HBV immunological research

Salim Khakoo

BASL SIG 2018

Overview

- When can I stop treatment?
  - Does the immune response predict long term outcome?
- Who is going to develop HCC?
  - Are there immune features that precede the development of HCC?
- New treatments
  - How do they work?
  - Who will benefit?
  - How best to use with currrent therapies?
  - Rationale design for combination?
- Mechanistic immunology
  - Identify new therapeutic possibilities?
- Big picture/translational driver
  - Different populations

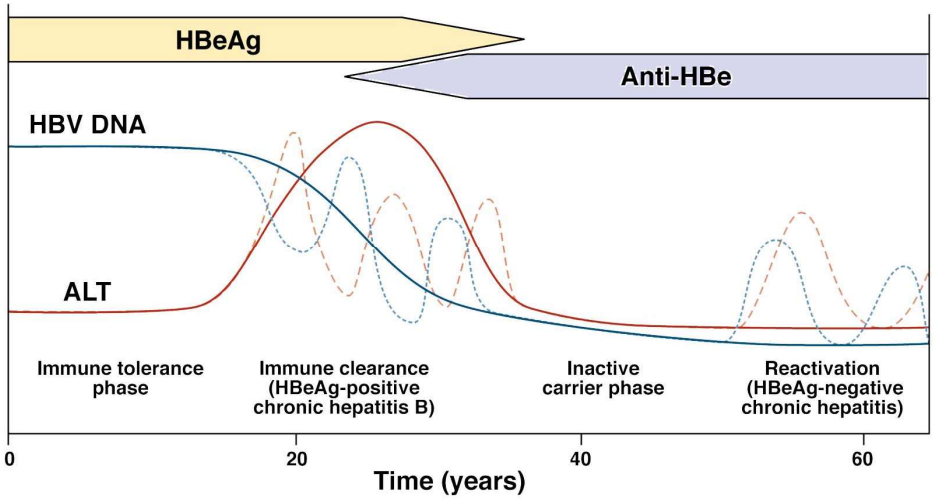
HBV and immune hyporesponsiveness?

Phases of HBV infection

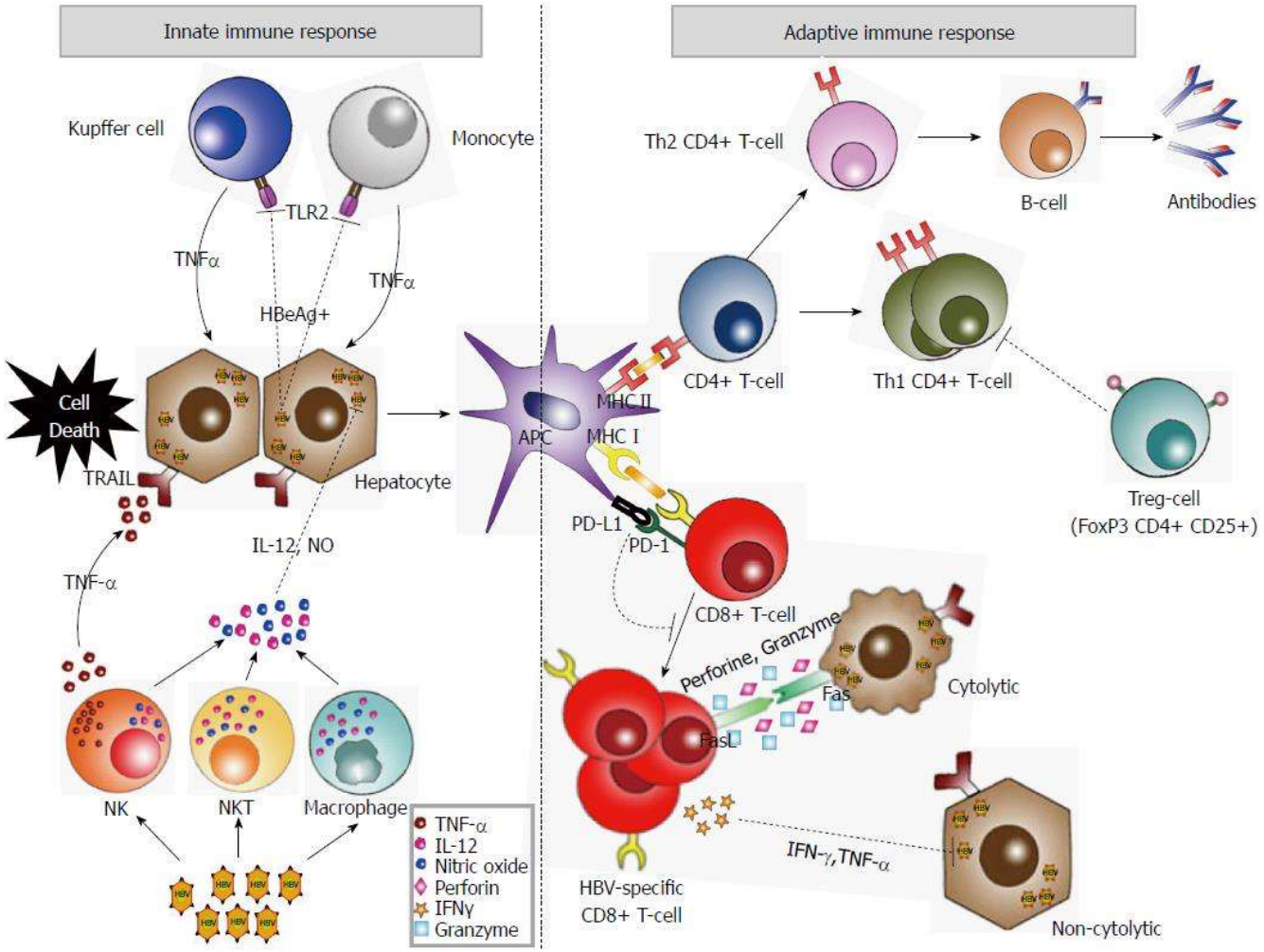
Phase	DNA	serology	ALT	Histology	Old name
1	Very high	eAg+	normal	Minimal inflammation	Immunotolerant
2	High	eAg+	elevated	Mod/severe inflammation	HBeAg+ chronic hepatitis
3	Low <2,000iu/ml	eAb+	normal	Minimal inflammation	Inactive carrier
4	Mod-high	eAb+	Fluctuating elevated	Mod/severe inflammation	HBeAg- chronic hepatitis
5	Neg (cccDNA+)	HBsAg-anti-HBc+	normal	-	Occult HBV

Weaker immune response

Stronger immune response



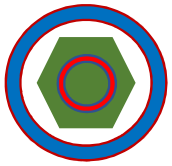
EASL guidelines 2017



You CR, Lee SW, Jang JW, Yoon SK. World J Gastroenterol 2014; 20(37): 13293-13305

HBV and immunotolerance

Viral factors



High levels of
HBsAg and HBeAg

Hepatic factors

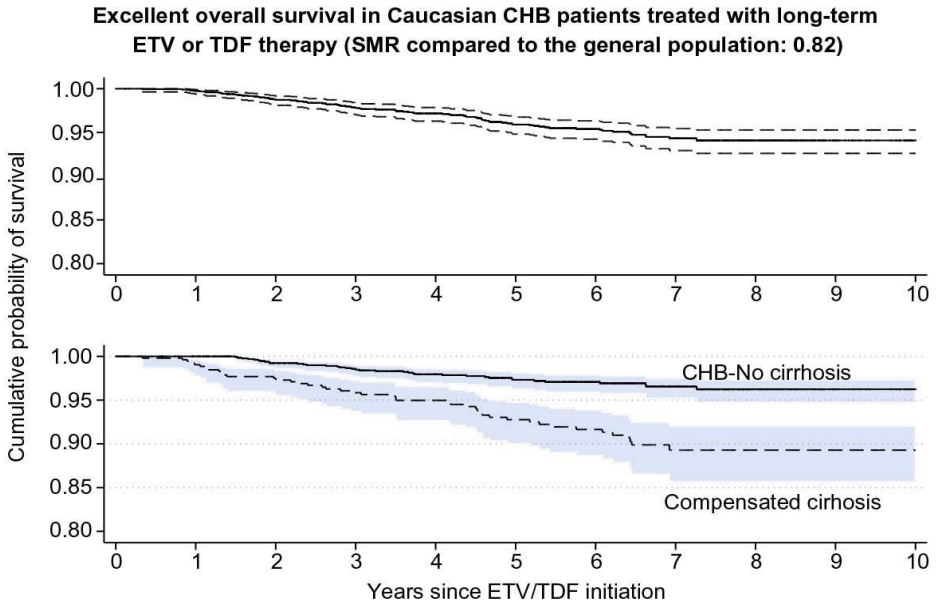
Cytokines: IL-10, TGF-β,
Cells: Tregs, MDSCs
Nutrient deprivation

Exhausted CD8+ T cell

Expression of inhibitory receptors
Apoptosis prone
Weak response to cytokine stimulation
Altered metabolism

HBV suppression is successful

Long term NA therapy
>95% virological response
50% eAg loss
10% HBsAg loss ⎫ HBeAg+ chronic HBV



Papatheodoridis et al. J Hepatol. 2018 Jun;68(6):1129-1136

NA discontinuation EASL 2017:

1. NAs should be discontinued after confirmed HBsAg loss

2. NAs can be discontinued in non-cirrhotic HBeAg positive CHB patients who achieve stable HBeAg seroconversion and undetectable HBV DNA and who complete at least 12 months of consolidation therapy.

3. Discontinuation of NAs in selected non-cirrhotic HBeAg-negative patients who have achieved long-term virological suppression under NA may be considered

Immune factors in viral control HBeAg- chronic hepatitis

HBeAg- CHB
treatment stopped
N=23

Virological remission
(DNA<20,000 at 6 months)
N=10
EOT/6months

No virological remission
(DNA<20,000 at 6 months)
N=13
EOT

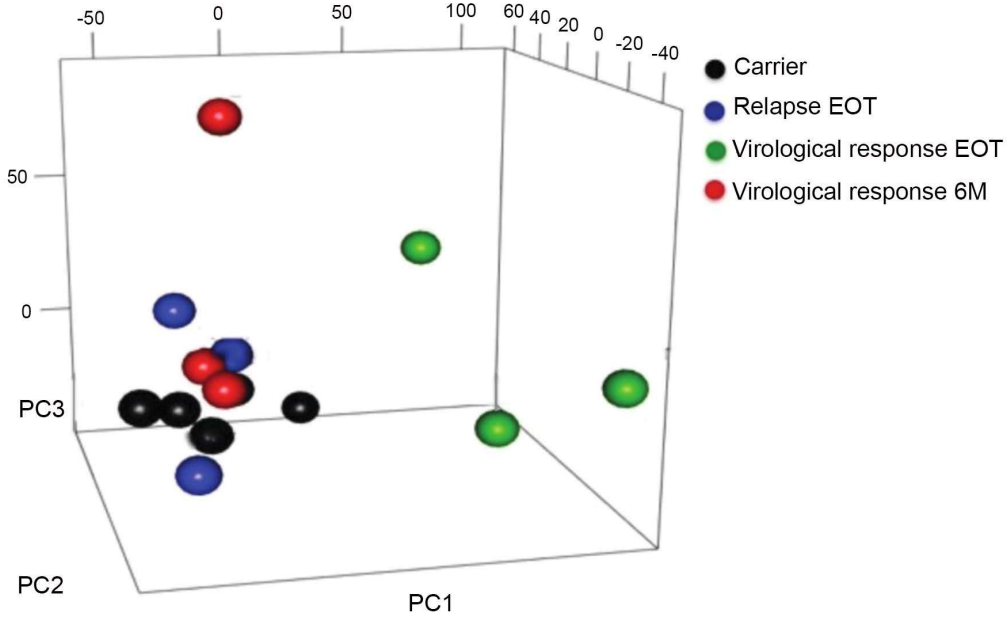
Controls:
Chronic carrier

Micro array on PBMC
(N=3 per group)

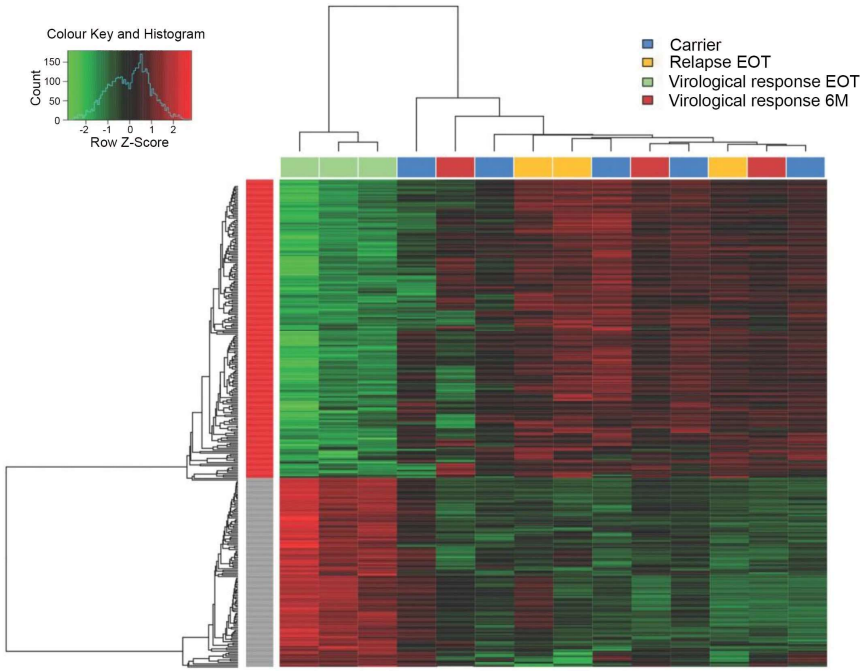
Validation by qPCR
in remainder

H Kranidioti, unpublished

Initial survey

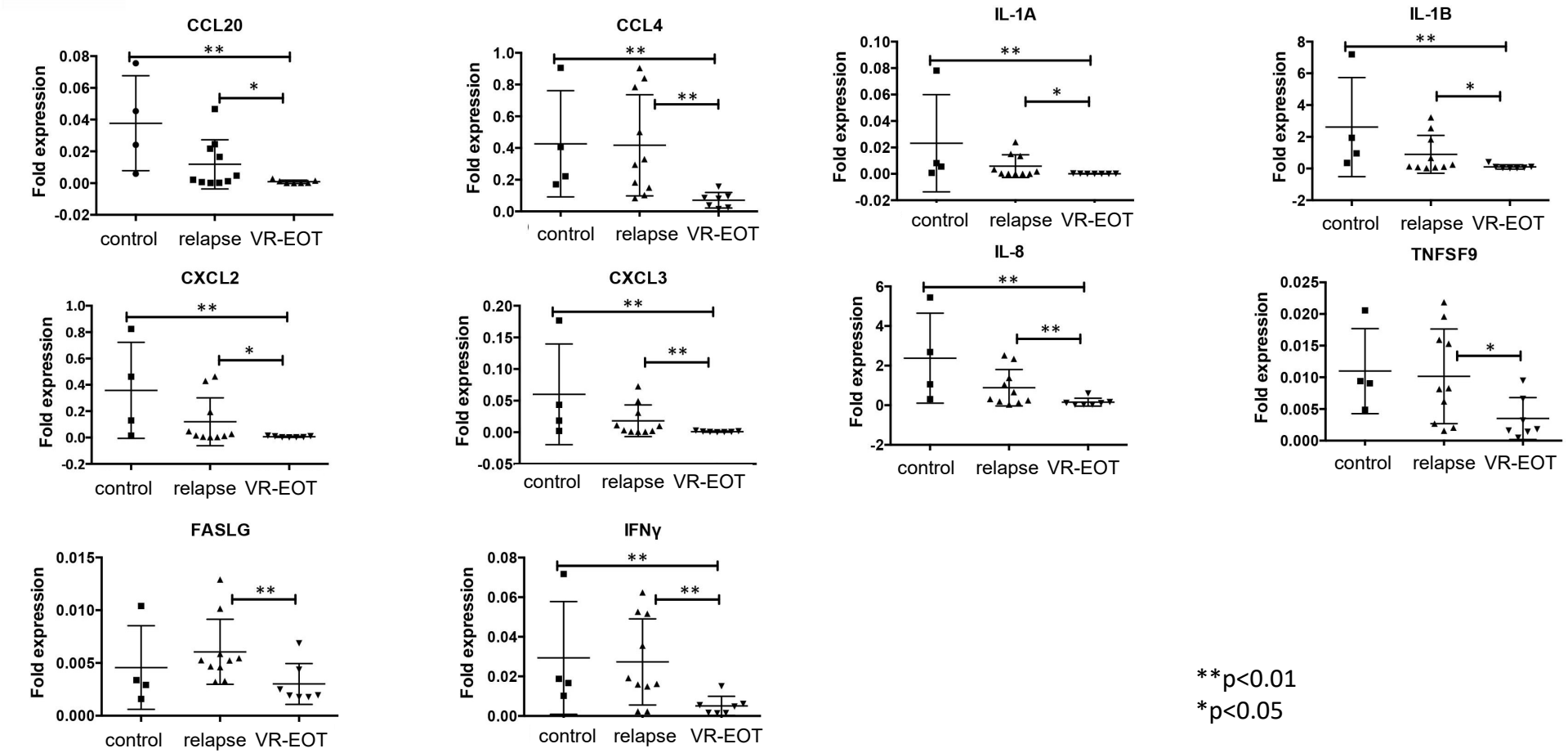


Principle component analysis



Heatmap

Validation

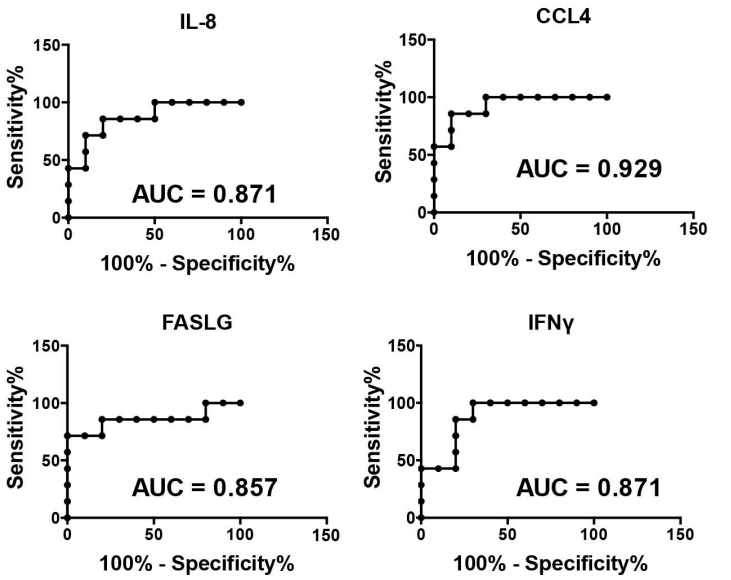


**p<0.01
*p<0.05

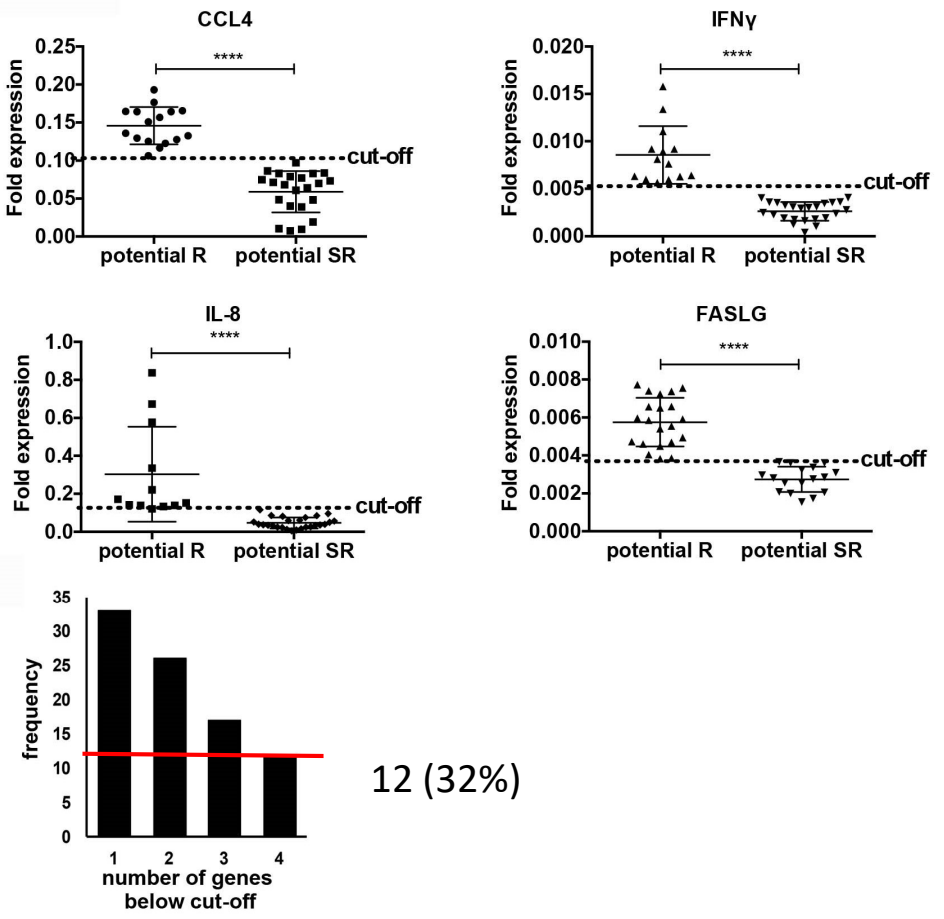
Logistic regression analysis of target genes

Variables	B	S.E	p-value	Odds Ratio	95% CI of OR	
					Lower	Upper
CCL20	0.653	0.344	0.057	1.922	0.980	3.769
CCL4	3.317	1.911	0.053	27.568	0.652	1165.958
CXCL2	0.954	0.535	0.074	2.596	0.910	7.401
CXCL3	1.257	0.663	0.058	3.514	0.958	12.894
FASLG*	3.394	1.568	0.030	29.783	1.379	643.079
IFNγ*	1.242	0.580	0.032	3.463	1.112	10.788
IL-1A	0.618	0.332	0.063	1.855	0.968	3.555
IL-1B	0.858	0.484	0.076	2.358	0.914	6.083
IL-8*	1.090	0.550	0.048	2.973	1.012	8.737
TNFSF9	1.188	0.625	0.057	3.280	0.963	11.166

ROC curves



Expression analysis in 38 on-treatment patients with chronic HBeAg- hepatitis



12 (32%)

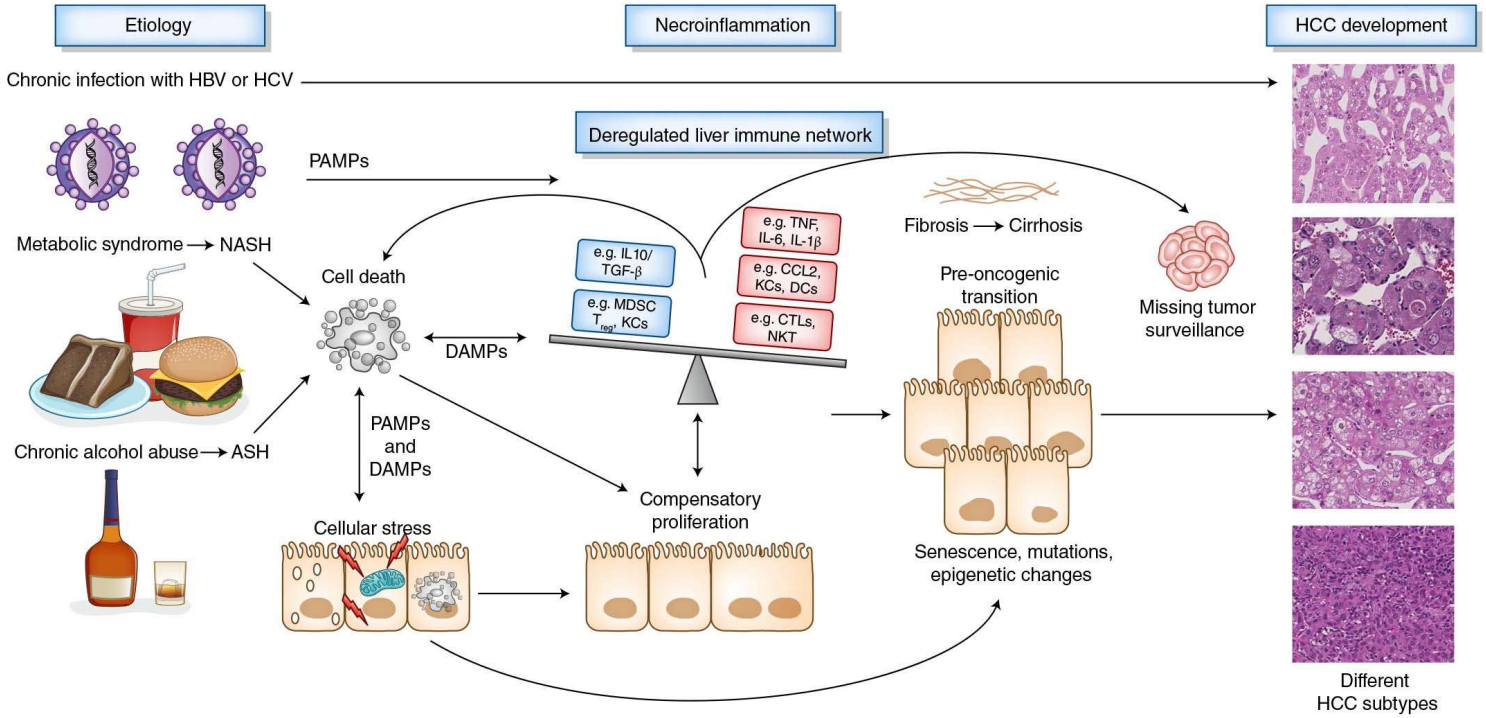
Conclusions

- Individuals with a virological remission form a distinct group at cessation therapy
- Virological remission associated with lower levels of immune response genes
- Up to 1/3 individuals may be candidates for stopping therapy
- May be “immunological drift” back to relapser phenotype ?long-term benefit

Questions which can be addressed

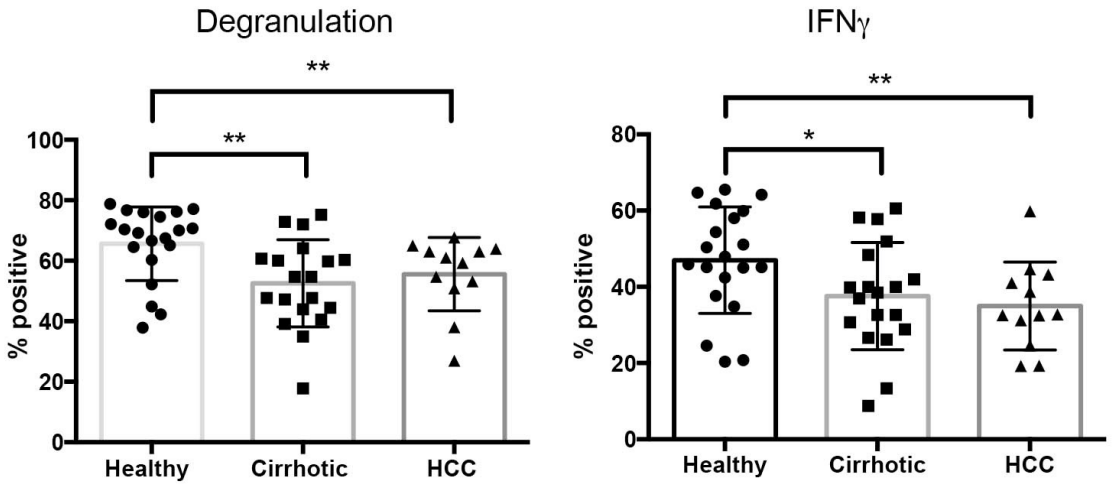
- When can I stop treatment?
  - Does the immune response predict long term outcome?
- **Who is going to develop HCC?**
  - **Are there immune features that precede the development of HCC?**
- New treatments
  - How do they work?
  - Who will benefit?
  - How best to use with currrent therapies?
  - Rationale design for combination?
- Mechanistic immunology
  - Identify new therapeutic possibilities?
- Big picture/translational driver
  - Different populations

HCC



Ringelhan et al, Nature Reviews Immunology, 19: 222-232

NK cell activity is suppressed in cirrhosis



Healthy n=20
Cirrhotic n=18
HCC n=12

N Kumar, unpublished

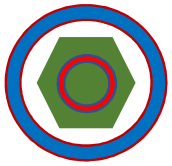
Questions which can be addressed

- When can I stop treatment?
  - Does the immune response predict long term outcome?
- Who is going to develop HCC
  - Are there immune features that precede the development of HCC?
- **New treatments**
  - How do they work?
  - Who will benefit?
  - How best to use with currrent therapies?
  - **Rationale design for combination?**
- Mechanistic immunology
  - Identify new therapeutic possibilities?
- Big picture/translational driver
  - Different populations

HBV: co-ordinating the immune response

Viral factors

Viral suppression



High levels of
HBsAg and HBeAg

Hepatic factors

Cytokines: IL-10, TGF-β,
Cells: Tregs, NKs, MDSCs
Nutrient deprivation

Modulating the immune environment

Exhausted CD8+ T cell

Expression of inhibitory receptors
Apoptosis prone
Weak response to cytokine stimulation
Altered metabolism

Resuscitating T cells

Generating new and better T cells

Final thoughts

- HBV: viral suppression is successful but has limitations
- Exciting therapeutic possibilities for HBV based on immune system
- Understanding the immunology may aid rationale treatment
- Data pooling/collaborative research has proven benefit: HCV research UK (STOP-HCV), STOPAH, PBC-UK
- Link with HCC-UK