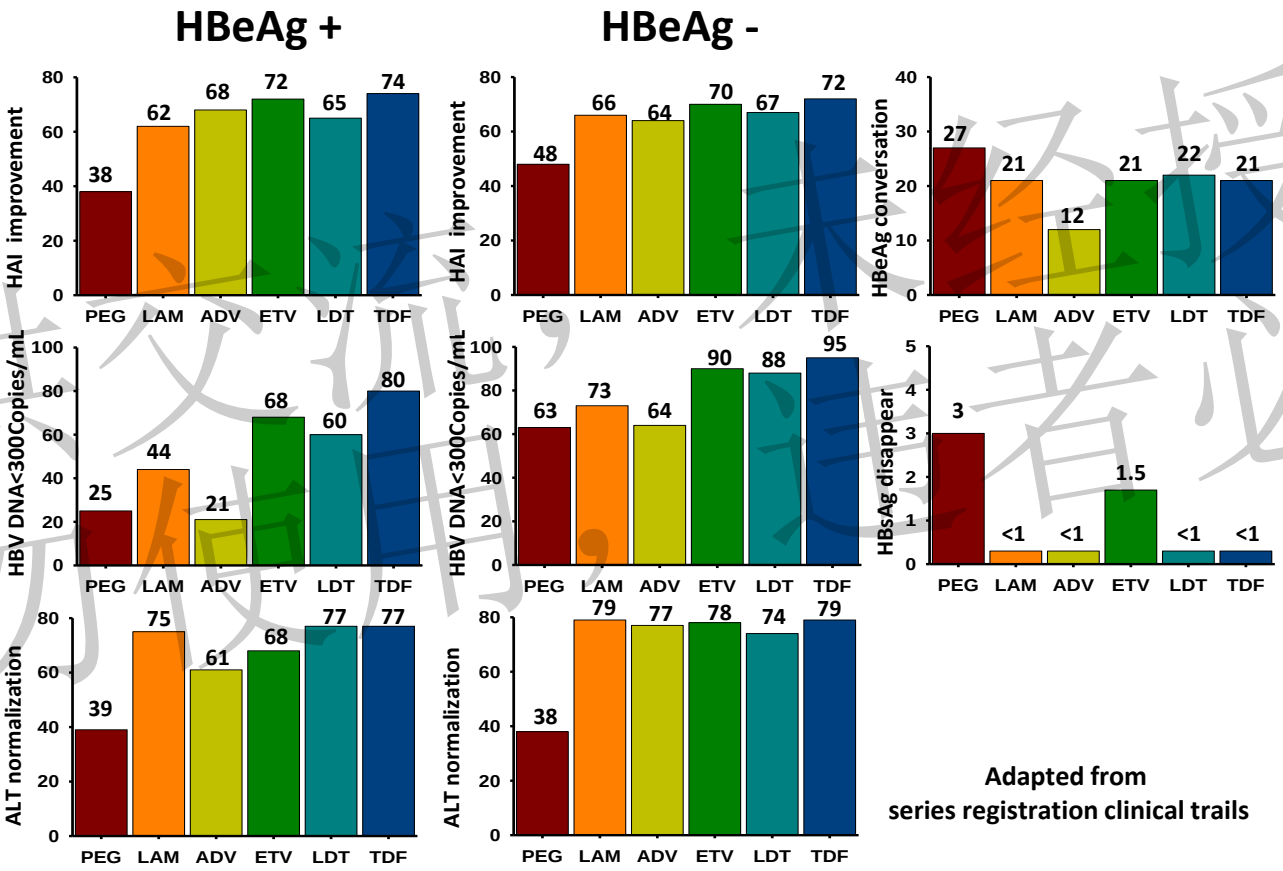
功能学治愈(免疫学)：

-HBsAg 转阴/血清学转换

疾病治愈:

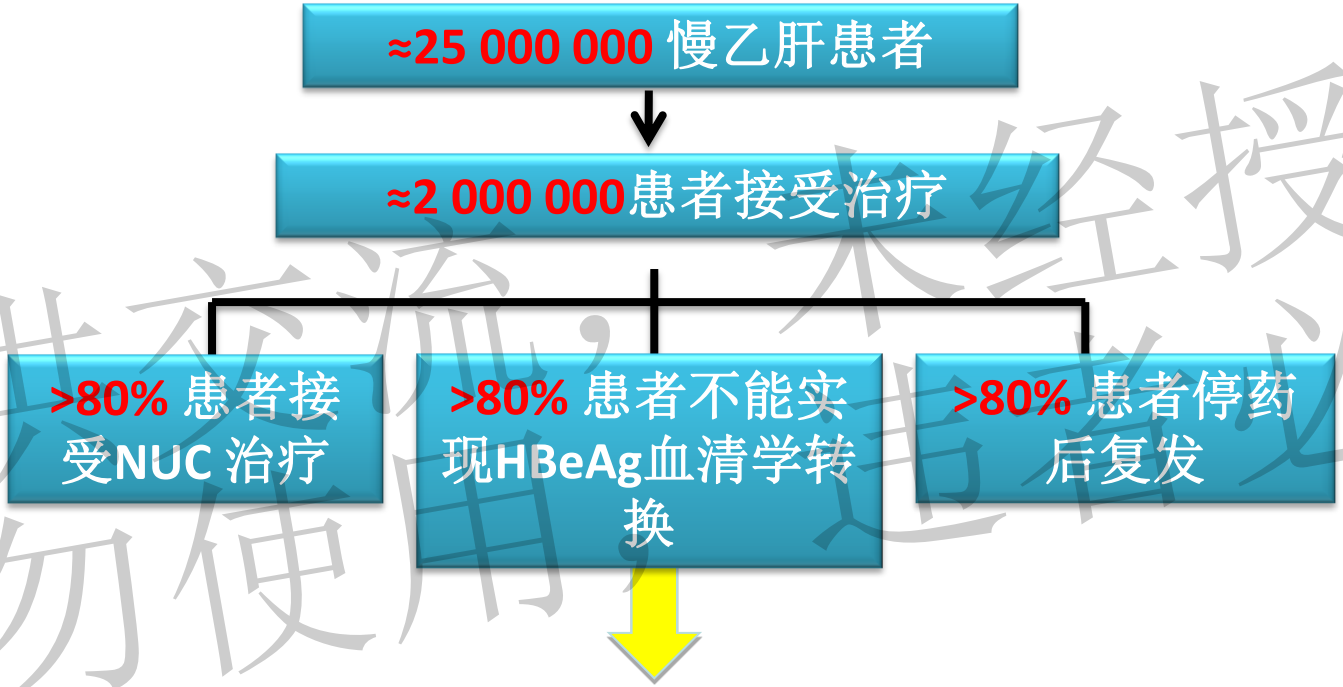
-没有进展为肝硬化、肝衰竭或肝癌的风险

现有抗病毒药物的治疗效能



Adapted from
series registration clinical trails

慢乙肝临床治疗现状及重大需求



如何提高NUC经治患者HBeAg转换率和HBsAg阴转率是目前临床重大需求

Data from a hospitals based survey 2015

慢乙肝治愈的主要障碍

- **病毒学障碍**

cccDNA
HBsAg
} NUC治疗均不能 直接影响

- **宿主免疫学障碍**
  - T细胞功能性耗竭
  - 天然和获得性免疫的免疫耐受状态

强效NUC联合免疫调节剂的联合干预新策略，将重塑机体抗病毒免疫效能以提高慢乙肝临床治愈率

概论

- 慢乙肝患者疾病谱及临床重大需求
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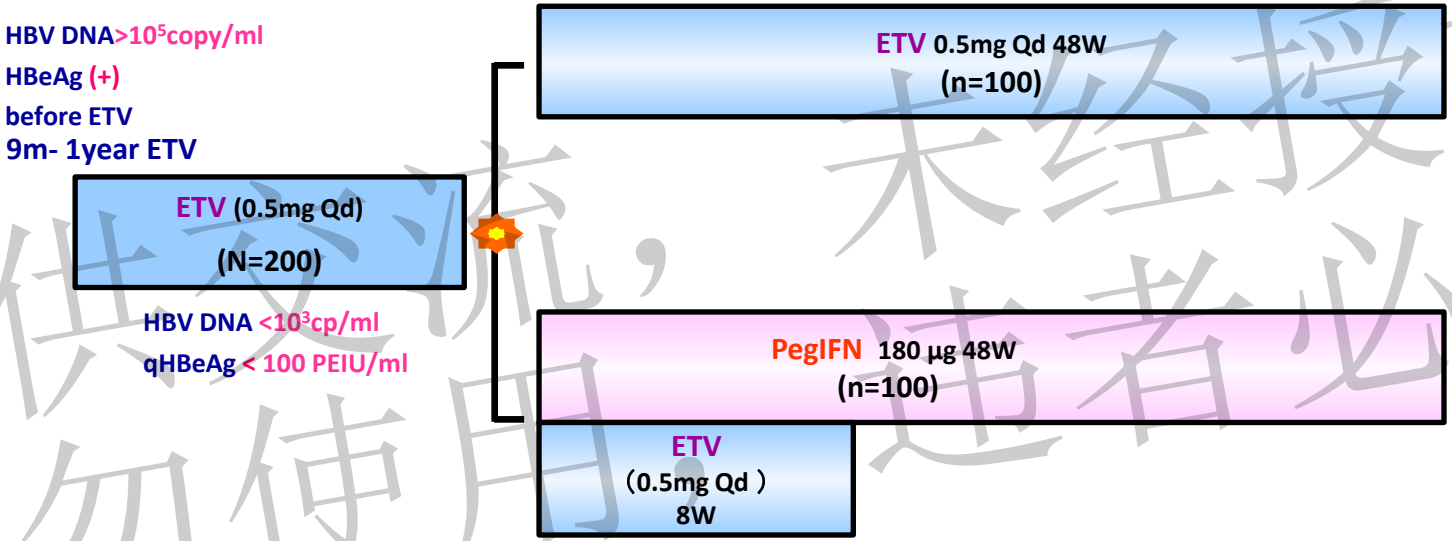
干扰素联合/序贯治疗研究队列

In China	In West
OSST Study	PEGAN Study
New switch study	PEGON study
Endeavor Study	HERMES Study
Anchor Study	.....
.....	

OSST研究方案



Randomized, Open Label， Multi-center Study,

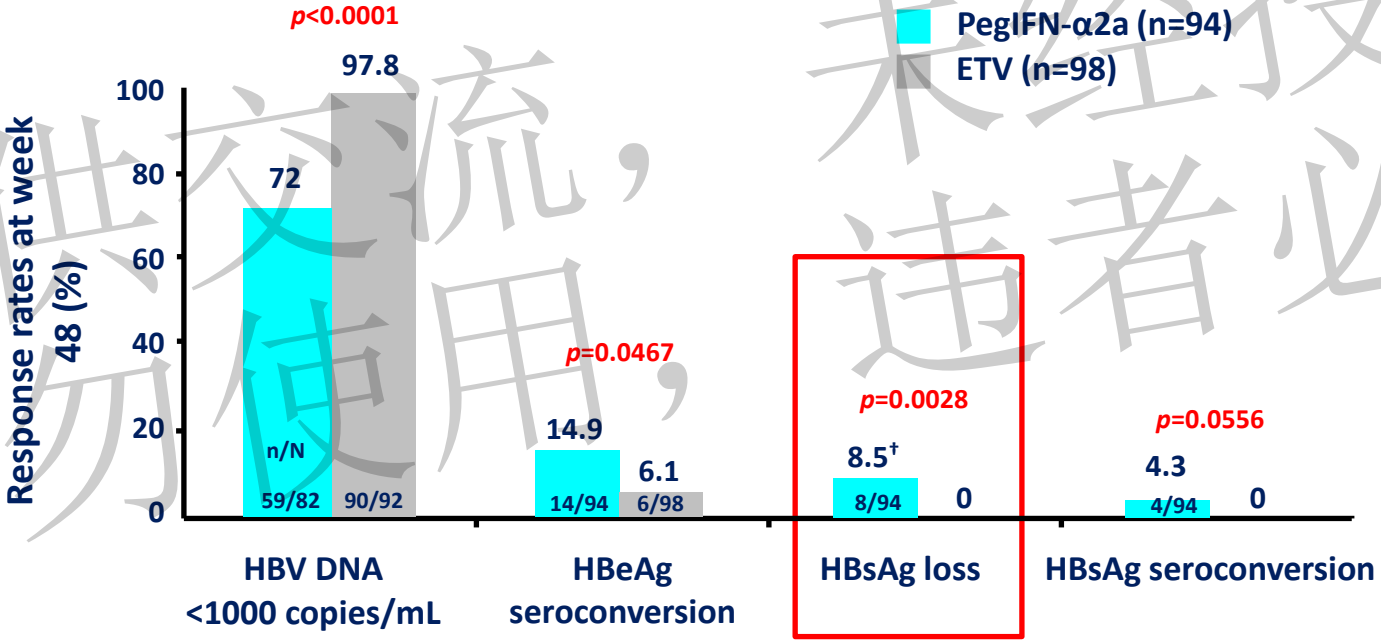
Endpoints: HBeAg Clearance/Seroconversion, HBsAg Clearance

Randomization 1:1

Ning edt al..J Hepatol. 2014;61(4):777-84

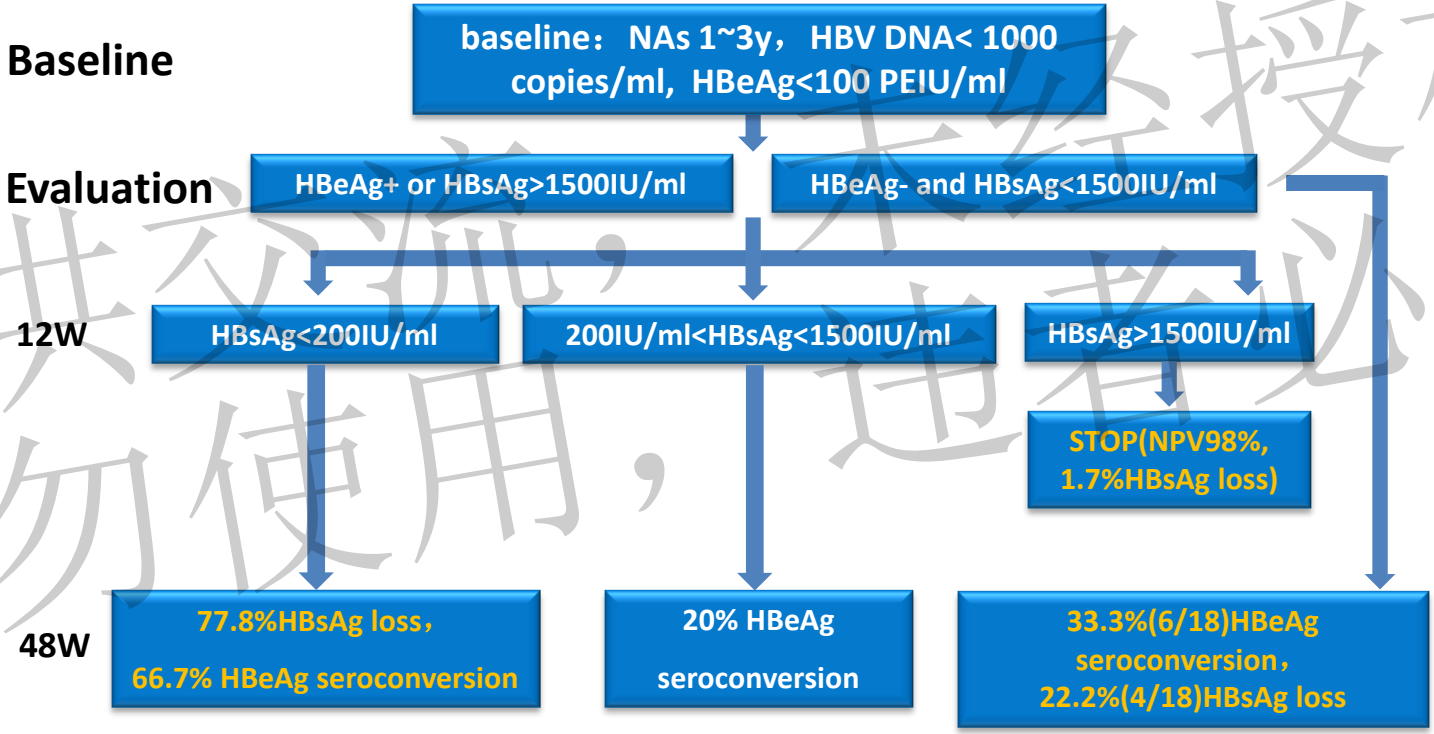
Peg IFN序贯联合治疗可显著提高ETV经治慢乙肝患者的HBsAg阴转率

- Peg-IFN alfa-2a + ETV results in significantly greater serological and virological response rates at week 48 than ETV monotherapy



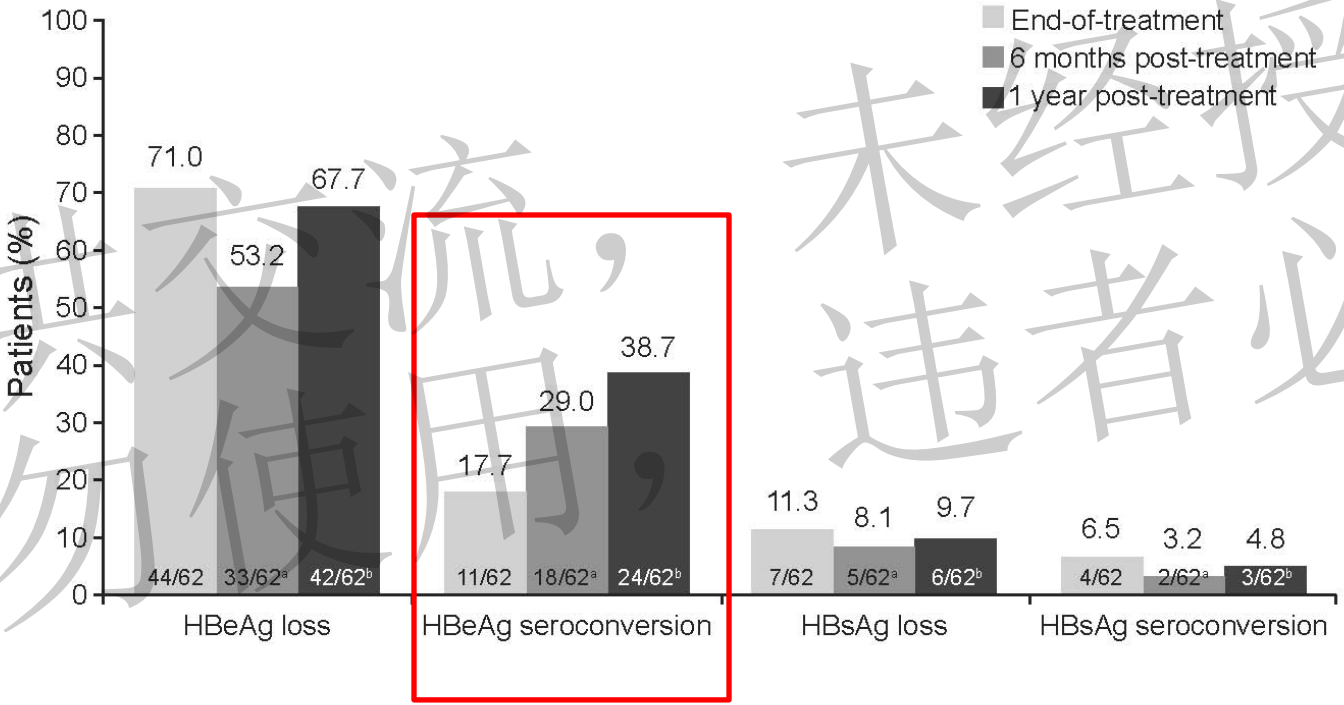
Ning et al. J Hepatol. 2014;61(4):777-84

核苷经治慢乙肝患者干扰素联合/序贯治疗路线图



Ning et al. J Hepatol. 2014;61(4):777-84

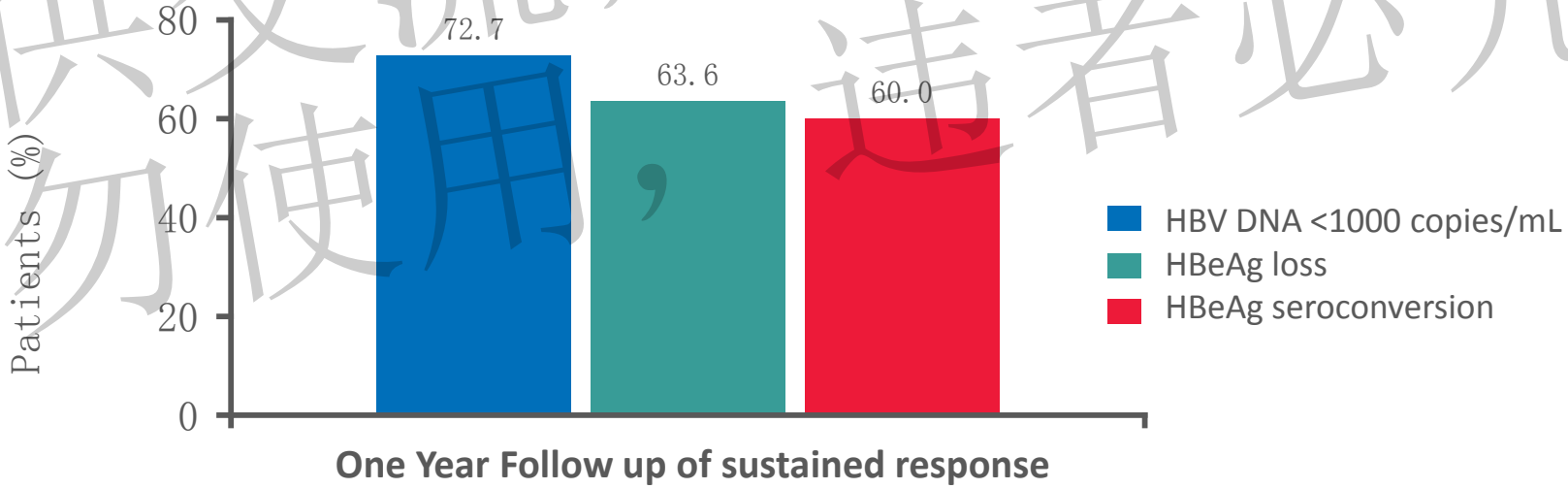
OSST 研究的1年随访：
Peg-IFN alfa联合治疗停药6个月和1年的持续血清学应答率



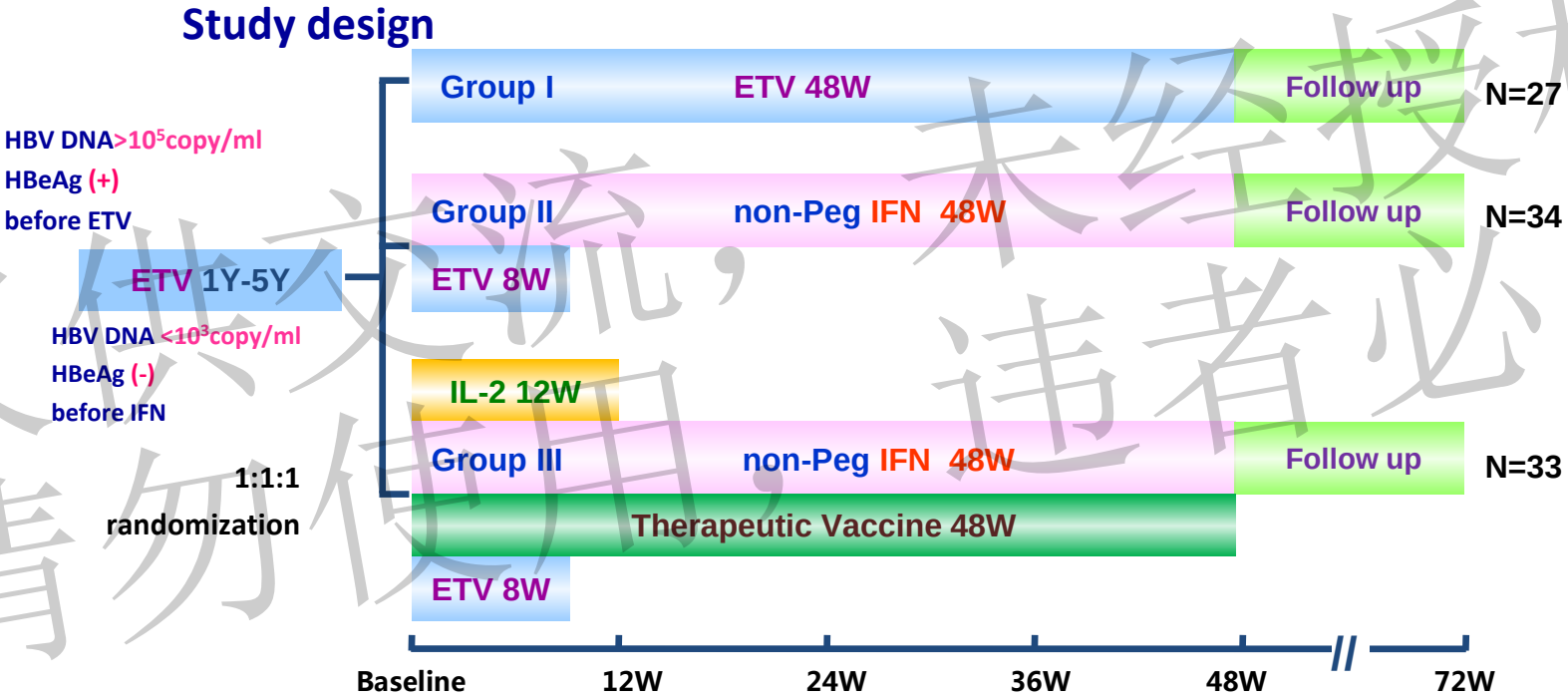
Han M, et al. Antivir Ther. 2016. [Epub ahead of print]

OSST 随访研究:
Peg-IFN alfa联合治疗停药1年的持续应答率

- At 1 year of follow-up, serological and virological responses were durable in patients who switched from ETV to Peg-IFN alfa-2a
- A total of 85.7% of patients who had HBsAg loss at end of treatment sustained this response for the 1 year follow-up



十二五科技重大专项研究课题: Endeavor 研究
(多靶点、探索性、概念验证性研究)



Randomized, Open Label, Multi-center Study

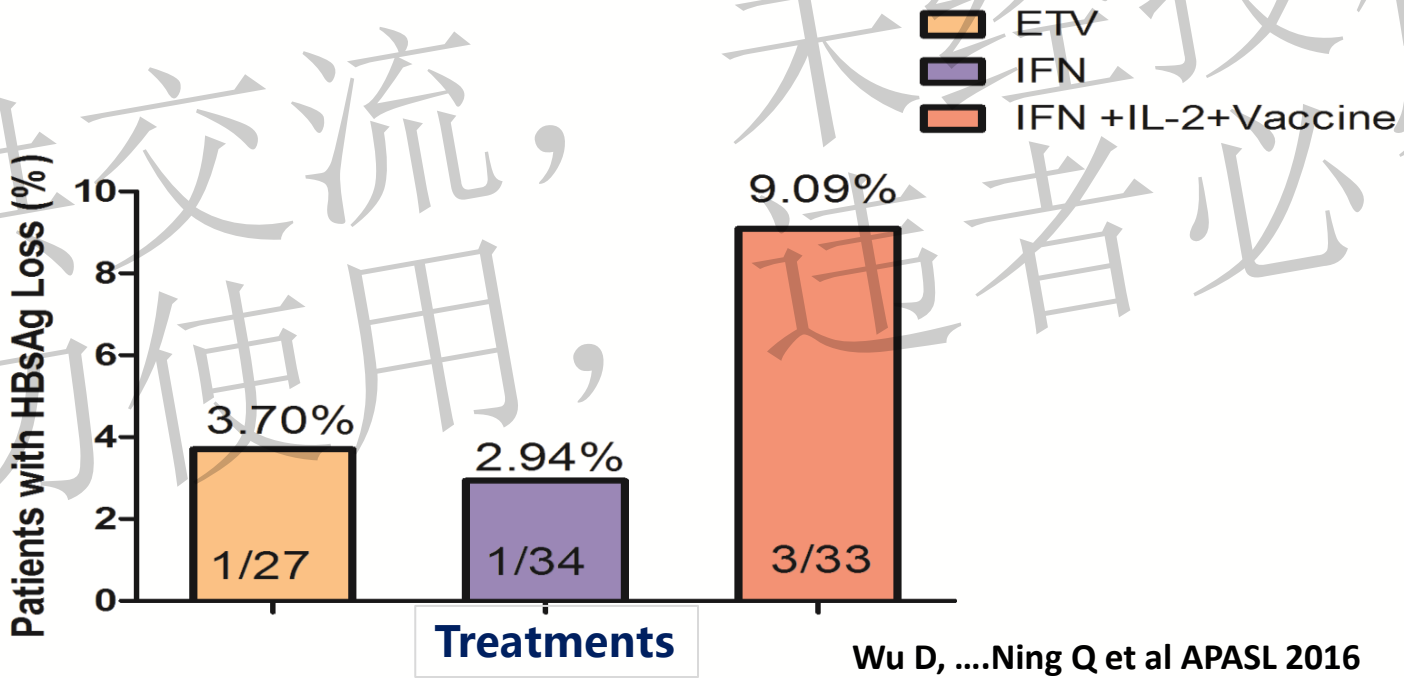
Endpoints: HBsAg Clearance at week 48

基线特征: ITT 人群

Baseline characteristics		*Group* *ETV (N=27)*	*Non-Peg IFN (N=34)*	*Non-Peg IFN+ IL2 + TV (N=33)*	*P value*
Age, year	Mean (S.D)	35.0 (10.54)	36.4 (9.59)	32.7 (10.21)	0.3196
Gender	male	21 (77.8%)	26 (76.5%)	23 (69.7%)	0.7973
BMI, kg/m^2	Mean (S.D)	23.14 (3.713)	22.38 (2.447)	21.49 (2.557)	0.0922
ETV, year	Mean (S.D)	3.72 (2.248)	3.52 (1.899)	3.32 (2.018)	0.8237
Baseline HBsAg, log_{10}IU/ml	Mean (S.D)	2.706 (0.6716)	2.874 (0.7745)	2.962 (0.6169)	0.3792
Baseline HBV DNA, log_{10}copies/ml	Mean (S.D)	2.441 (0.5558)	2.577 (0.4515)	2.456 (0.4905)	0.5227
Baseline ALT, U/L	Mean (S.D)	20.7 (9.97)	25.0 (17.26)	16.9 (7.06)	0.0307*
Baseline HBeAb, log_{10}PEIU/ml	positive	13 (50.0%)	14 (42.4%)	15 (48.4%)	0.8642

Endeavor研究（多靶点）中期数据
NUC经治CHB患者干扰素多靶点联合治疗HBsAg阴转率

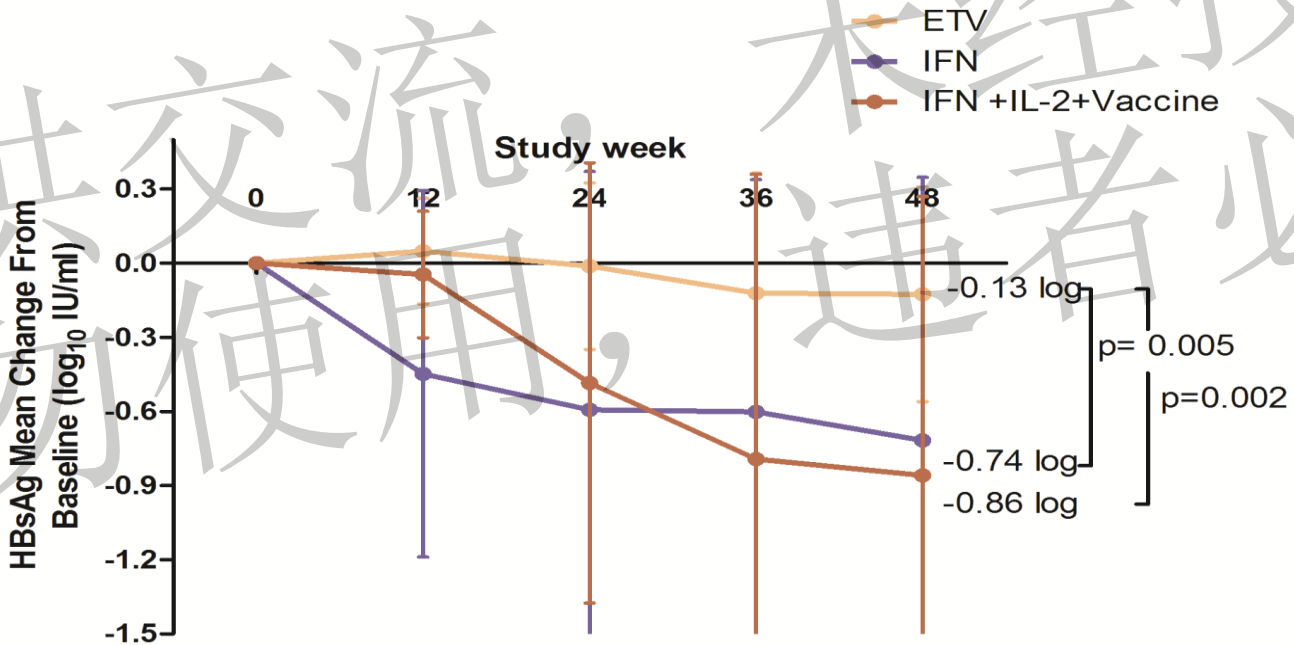
A combination of immune modulation IFN, IL-2 and therapeutic vaccine results in greater HBsAg loss in ETV suppressed patients



Wu D, ….Ning Q et al APASL 2016

干扰素多靶点联合治疗48周HBsAg下降最显著(ITT 人群)

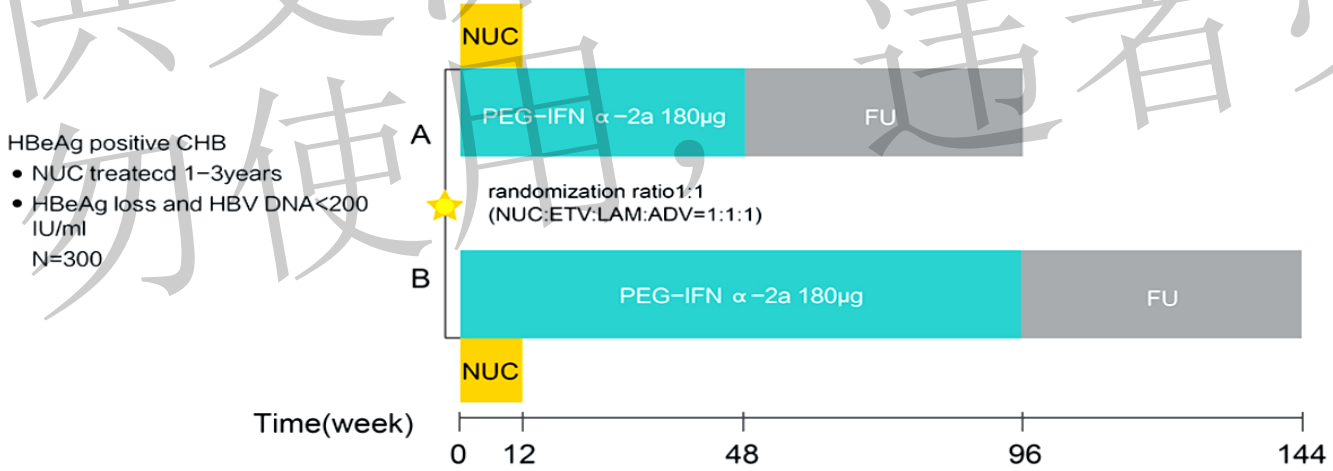
Sequential IFN based immune modulation therapy lead to a significant decline of HBsAg level



Wu D, ….Ning Q et al APASL 2016

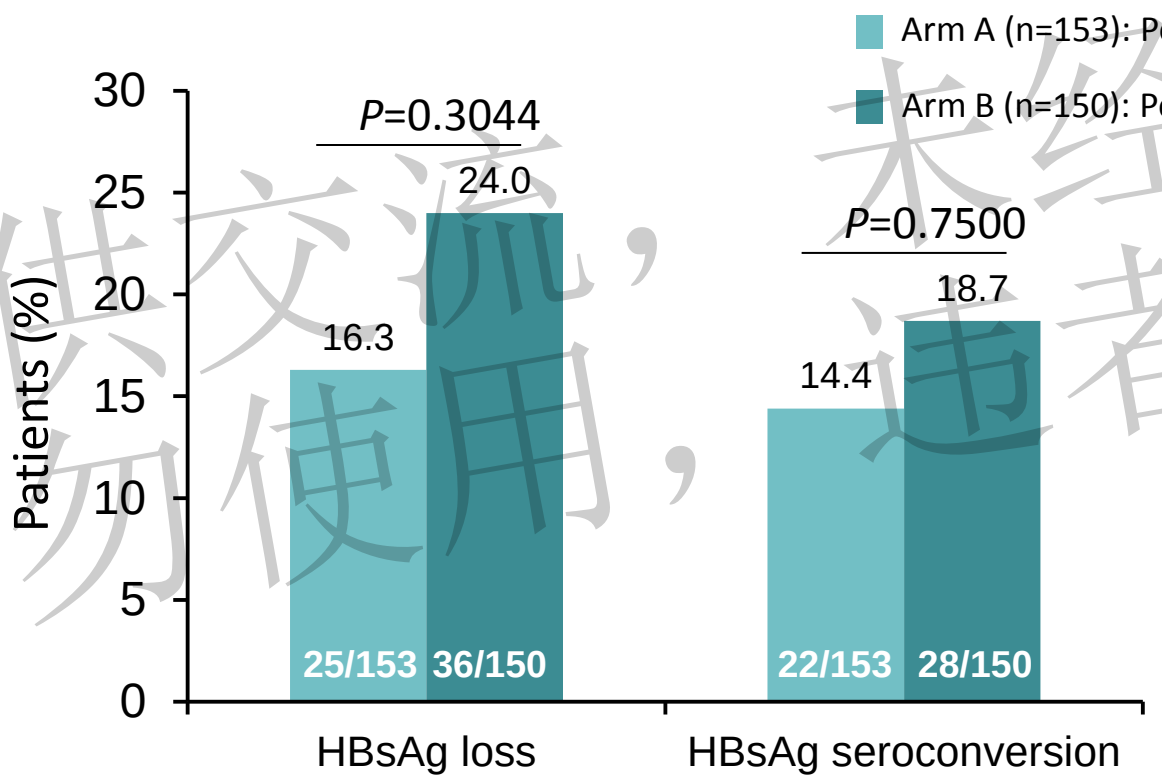
NEW SWITCH 研究

- A multi-centered randomized open-labeled study.
- HBeAg positive CHB patients who achieved partial responses with a prior NUC history for 1-3 years were included. (*Figure 1*)
  - partial response defined as HBV DNA<200IU/ml and HBeAg loss
- All participants were switched to PEG-IFN α-2a treatment for either 48 or 96 weeks
  - with the first 12 weeks overlapping NUC therapy
  - randomization ratio of 1:1
  - followed-up for 48 weeks after the discontinuation of PEG-IFN α-2a
- HBsAg loss rate at week 48 since randomization was the primary endpoint in this interim analysis



Hong Ren, APASL, 2016

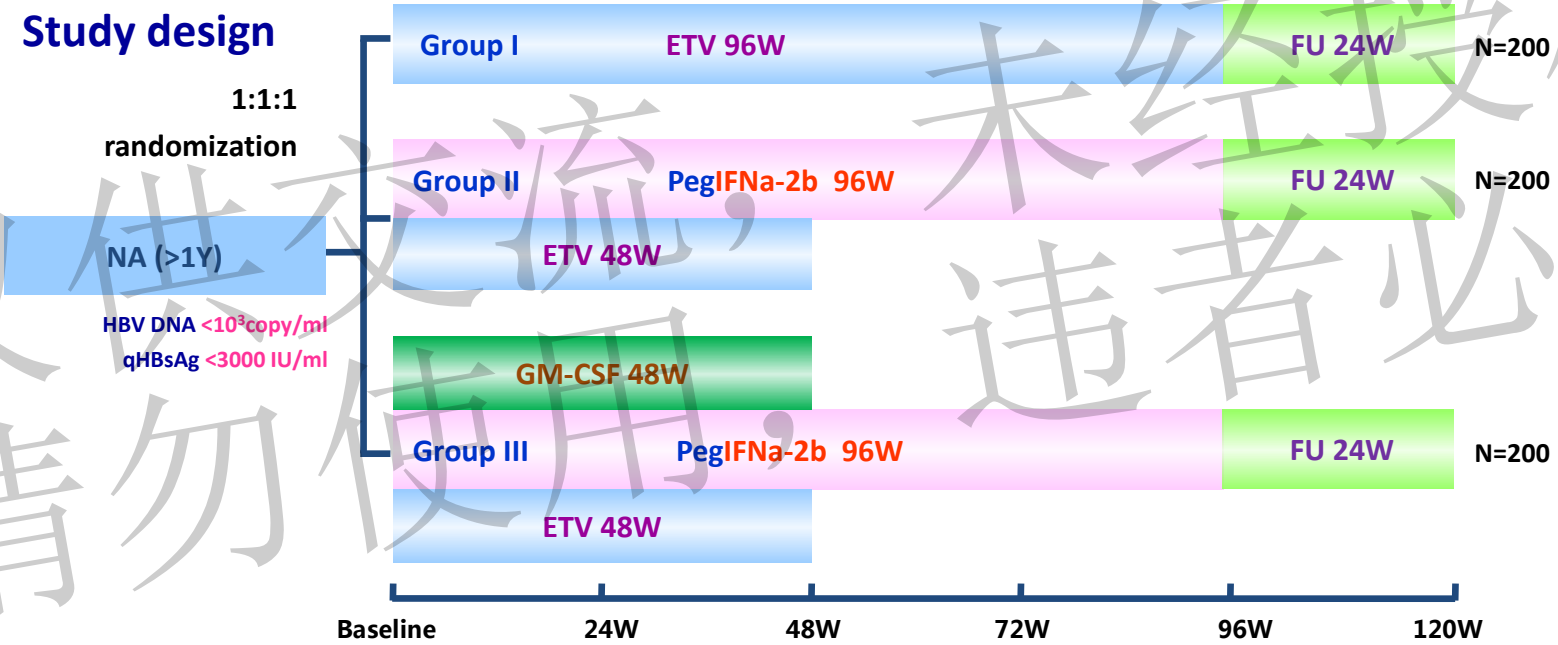
NEW SWITCH 研究
联合治疗疗程延长可能提高HBsAg阴转率



十二五科技重大专项研究课题：Anchor 研究

A combination of NAs and immune modulation
Combination/sequential

Study design



Randomized, Open Label, Multi-center Study,
Endpoints: HBsAg Clearance at week 96

概论

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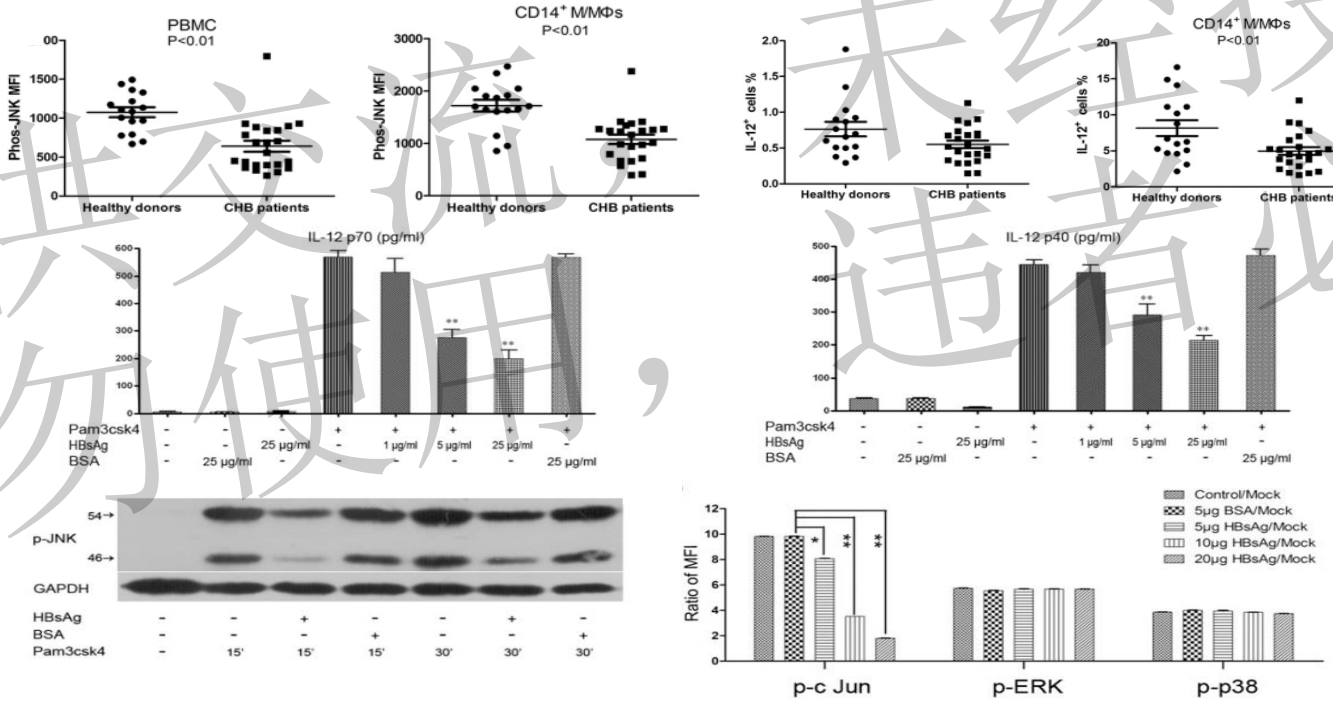
- 序贯/联合治疗和临床治愈
- 序贯/联合治疗重塑机体抗病毒免疫效能，实现HBsAg阴转

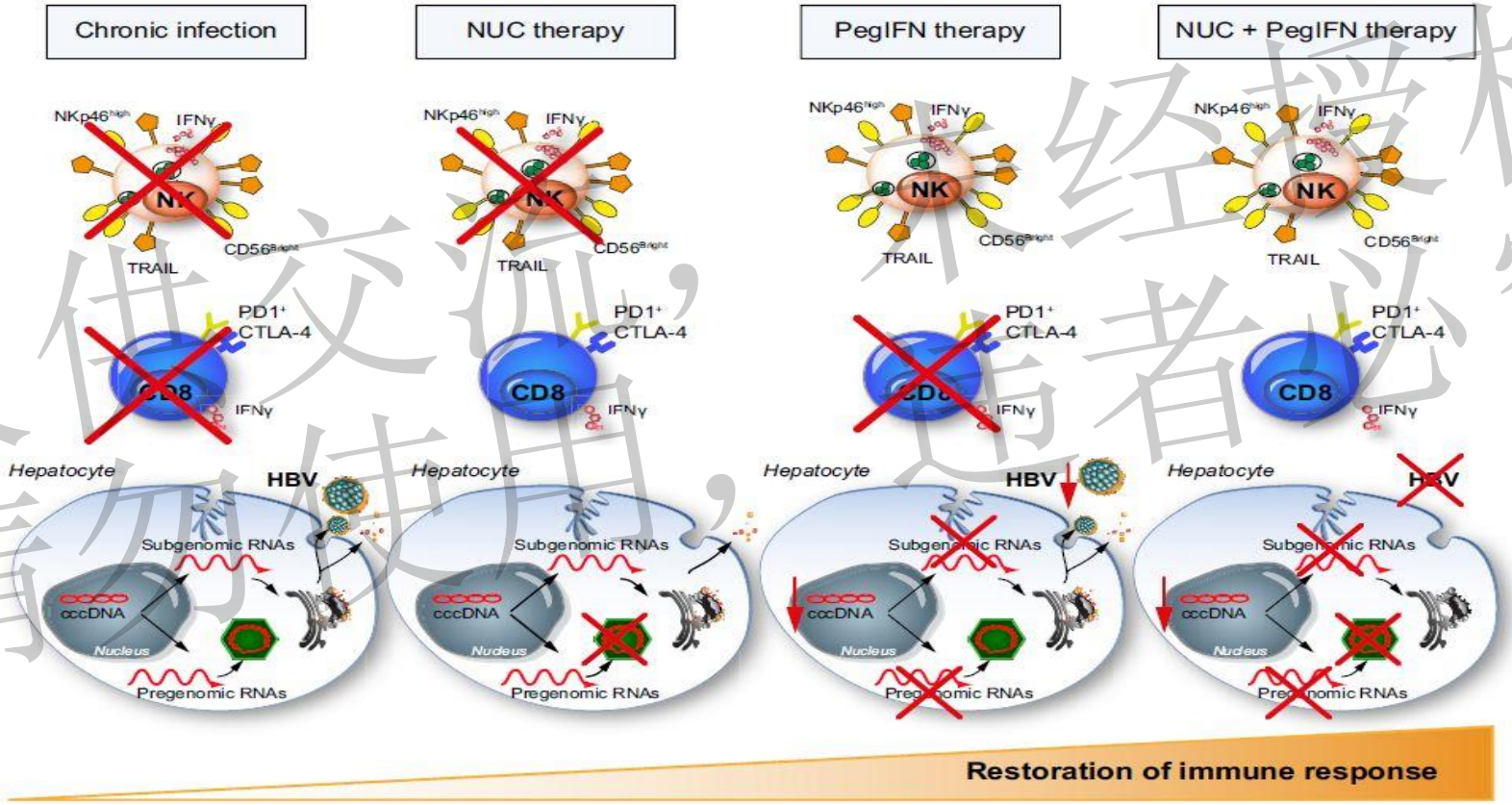
HBsAg的免疫抑制：通过干扰JNK活化选择性抑制单核/巨噬细胞中TLR2 配体诱导的IL-12表达

Sen Wang,*,[1] Zhiao Chen,*,†,[1] Conghua Hu,‡ Fangxing Qian,§ Yuming Cheng,‡
Min Wu,* Bisheng Shi,* Jieliang Chen,*,‡ Yunwen Hu,* and Zhenghong Yuan*,‡



The Journal of Immunology 2013

NUC+IFN联合治疗策略促进免疫功能修复



Robert Thimm. J Hepatol. 2012

OSST 免疫学研究

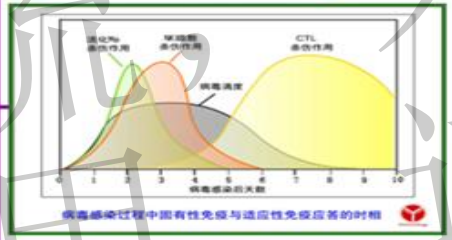
samples from CHB patients

systematic and dynamic immune features

combine clinical data with immunological indicators

Innate immune response

Adaptive immune response



NK cells

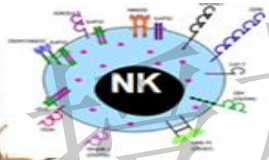
DCs

TLRs

T cells

Tregs

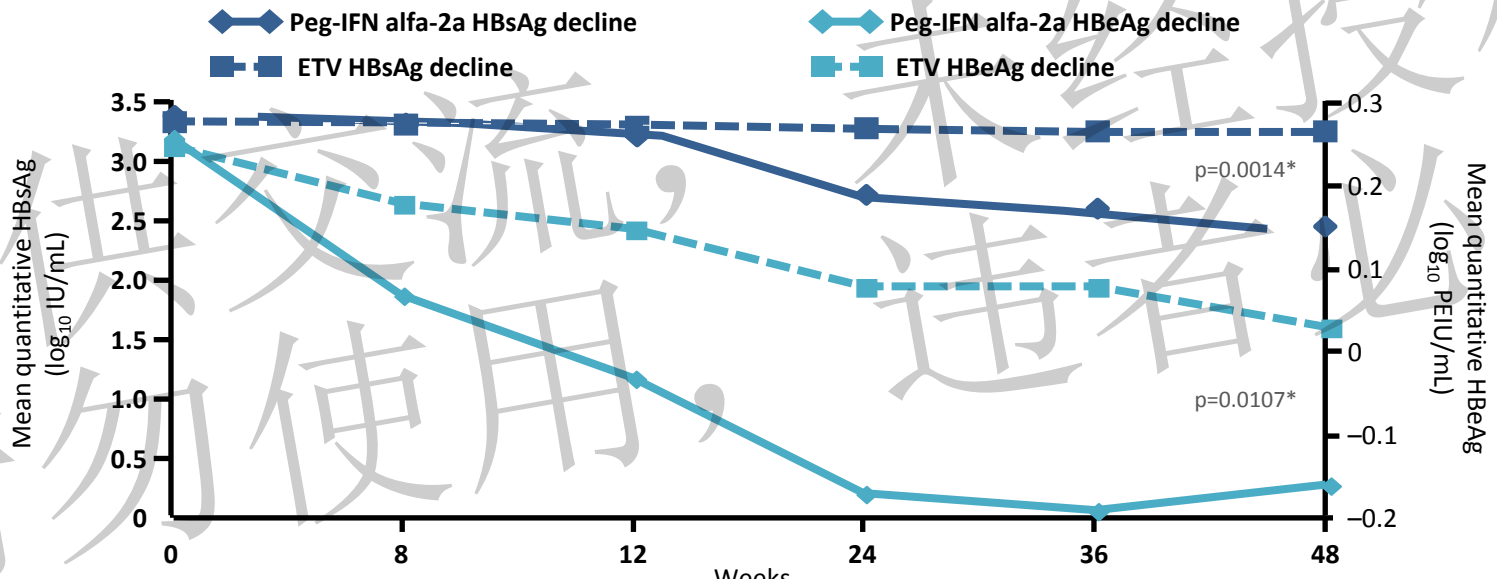
PD-1



Reveal potential immune biomarkers of sustained immune control

Peg-IFN序贯治疗较ETV治疗相比，HBsAg和HBeAg下降更显著

- **Sequential Peg-IFN alfa-2a + ETV resulted in significantly greater on-treatment HBsAg and HBeAg decline than ETV monotherapy**

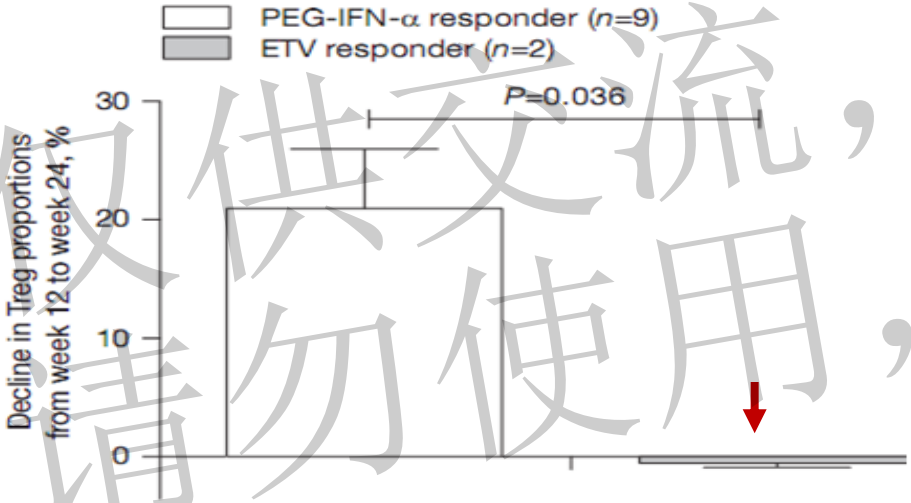


N						
Peg-IFN alfa-2a	93	93	94	91	88	85
ETV	95	97	97	97	94	92

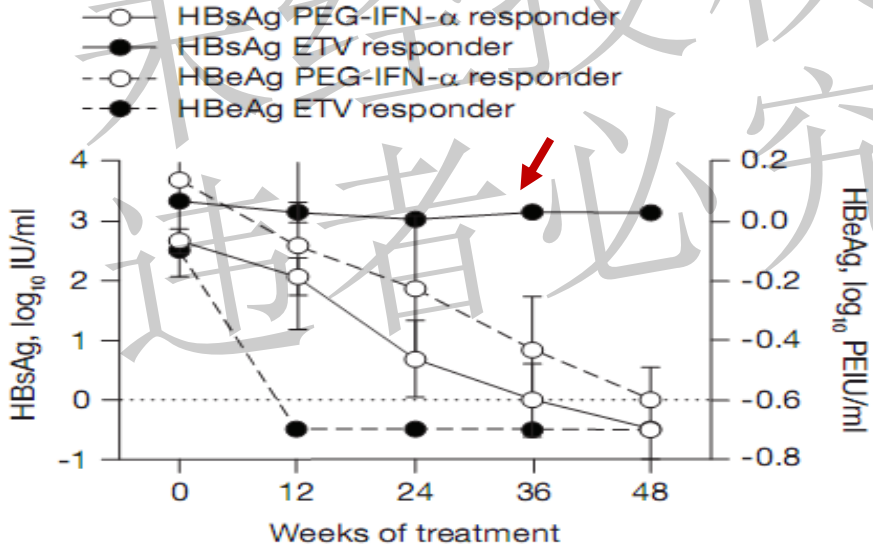
*p value at week 48

Ning Q, et al. J Hpatology 2014

PEG IFN应答者HBsAg水平伴随Treg比例下降的幅度较ETV应答者更显著



Fold decrease of Treg cells at W12-24

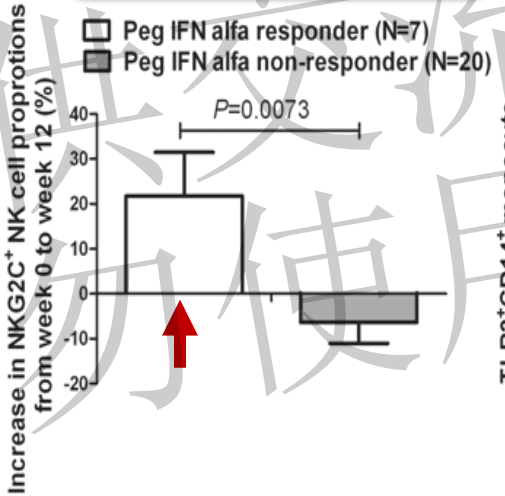


P-values between two groups:
Decline of mean HBsAg from baseline to week 48: *P*=0.033
Decline of mean HBeAg from baseline to week 48: *P*=0.84

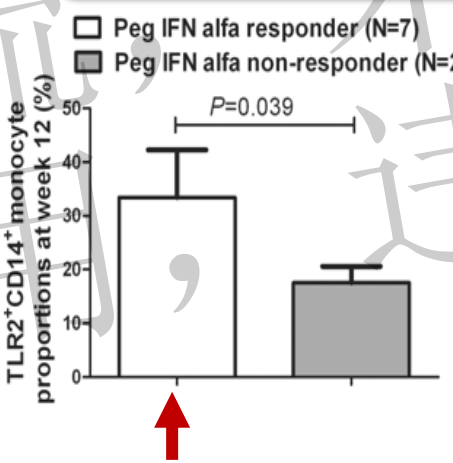
Yan et al. Antivir Ther. 2015

IFN应答者在治疗早期其抗病毒免疫功能得以显著修复

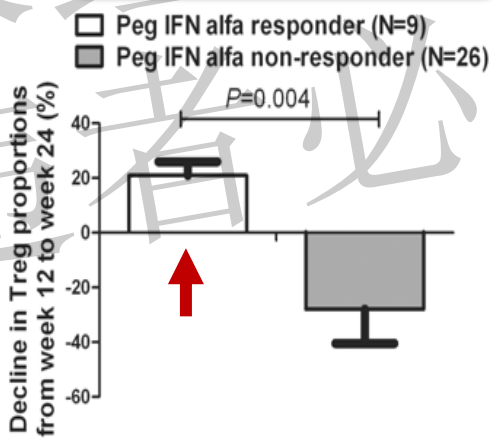
0-12W increased functional NKG2C+NK cells



12W higher TLR2+monocytes

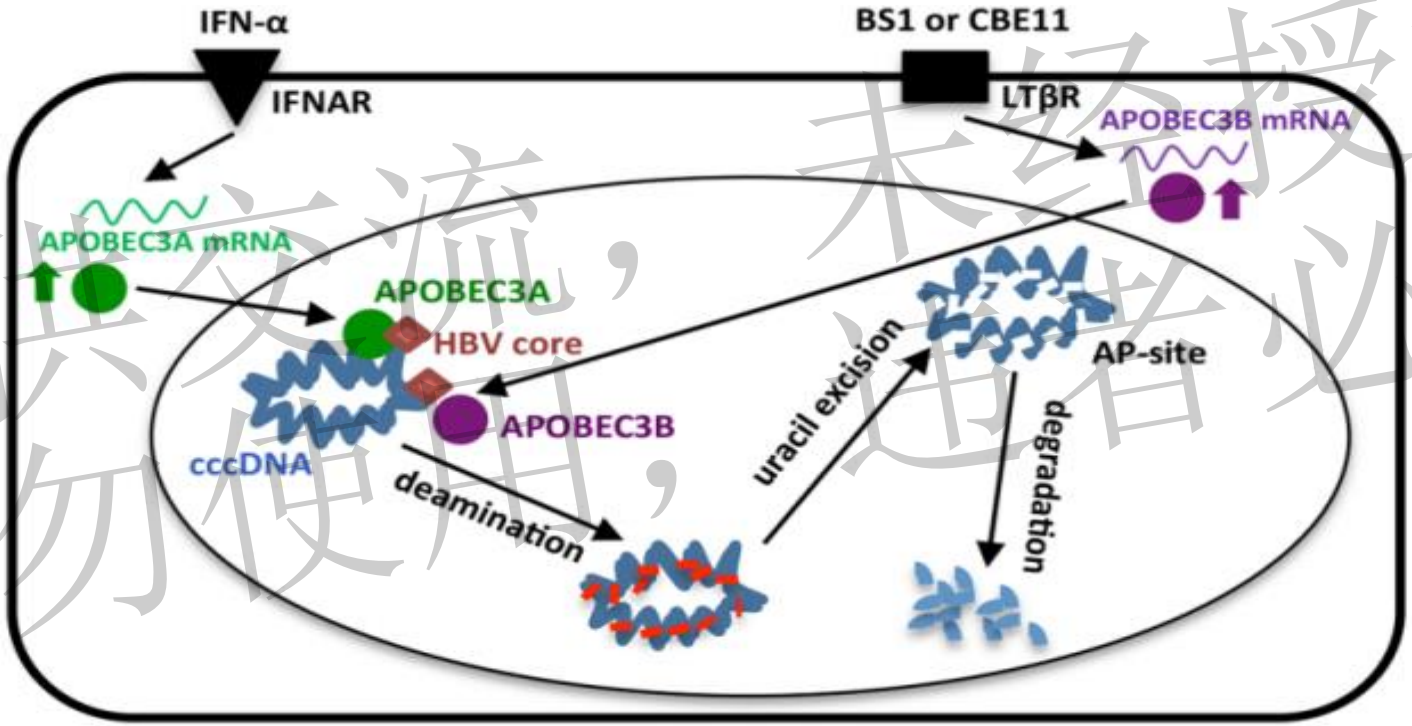


12-24W decreased inhibitory Treg



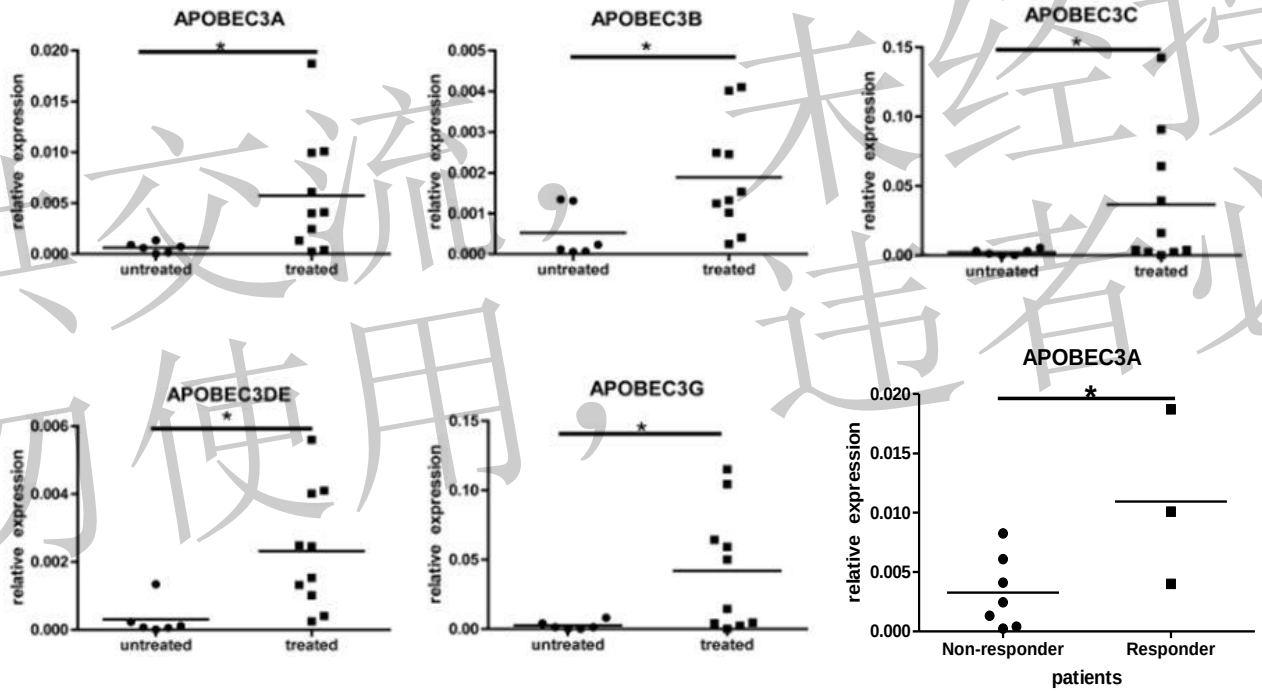
Yan WM… Ning Q et al. Antivir Ther. 2015

IFN通过上调APOBEC 3A/3B降解cccDNA



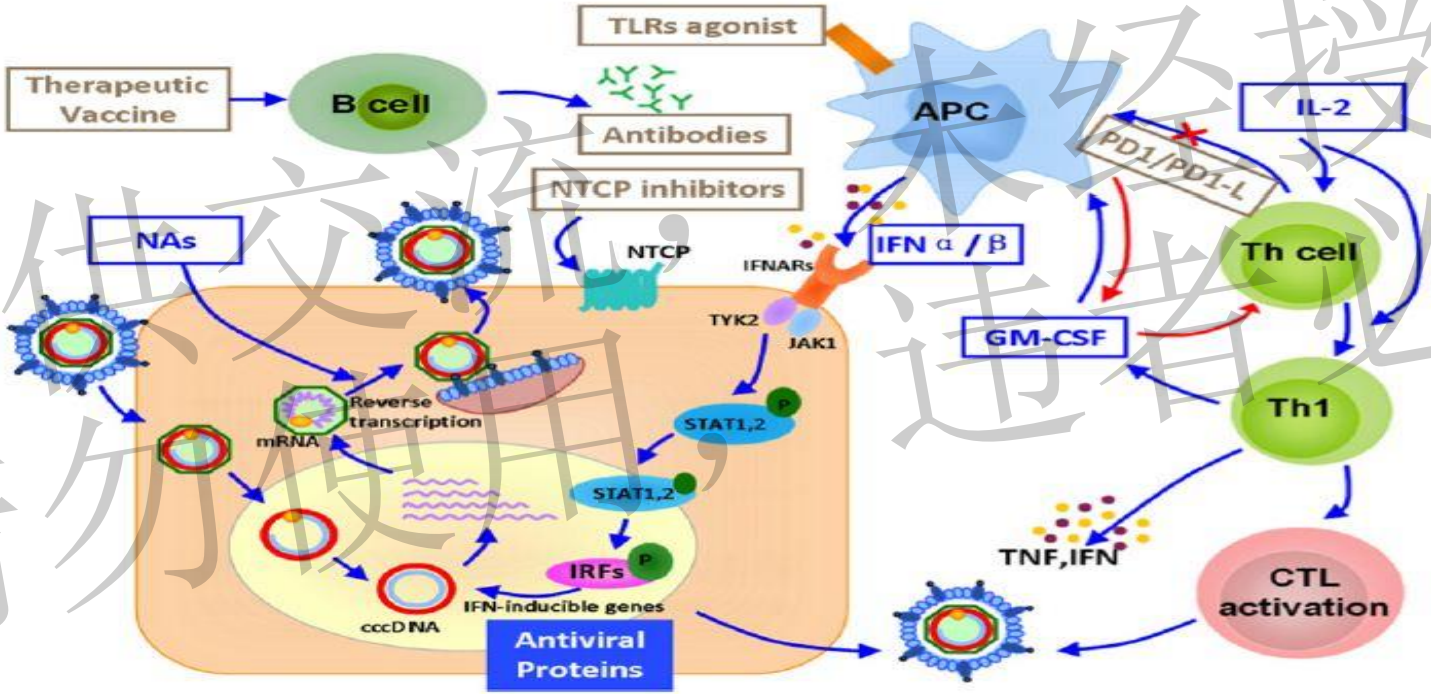
Lucifora, J et al 2014. Science;343(6176):1221-8

Peg-IFN治疗过程中，肝脏APOBEC mRNAs水平升高
Peg-IFN治疗应答与治疗结束高水平的APOBEC3A mRNA水平相关



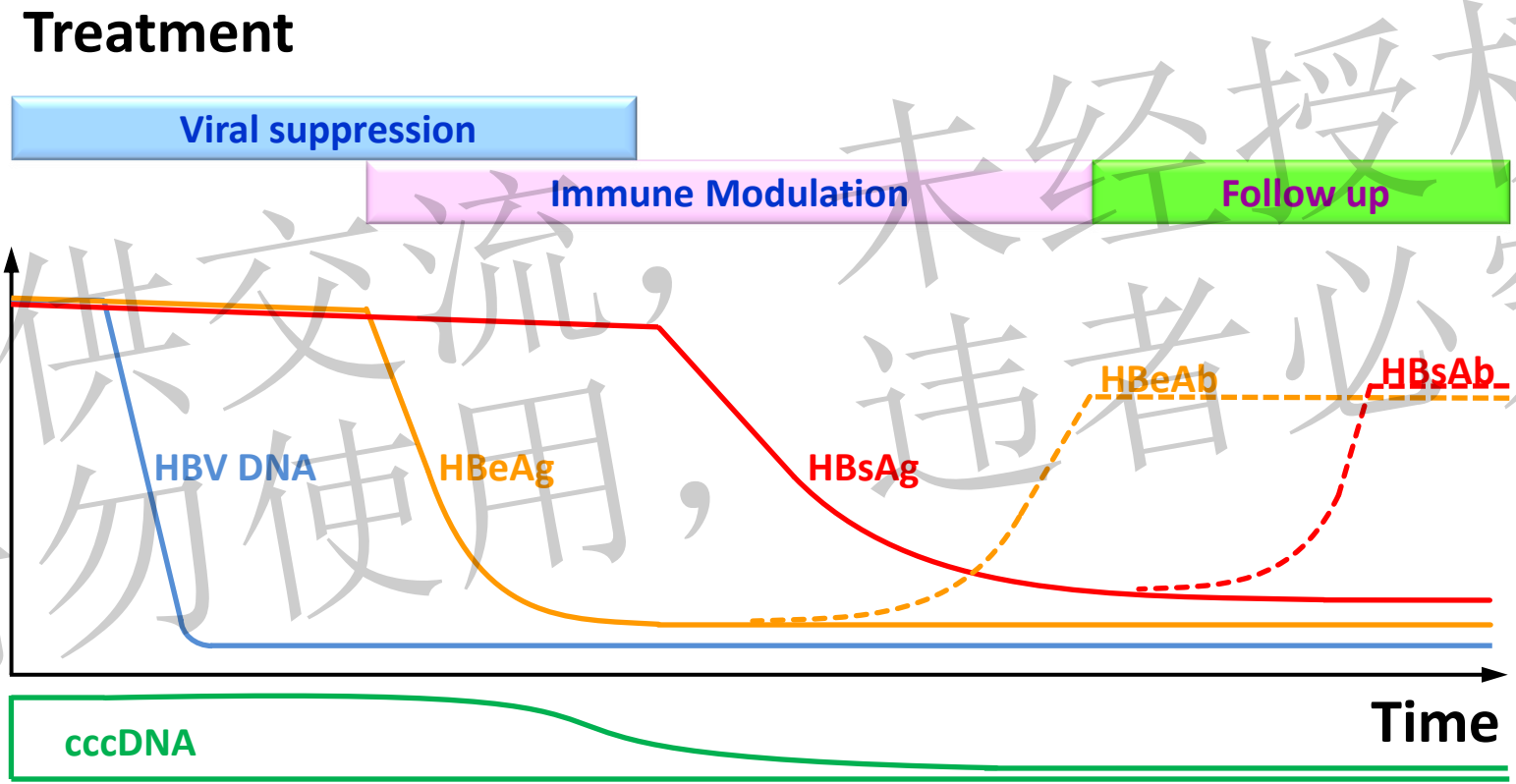
Li Y, Xia Y … Protzer U, Ning Q et al unpublished data 2016

持续病毒控制基础上联合免疫调节的多靶点干预，重塑机体抗病毒免疫效能：慢乙肝患者的未来？



Wu D, Han MF, Qin Ning, et al J Hepatol. 2015;62(1):240-1.

慢乙肝临床治愈展望



Dr. Qin Ning China

总结

- 有限的治疗策略导致NUC经治及难治性慢乙肝患者增加
- 免疫修复是提高慢乙肝治疗疗效、实现HBV清除的关键因素
- 持续病毒控制基础上联合免疫调节的多靶点干预，重塑机体抗病毒免疫效能：慢乙肝患者的未来？

致谢

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