JOURNAL
OF HEPATOLOGY

From the Editor's Desk. . .

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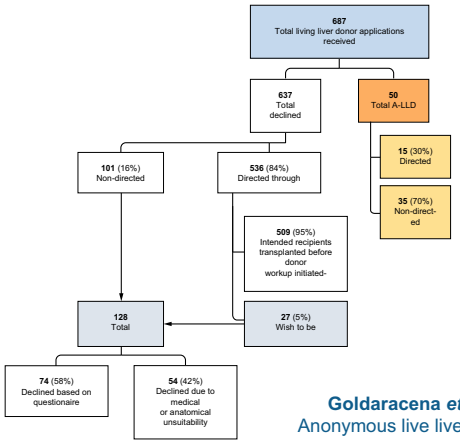
SELECTION OF THE MONTH

Anonymous live liver donation

Despite attempts to increase donation rates after death, organ scarcity accounts for mortality rates of 5–20% in transplant centres. From the ethical perspective anonymous live liver donation (A-LLD) is extremely difficult to introduce into clinical practice. **Goldaracena *et al.* report the results of a pioneering programme of 50 A-LLDs undertaken at the Toronto General hospital over a 12-year period. Their carefully conducted study showed that anonymous donation was provided by individuals for altruistic reasons and none of the donors regretted their decision.** Liver transplantation was performed successfully in all, with a 1-year survival of 91% amongst the 22 adults and 97% in the 28 children. Serious complications amongst the donors were limited to a single case, which resolved completely. This ground-breaking study is likely to open the door for A-LLD in other centres.



Goldaracena *et al.*, 2019.
Anonymous live liver donation

ORGANOIDS

Human pluripotent stem cell (PSC)-derived hepatic organoids

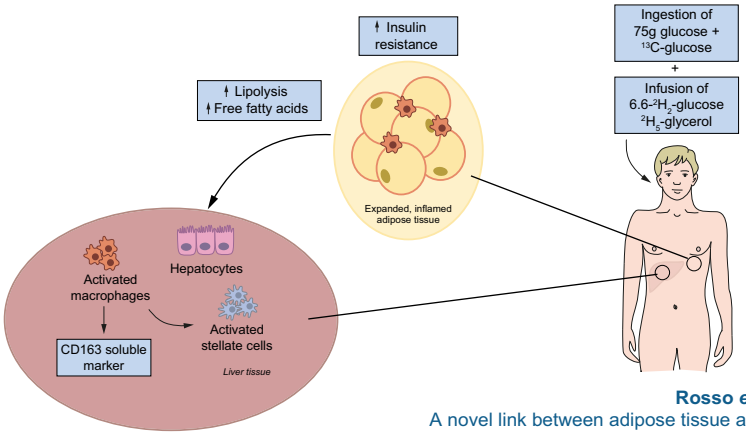
Developing hepatic models capable of long-term expansion with competent liver functionality in a personalised setting is a technical challenge. Stem cell-based organoid technologies can provide an alternative source of patient-derived primary hepatocytes. Self-renewing and functionally competent human PSC-derived hepatic organoids have not yet been developed. **Mu *et al.*** developed a novel method to efficiently and reproducibly generate functionally mature human hepatic organoids derived from PSCs, including human embryonic stem cells and induced PSCs. Here, they show that their **organoids are morphologically indistinguishable from adult liver tissue-derived epithelial organoids and exhibit self-renewal. The organoids preserve mature liver properties**, including serum protein production, drug metabolism and detoxifying functions, active mitochondrial bioenergetics, and regenerative and inflammatory responses. **The organoids exhibit significant toxic responses to clinically relevant concentrations of drugs** that had been withdrawn from the market due to hepatotoxicity and recapitulate human disease phenotypes such as hepatic steatosis. The authors conclude that "organoids may provide a versatile and valuable platform for physiologically and pathologically relevant hepatic models in the context of personalized medicine."

ALCOHOL-RELATED LIVER DISEASE (ALD) AND NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

Sirtuin 6 protects against ALD, ALDH2 deficiency promotes alcohol-induced HCC, a novel link between adipose tissue and NAFLD

Sirtuin proteins which belong to the histone deacetylase superfamily, are a class of proteins that possess either mono-ADP-ribosyltransferase, or deacylase activity, including deacetylase, desuccinylase, demalonylase, demyristoylase and depalmitoylase activity. Among sirtuins, the NAD-dependent protein deacetylase sirtuin 6 (encoded by *Sirt6*), is involved in the regulation of metabolism, DNA repair, and inflammation. Because the role of sirtuin 6 in ALD is unclear, **Kim *et al.*** addressed this question using *Sirt6* knockout (KO) and transgenic mouse models that were treated with either control or ethanol diet. They now show that ***Sirt6* KO mice develop severe liver injury with marked increases in oxidative stress and inflammation whereas the *Sirt6* transgenic mice are protected from ALD via normalisation of hepatic lipids, inflammatory response, and oxidative stress.** This study suggests that the NAD-dependent protein deacetylase sirtuin 6 plays a critical protective role against ALD and it may serve as a potential therapeutic target for ALD.

The mechanisms of hepatocellular carcinoma (HCC) in the setting of ALD are not completely understood. One-third of the Asian population is deficient for aldehyde dehydrogenase 2 (ALDH2), yet the implications of this genetic trait in HCC development are uncertain. In this issue, **Seo *et al.*** studied the role *ALDH2* polymorphisms in a large cohort of patients with hepatitis B virus infection with or without alcohol drinking, as well in a new animal model of ethanol-induced HCC. ***ALDH2* deficiency was associated with increased risk of HCC development in cirrhotic patients with hepatitis B virus and excessive alcohol consumption**. At the experimental level, *Aldh2*-deficient mice were more susceptible to CCl_4 plus alcohol-associated liver fibrosis and HCC. Interestingly, ***Aldh2*-deficient hepatocytes produced a large amount of harmful oxidised mitochondrial DNA via extracellular vesicles**, which were then transferred into neighbouring HCC cells and together with acetaldehyde activated multiple oncogenic pathways, thereby promoting HCC. This translational study revealed that *ALDH2* deficiency is associated with an increased risk of alcohol-related HCC and that extracellular vesicles may play an important role.



Rosso *et al.*, 2019.
A novel link between adipose tissue and NAFLD.

In another interesting article in this issue, **Rosso *et al.*** uncovered new mechanisms linking excessive adipose tissue and the development of NAFLD. In particular, the authors studied the interplay between macrophage activation, insulin resistance (IR) and hepatic damage in patients with biopsy-proven NAFLD. **sCD163 levels, a marker of macrophage activation, paralleled with plasma free fatty acid levels and the degree of lipolysis and IR from the adipose tissue**. *In vitro,* exposure of human macrophages to palmitate enhanced sCD163 secretion. **In the liver, hCD163 positively correlated with sCD163 expression and the degree of steatosis**. Overall, these results strongly suggest a link between lipolysis, adipose tissue IR, a subsequent increased pool of free fatty acids and hepatic macrophage activation, leading to steatosis and liver injury. Pharmacological interventions capable of attenuating adipose tissue IR and activation of hepatic macrophages should be tested in patients with obesity-induced NAFLD.

HEPATITIS B VIRUS (HBV) INFECTION

Curing infantile hepatitis B – timing matters, immune-checkpoint inhibition restores HBV-specific immune responses

The chances of achieving a treatment-induced cure of chronic HBV infection may critically depend on timing of treatment initiation, and seem to be higher when treatment is started at earlier rather than later stages of the disease. In line with this concept, **Zhu *et al.*** performed a real-world cohort study in which consecutive HBV-infected infants suffering from an infantile-onset hepatitis B with persistent elevation of alanine aminotransferase and high viral load were either treated immediately when diagnosed or at a later stage beyond the age of 1 year. **Early onset treatment under 1 year of age was associated with a cumulative HBsAg loss rate of 83% after 12 months of treatment in comparison to 36% when treatment was deferred.** These intriguing observations may hopefully stimulate further research and randomised comparisons evaluating the importance of timing of antiviral treatment for this unusual yet serious condition in HBV-infected infants.

The increased expression of programmed death ligand 1 (PD-L1) in HBV-infected hepatocytes as well as programmed death receptor 1 (PD-1) on HBV-specific T cells likely contribute to the well-known T-cell effector dysfunction seen in patients with chronic HBV infection. Early studies evaluating nivolumab, a human monoclonal antibody that blocks the interaction between PD-1 and PD-L1/2, in HBV-induced HCC showed HBsAg declines in some of the patients suggesting that disrupting PD-1 immune-checkpoint signalling may restore HBV-specific immune responses. In a phase Ib study, **Gane *et al.*** studied for the first time the immunological and antiviral effects of nivolumab when given either alone or in combination with GS-4774, an HBV therapeutic vaccine, in patients with HBeAg-negative chronic hepatitis B receiving oral antiviral treatment. **Nivolumab treatment led to some reduction in HBsAg levels in almost all patients, but a significant reduction of >0.5 log IU/ml was seen in 3 of the 22 patients at week 24 post nivolumab dosing and a single patient achieved sustained HBsAg clearance preceded by a significant alanine aminotransferase flare**. This proof of concept pilot study provides the first evidence that immune-checkpoint inhibition can restore HBV-specific immune responses in patients with chronic HBV infection, and its long-term safety and efficacy should be explored in future combination strategies towards functional cure of chronic HBV infection.

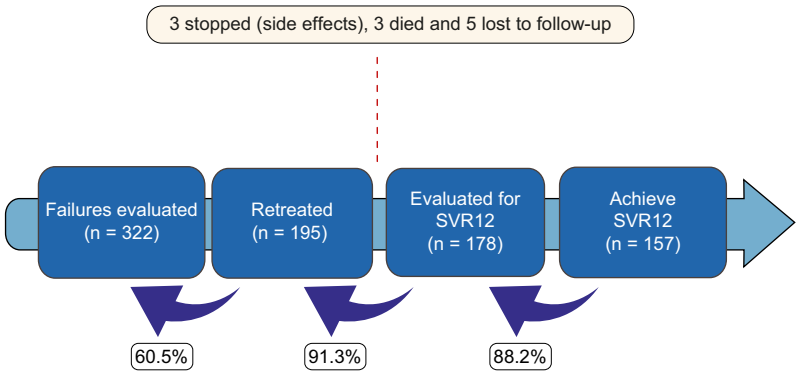
HEPATITIS C VIRUS (HCV) INFECTION

Mechanisms of HCV-associated autoimmunity, Once exhausted, always exhausted? Individualised resistance-guided re-treatment for DAA failure

Chronic HCV infection is an important trigger for the development of extrahepatic autoimmune disorders such as cryoglobulinemic vasculitis (CV). It remains, however, unclear why only a minority of all HCV-infected patients develop this type of immune complex-mediated extrahepatic manifestation. In this issue of the *Journal*, **Comarmond *et al.*** characterised the mechanisms by which atypical memory B cells and their antibody production contribute to this HCV-associated autoimmunity. They showed that **TLR9-stimulated atypical memory B cells secrete TNFα and IgM with rheumatoid factor activity in patients with HCV, induce CV but do not cross-react with HCV antigens, and largely disappear after antigen removal by direct-acting antiviral (DAA) therapy**. Taken together, these data suggest that TLR9 activation of atypical memory B cells plays a central role in breaking tolerance and is as an important mechanism underlying the development of HCV-CV.

Chronic HCV infection has been associated with multiple alterations of the immune system with one hallmark being the functional impairment of HCV-specific CD8+ T cells. It is believed that persistent antigen stimulation mainly drives this exhausted phenotype. **Aregay *et al.*** aimed to investigate if HCV clearance by DAAs could restore the functionality of exhausted HCV-specific CD8+ T cell responses by comprehensively analysing the main functional characteristics of exhausted HCV-specific CD8+ T cells during successful IFN-free DAA mediated cure of HCV infection. One of the main findings of this elegant study was that impaired **HCV-specific CD8+ T cell responses during chronic HCV infection are not restored in the majority of patients following successful HCV clearance**. These interesting data further expand our knowledge of long-term immunological consequences of chronic viral persistence and could help to explain why HCV cure does not lead to protective immunity and HCV reinfections can occur.

The triple DAA regimen containing sofosbuvir, velpatasvir and voxilaprevir (SOF/VEL/VOX), targeting 3 major HCV replication proteins, is currently recommended as treatment of choice in patients failing previous DAA-based antiviral regimens. Its real-world efficacy has also



Pérez *et al.*, 2019.
Individualized resistance-guided re-treatment for DAA failure.

recently been demonstrated in a large study from Spain published in the October issue of the *Journal* (Llaneras *et al. J Hepatol* 2019). However, many HCV high endemic regions have limited access to this expensive single tablet rescue regimen. In order to provide data on how to use resistance information to optimise retreatment after a DAA failure, **Pérez *et al.*** analysed retreatment efficacy in patients who failed NS5A inhibitor-based regimens in the GEHEP-004 cohort, the largest cohort study conducted in Spain and one of the largest international cohort studies regarding DAA failures. The study showed that **when taking individual resistance data into account nearly 90% of patients with previous failure of a NS5A-based DAA regimen can be cured with individualised resistance-tailored "older" first generation regimens**. This study provides important information on how to use resistance information to best individualise re-treatment regimens to treat the unfortunate few who failed a previous DAA therapy, in situations where new and more effective DAA regimens are either not available nor affordable.

CHOLESTASIS

Risk stratification in patients with primary sclerosing cholangitis, increased risk of gallstones with obeticholic acid (OCA)

In clinical practice, defining the prognosis of patients with primary sclerosing cholangitis is difficult. The Amsterdam-Oxford Model (AOM) was introduced to try and overcome this difficulty but the model has not been adequately validated. **Goet *et al.*** performed a multicentre study to validate the AOM model in 534 patients and collected sequential data of these patients at yearly intervals from the time of diagnosis to death or liver transplantation with a median follow-up of about 8 years. **Their data show adequate discriminative performance of AOM with a C-statistic of 0.67 at 1-year increasing to 0.75 at 5 years, confirming its validity.** These data provide an important alternative to the Mayo-Risk score to define prognosis of patients with primary sclerosing cholangitis that can be incorporated readily into clinical practice.

OCA is an FXR agonist that has recently been licensed to treat primary biliary cholangitis. OCA has many effects on bile acid metabolism that have primarily been studied in murine models and its effects on the gallbladder and bile in humans is scarce. **Al-Dury *et al.*** describe the results of an important double-blind randomised controlled clinical trial to study the effects of OCA on the gallbladder in patients due to undergo cholecystectomy. **Their data show for the first time that the OCA treated patients have evidence of enrichment of the bile with FGF-19, increased cholesterol saturation and bile acid hydrophobicity.** Taken together, these changes may enhance the risk of gallstone formation. The data have important implications for monitoring of patients being treated with OCA.

CIRRHOSIS

Hemoxygenase-1 (HO1) triggers ammonia-induced senescence in hepatic encephalopathy, modelling post-hepatectomy liver failure in cirrhosis

Although ammonia is thought to be central in the pathogenesis of hepatic encephalopathy, recent studies highlight the role of oxidative stress and senescence in its pathogenesis, but how these relate to hyperammonemia is unknown. **Borg *et al.*** describe the results of a series of elegant experiments where they provide data from studies of post-mortem human brains from patients dying with hepatic encephalopathy and methodologically detailed findings in cultured astrocytes. **Their studies provide incontrovertible evidence that ammonia elevates HO1, which triggers endoplasmic reticulum stress and sets off a cascade of events leading to alteration in iron-related gene expression.** Critically, they identified O-GlcNAcylation-dependant upregulation of HO1 as a novel mechanism underlying the pathogenesis of hepatic encephalopathy, providing future novel therapeutic targets.

Prognostic models of hepatectomy are needed to define the risk of mortality of patients undergoing resection on the background of existing cirrhosis, particularly in the present era as the surgical techniques, anaesthetic expertise and intensive care support are improving. **Prodeau *et al.*** performed an important study describing the risk of performing hepatectomy on the background of cirrhosis in 343 patients included from 6 French centres. **They identified platelet-count, liver remnant ratio and intention to treat laparoscopy as pre-operative variables; per-protocol laparoscopy and intraoperative blood loss as post-operative variables; as factors associated with survival.** Both the models performed adequately. This simple model can be translated and used to risk-stratify patients both prior to and after hepatectomy.

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