

## From the Editor's Desk October 2019

### FINAL

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### SELECTION OF THE MONTH

**Big Title:** iLIFT: Ready to deploy in Primary Care?

**Small Titles:**

Is there a best system to allocate organs for transplantation?

sCD100 enhances HBV-specific CD8 T cell functions and HBV clearance

Treatment of DAA failure – certain risk groups may fail again

Prediabetes/diabetes and NAFLD in children and adolescents

### NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

**Diabetes/prediabetes and the development of NAFLD in children/adolescents and global prevalence of NAFLD in type 2 diabetes (T2DM)**

The prevalence of NAFLD among children and adolescents is alarmingly increasing worldwide. Factors associated with the development of NAFLD in this young population are only partially known. In this issue, **Nobili et al.** performed a large cross-

sectional study of nearly 600 children/adolescents with and without NAFLD. The authors found that **patients with NAFLD had a significantly higher prevalence of abnormal glucose tolerance (prediabetes or diabetes)** than those without NAFLD (20.6% vs 11%). The combined presence of prediabetes and diabetes was associated with a two-fold increased risk of NASH. Importantly, both the *PNPLA3* rs738409 polymorphism and waist circumference were associated with the development of NASH. This important study indicates that abnormal glucose tolerance (especially prediabetes) is highly prevalent among children/adolescents with biopsy-proven NAFLD and that **genetic and environmental factors (diet-induced central obesity) participate in the early development of fatty liver**. Campaigns promoting healthy lifestyle, especially among genetically predisposed children, are needed to reduce the burden of NAFLD among young population. In another epidemiological study, **Younossi et al.** performed a systematic review to estimate the prevalence of NAFLD, NASH, and advanced fibrosis among T2DM patients in 20 different countries across the world. **Among nearly 50,000 patients with T2DM, the overall prevalence of NAFLD among was 55.5%**. Unexpectedly, studies from Europe reported the highest prevalence (68%). On the other hand, the overall prevalence of NASH was 37%. A focused analysis including studies that estimated the prevalence of **advanced liver fibrosis, it was detected in 17% of the patients with T2DM**. This important study provides an estimate of the global prevalence rates for NAFLD, NASH, and advanced fibrosis in patients with T2DM. These data can be used to model the potential prevalence of NAFLD and associated fibrosis in this common at-risk population.

## HEPATITIS B VIRUS (HBV) INFECTION

### sCD100 enhances HBV-specific CD8 T cell functions and HBV clearance

Clearance of HBV-infected hepatocytes is mainly driven by T cells which, however, show an exhausted phenotype in chronic infection. Unraveling the mechanisms involved in this HBV-associated immune dysregulation is critical for designing new immune-based treatment approaches. By promoting immune cell activation and responses, both membrane bound mCD100 (also called Semaphorin-4D), mainly expressed abundantly on the surface of resting T cells, but also its soluble form (sCD100) being derived from cleavage from cell surface by matrix metalloproteases, display important immune regulatory functions. By studying the role of CD100 in HBV clearance, Yang et al. demonstrated for the first time that chronic HBV infection does

not only result in altered mCD100 expression and serum sCD100 levels but also that enhanced membrane CD100 shedding, and subsequent sCD100 formation, increases anti-HBV CTL responses and accelerate HBV clearance. **This study describes sCD100 as a potential new biomarker for evaluating the immune activation status in patients with chronic hepatitis B which also might have the potential to become a therapeutic target in future treatment strategies.**

## HEPATITIS C VIRUS (HCV) INFECTION

### Treatment of DAA failure – certain risk groups may fail again; the safety of sofosbuvir in end-stage renal disease

Failing antiviral treatment has fortunately become a rare event when treating chronic hepatitis C with current DAA-based regimen. Although rare, the cumulative number of patients not achieving SVR may ultimately become significant when considering the huge global epidemiological burden of this infection. A rescue approach with the triple DAA regimen containing sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX) has demonstrated high efficacy in well-controlled phase III clinical trials, but its effectiveness in the real-world setting has not been sufficiently studied yet. Llaneras et al. conducted a large prospective multicentre study including previously DAA-treated patients who were retreated with SOF/VEL/VOX in Spain. **The overall SVR rates were high with 95%, but in certain subgroups as those with genotype 3 and cirrhosis they become as low as 69%.** The intriguing question arising from this first large real-world study that need to be addressed further is whether by re-treatment intensification, for instance by adding ribavirin, cure rates can be improved in certain at-risk DAA failure populations with cirrhosis.

Whether sofosbuvir-based regimens are safe in patients with end-stage renal disease (ESDR) is still highly debated but remains an important question as these regimens are the only one that are recommended for patients with decompensated liver disease. Indeed, the predominant circulating metabolite of sofosbuvir, GS-331007, is renally cleared and accumulates in patients with severe renal impairment, being the reason that sofosbuvir-based regimens are not licensed in ESDR. The phase II multicentre study by Borgia et al. evaluated the safety and efficacy of sofosbuvir plus velpatasvir in patients with ESRD who were undergoing dialysis in order to expand our knowledge regarding the use of sofosbuvir-based regimens in these patient populations. **Although the plasma exposures of sofosbuvir, GS-331007, and velpatasvir were**

higher in HCV-infected patients with ESRD, the treatment regimen was well tolerated with no treatment-related discontinuations or serious adverse events and also achieved a 95% SVR. Collectively, the data from this phase II study support the applicability of sofosbuvir plus velpatasvir as a safe, and highly effective treatment option for HCV-infected patients undergoing dialysis for ESRD.

## HEPATITIS E VIRUS (HEV) INFECTION

### HEV T cell receptor engineered T cells – a first step towards future T-cell based therapy

Ribavirin-resistant chronic HEV infection is associated with a significant risk of developing liver-related complications, and describes an unmet need scenario for which alternative treatment concepts are urgently needed. Stimulated by recent immunotherapeutic approaches in HBV-related liver disease using redirected HBV-specific T cells, Soon et al. investigated the possibility of generating HEV-cytotoxic T cells by the transfer of engineered T cell receptors (TCR) to pave the way for the development of a HEV immunotherapy. **After having identified TCRs targeting conserved HEV epitopes, this proof of concept study was able to demonstrate, that TCR-redirectioned T cells from patients with chronic hepatitis E, who normally show no or low HEV-specific CD8+ T cell responses, were conferred with immunogenicity against epitope-loaded target cells.** Although this work is still in its infancy, as stated by the authors, it does represent an important step towards future developments into viable immunotherapy for patients with chronic HEV infection.

## PRIMARY CARE HEPATOLOGY

### Is iLIFT ready to deploy in primary care?

The number of patients presenting to primary care with abnormal liver function tests or those that have risk factors for liver disease is increasing. Conventional approach to these abnormal liver function tests is a step-wise approach that has the potential to miss many patients with advanced liver disease. **Dillon et al. describe the results of an extremely important study in which they developed and tested the automated iLIFT system, which integrates clinical and biochemical data, and provides recommendations and management plans.** They used a stepped-wedged trial design to evaluate this new system compared with conventional practice. Their data clearly show that the iLIFT system improved the diagnosis of advanced liver disease

by 43%, whilst saving the health service approximately £3216 per patient. If this system can be further validated, it is likely to change the way abnormal liver function tests are handled in primary care.

## CHOLESTASIS

### Interferon $\gamma$ (IFN $\gamma$ ) is important in the pathogenesis of sclerosing cholangitis, regulation of bile acid synthesis by infiltrating T cells in cholangitis

The pathogenesis of primary sclerosing cholangitis (PSC) is unknown. Considerable interest is focused on hepatic IFN $\gamma$  producing lymphocytes. **Ravichandran *et al.* describe the results of an exciting study exploring the role of IFN $\gamma$  in tissue biopsies from patients and also in animal models. Their results show increased levels of IFN $\gamma$  in the serum of patients with PSC and also evidence of infiltration of the liver with NK cells.** Using multiple knock out animals and cell depletion techniques they showed convincingly that IFN $\gamma$  changed the phenotype of the immune cells towards cytotoxicity and its absence attenuated the severity of liver injury providing a potential novel therapeutic approach for patients with PSC.

It is well known that bile alters T cell function but whether T cells can alter bile acid metabolism is unknown. **Glaser *et al.* explored this question in MDR knock out animals. They produce T cell-induced cholangitis in these animals and showed that this resulted in low bile flow. They went on to show that this process was dependent TNF and IFN $\gamma$  in an FXR dependent manner.** These important data increase our understanding of the relationship between inflammation and bile acid metabolism and allows the development of potentially new therapeutic strategies.

## LIVER TRANSPLANTATION

### Is there a best system of organ allocation for transplantation? YAP activation: A therapeutic target to limit ischemia-reperfusion injury

As the availability of organs for transplantation limits access of patients to liver transplantation, issues surrounding policies for allocation of organs become hugely important. It is clear that the practice of how organs are allocated vary from country to country. **Tsuchuor *et al.* describe the results of a hugely important study where they evaluated the current world-wide practice of how liver allografts are allocated. Their data confirm that the sickest first policy is the most reasonable strategy and that**

**currently MELD score is the most widely used but with many adjustments that are different from country to country.** They suggest that there is a need to develop a globally applicable strategy that combines donor and recipient factors to provide the best outcomes for patients on the waiting list and following liver transplantation.

Ischemia reperfusion injury exacerbates preservation injury and can result in delayed graft function or primary non-function. Many mechanisms have been postulated but have not been translated into clinical practice. **Liu *et al.*** describe the results of an impressive study where they show evidence of increasing YAP expression in human post liver transplant liver biopsies. **They went on to reproduce this in a murine model and then showed that activating YAP protected from hepatic injury, reduced synthesis of extracellular matrix proteins and diminished activation of the hepatic stellate cells, whereas inhibiting YAP had the opposite effect.** Their data provide compelling evidence that YAP may be possible target to reduce the severity of ischemia reperfusion injury.

## **CHOLANGIOCARCINOMA (CC), HEPATOCELLULAR CARCINOMA (HCC) – TRANSLATIONAL**

**Loss of Fbxw7 synergizes with AKT activation to promote c-Myc dependent carcinogenesis in CC, immune checkpoint molecules in CC, TLR3 downregulation promotes carcinogenesis in HCC, TOX promotes CD8 T cells exhaustion in HCC**

Although the ubiquitin ligase F-box and WD repeat domain-containing 7 (FBXW7) is recognized as a tumor suppressor in many cancer types due to its ability to promote the degradation of numerous oncogenic target proteins, its role in promoting intrahepatic CC is unknown. **Wang *et al.*** investigated this role in mouse models, intrahepatic CC cell lines, and human intrahepatic CC specimens. They show that **downregulation of FBXW7 is ubiquitous in human intrahepatic CC and cooperates with the protein kinase AKT to induce cholangiocarcinogenesis in mice via c-Myc-dependent mechanisms.** They speculated that targeting c-Myc might represent an innovative therapy against intrahepatic CC with low FBXW7 expression.

Whether CC is responsive to immune checkpoint antibody therapy is unknown, and little is known about its tumor immune microenvironment. **Zhou *et al.*** aimed to characterize tumor-infiltrating lymphocytes in cholangiocarcinoma and assess

functional effects of targeting checkpoint molecules on these lymphocytes. For this, they isolated tumor-infiltrating lymphocytes from resected tumors of cholangiocarcinoma patients and investigated their compositions compared with their counterparts in tumor-free liver tissues and blood, by flow cytometry and immunohistochemistry. They show here decreased numbers of cytotoxic immune cells and increased numbers of suppressor T cells with over-expression of co-inhibitory receptors in tumors suggesting that tumor microenvironment in cholangiocarcinoma is immunosuppressive. **They show that targeting immune checkpoint molecules such as GITR (glucocorticoid-induced TNF receptor), PD-1 (programmed death-1, also known as CD279), or CTLA-4 (cytotoxic T lymphocyte antigen-4, also known as CD152), enhances effector functions of tumor-infiltrating T cells, suggesting that these molecules are potential immunotherapeutic targets for patients with CC.**

Toll-like receptor (TLR) 3 is a pattern-recognition receptor located in the endosome where it recognizes double-stranded RNA (non-self and self). Recognition of double-stranded RNA leads to a TRIF-mediated inflammatory response whose objective is to attract immune cells. Engagement of TLR3 in cancer cells has been shown to result in apoptosis of these cells. Because TLR3 levels are low in the livers from patients with HCC, **Bonnin *et al.*** addressed the hypothesis of a defect in TLR3-induced apoptosis in HCC cells (human and mouse HCC cell lines, and human surgically-resected primary HCC tumors). They show here that **downregulation of TLR3 protects transforming hepatocytes from direct TLR3-triggered apoptosis, an effect which can contribute to hepatocarcinogenesis.**

The thymocyte selection-associated high mobility group box protein (TOX) plays a vital role in T cell development and differentiation, and may play a role in T cell exhaustion. **Wang *et al.*** aimed to investigate the role of TOX in regulating antitumor effect of CD8 T cells in HCC. They sorted different subsets of CD8 T cells from human HCC. Their results reveal that **in HCC, TOX promotes CD8 T cell exhaustion (i.e., a decrease in cytotoxic, antitumoral CD8 T cell action), by regulating endocytic recycling of PD-1.** Downregulating TOX expression in CD8 T cells exerts synergistic effects with anti-PD1 therapy, suggesting a promising strategy for immunotherapy in the context of HCC.