From the Editor's Desk March 2018

Draft #5

Richard Moreau*, Ramon Bataller, Thomas Berg, Jessica Zucmann-Rossi, Rajiv Jalan

Richard Moreau* at Centre de Recherche sur l'Inflammation (CRI), INSERM, Université Paris Diderot, Paris, France; DHU UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France; Laboratoire d'Excellence (Labex) Inflamex, COMUE Sorbonne Paris Cité, Paris, France;*Corresponding author *E-mail address*: richard.moreau@inserm.fr

Ramon Bataller at Division of Gastroenterology, Hepatology and Nutrition University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

Thomas Berg at Section Hepatology, Clinic for Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany.

Jessica Zucman-Rossi at Inserm UMR-674; Génomique Fonctionnelle des Tumeurs Solides; IUH; Paris, France; Université Paris Descartes; Labex Immuno-oncology; Faculté de Médecine; Sorbonne Paris Cité; Paris, France.

Rajiv Jalan at Liver Failure Group, Institute for Liver and Digestive Health, University College London, Royal Free Hospital, UK

SELECTION OF THE MONTH

Big Titles: New treatment strategies in hepatitis B: targeting TLR7, HBV gene expression, and cytoplasmatic nucleocapsid transport

Alcohol abuse in adolescence predicts future Cirrhosis

Small Titles:

Alcohol intake in early life and risk of severe liver disease

Unravelling mechanisms of NK cell activation

A new score to allow usage of livers from deceased donors

LIVER FIBROSIS

G proteins meets autophagy

Hepatic stellate cells (HSCs) play a central role in the development of liver fibrosis. The microenvironment of these cells exhibits elevated levels of signals whose cognate cell surface receptors are guanine nucleotide-binding (G)-protein-coupled receptors.

These receptors can use a G protein called guanine nucleotide-binding protein subunit alpha-12 (Gα12) to transduce the extracellular signal brought by the agonist. Because little is known about the effect of Gα12-mediated signal transduction on HSC, this question was addressed by Kim *et al.* in elegant mouse models. They found that **MiR-16 dysregulation in HSCs causes Gα12 overexpression, which activates HSCs by facilitating autophagy through the conjugation of ubiquitin-like protein ATG12 (encoded by *Atg12*) with autophagy protein 5 (encoded by *Atg5*).** The authors speculate that Gα12 and the regulatory molecules may serve targets in the amelioration of liver fibrosis.

ALCOHOLIC LIVER DISEASE

Alcohol consumption in early life predicts severe alcohol disease and performance of scoring systems in alcoholic hepatitis

Excessive alcohol consumption in young people is a major public health problem worldwide. Whether alcohol consumption early in life is associated with later development of severe liver disease is uncertain. In this issue of the *Journal*, Hagström *et al.* used data on alcohol consumption at conscription to military service from 43,296 men (18-20 years) in Sweden during the late 60s. During a mean follow-up of 38 years, 383 men developed severe liver disease. **Alcohol consumption in people 18-20-year-old was associated with an increased risk of development of severe liver disease in a dose-response pattern**. This important study highlights that alcohol consumption in young men is associated with an increased risk for severe liver disease. **The risk was dose-dependent, with no sign of a threshold effect**. Current guidelines for safe alcohol intake in men might have to be revised, and more effective campaigns aimed at preventing excessive alcohol consumption among young people should be launched. In another article in this issue, Forrest *et al.* studied the performance of several existing scoring systems in predicting survival in alcoholic hepatitis (AH), the most severe form of alcoholic liver disease. Using the large cohort from the STOPAH trial (1,068 patients), the authors compared ‘static’ scores at admission including Maddrey’s discriminant function (DF), MELD, ABIC and Glasgow (GASH). Also, the performance of the “dynamic” scores at 7 days including the Lille score were evaluated. **The area under the curve for the Maddrey’s DF was 0.670, significantly lower than for MELD, ABIC and GAHS at 0.704, 0.726 and 0.713 respectively**. 'Dynamic' scores and change in 'static' score by Day 7 had similar

performances. In patients with high 'static' scores without gastro-intestinal bleeding or sepsis, prednisolone reduced 28-day mortality. Overall mortality from treating all patients with a DF ≥ 32 and Lille assessment (90-day mortality 26.8%) was greater than combining newer 'static' and 'dynamic' scores. **The authors conclude that MELD, ABIC and GAHS are better prognostic scores than the DF**. Low scores have a favorable outcome not improved with prednisolone. Importantly, **combined baseline 'static' and Day 7 scores reduce the number of patients exposed to corticosteroids and improve 90-day outcome**.

HEPATITIS B VIRUS (HBV) INFECTION

An oral TLR 7 agonist in phase II, a novel HBV expression inhibitor, targeting the cytoplasmatic HBV nucleocapsid transport

The innate immunity plays a crucial role in controlling HBV infection and has become an attractive target for future HBV drug development. Vesatolimod (GS-9620), a selective and potent oral agonist of Toll-like receptor 7 (TLR7), an activator of innate and adaptive immune responses, has shown significant reductions in HBV DNA and HBsAg levels in chronically infected chimpanzees and woodchucks. This report by Janssen *et al.* summarizes the first of two phase 2 clinical trials to examine the efficacy and safety of vesatolimod in patients with chronic HBV infection who were virally suppressed on oral antiviral treatment. **Despite demonstrating a vesatolimod dose-dependent and transient induction of ubiquitin-like protein ISG15 (also known as Interferon-induced 15 kDa protein), no significant declines in hepatitis B surface antigen levels were observed**. An ongoing phase 2 study now examines the efficacy and safety of vesatolimod in treatment-naïve and viremic patients with chronic hepatitis B (NCT02579382).

High levels of viral antigens such as HBsAg may contribute to the exhaustion of innate and adaptive immune function seen in patients with chronic hepatitis B. Several lines of evidence suggest a potential therapeutic role for antiviral agents that reduce HBsAg levels hereby restoring virus-specific immune responsiveness. The antiviral properties of RG7834, an orally available small molecule HBV expression inhibitor, were evaluated by Mueller *et al.* in natural HBV infection assays as well as in HBV-infected humanized mouse model either alone or in combination with entecavir. **RG7834 led to a fast and selective reduction in HBV mRNAs hereby leading to a significant reduction in both levels of HBV DNA and viral proteins including HBsAg**. Further

studies are needed to see whether reduction of the intracellular and circulating HBsAg may also lead to a reversal of antiviral immunity as a novel therapeutic approach.

The mechanisms involved in transporting the HBV nucleocapsid to the nuclear pore for delivery into the nucleus and release of the viral genome are poorly understood. In an elegant study, **Osseman *et al.* identified a chaperone called dynein light chain 1, cytoplasmic (encoded by *DYNLL1*) as the major functional binding partner needed for the cytoplasmic transport of mature, viral genome containing, HBV nucleocapsids to the nucleus, hence describing for the first time the evidence of a viral cargo**. Targeting the HBV nucleocapsid transport by inhibiting the capsid-dynein LL1 interaction may become a fascinating approach to inhibit new hepatocyte infections but also to increase elimination of already infected hepatocytes.

HEPATITIS C VIRUS (HCV) INFECTION

How alcohol-use disorders drive HCV disease, treatment as prevention, unravelling mechanisms of NK cell activation

The course of chronic HCV infection can be highly variable and certain cofactors like age and chronic alcohol-use contribute to the individual rate of disease progression (to cirrhosis). To figure out the relative contribution of alcohol-use disorders to HCV-related decompensated cirrhosis development, Alavi *et al.* performed a large population-based study including nearly 175,000 HCV-infected patients in British Columbia, Canada, New South Wales, Australia, and Scotland. Among the 7,233 patients with decompensated cirrhosis diagnosis 28%-50% had an alcohol-use disorder. **The alcohol-use disorder-associated population attributable fractions of decompensated cirrhosis related to alcohol-use disorders were 13%, 25%, and 40% in Canada, Australia, and Scotland, respectively**. Authors made the point that continued heavy alcohol intake is likely to impact potential benefits of direct-acting antivirals (DAAs)-based cure on individual-level liver disease progression and population-level liver disease burden, and action against alcohol-use disorders should form a strong component of HCV public health strategies.

Preventing HCV transmission among people who inject drugs (PWID) is critical to limit future liver disease burden worldwide. The arrival of highly effective and short duration DAAs with cure rates above 95% has made HCV “treatment as prevention” more than a theoretical possibility. In this issue of the Journal, Fraser *et al.* estimated the current HCV treatment rates and coverage of opioid substitution therapy (OST) and needle

and syringe programs (NSP) in PWID across 11 different sites in Europe, and assessed the impact of scaled-up HCV treatment rates and other primary preventions on the HCV prevalence and incidence over the next ten years. The projected HCV prevalence in PWID in 2016 varied from <25% to > 55% according to the different countries but only <2%-5% of those being chronically infected were treated annually. **The authors clearly show that treatment scale-up is needed to achieve observable reductions in chronic HCV prevalence among PWID in most sites in Europe**.

Natural killer (NK) cells comprise 30% of liver lymphocytes, a percentage that can increase up to 80% in HCV-infected patients, and exert their anti-viral effector function primarily by the production of IFN-γ that directly suppresses HCV replication. The aim of the remarkable study by Cerwenka *et al.* was to dissect mechanisms leading to NK cell activation and proliferation in response to HCV. **Main findings were that NK cells become activated and proliferate when they are co-cultured with HCV-containing liver cells, highlighting to a novel cell-cell-mediated pathway of the interplay between infected hepatocytes, monocytes and NK cells to achieve NK cell anti-viral functionality**. The data further imply the cell surface molecule OX40 and OX40L axis as an important activation module in the cross-talk between NK cells and monocyte-derived cells/HCV-infected hepatocytes that might play an important role not only in HCV but also in other viral infections.

LIVER TRANSPLANTATION

Development and validation of the UK-DCD-Risk score to select livers from deceased donors (DCD) for transplantation

Organ shortages lead to the death of substantial number of patients with advanced liver disease. One of the strategies to increase the number of organs available for transplantation is to use organs from deceased donors. Many observational studies have shown that selection of DCD organs is the key to using them successfully. **Schlegel *et al.* have developed and validated, for the first time, a new score, the UK-DCD-Risk score, which includes clinical and easily obtained donor and recipient factors that can be used to select organs and suitable recipients for transplantation.** With further validation, this scoring system can allow better usage of organs that are often discarded or used inappropriately and change clinical practice.

ACUTE ON CHRONIC LIVER FAILURE (ACLF) IN CHILDREN

Validation of the CLIF scores a prognostic tool for pediatric patients with ACLF

ACLF is a devastating syndrome that occurs in cirrhotic patients and is characterized by organ failures and high risk of short-term mortality. The available data in adults have shown that this syndrome is distinct to acute decompensation and can be diagnosed using an organ failure scoring system but whether this is true in children has thus far been unknown. **Bolia *et al.* studied cirrhotic children with acute decompensation and developed a new score, with high sensitivity and specificity, the pediatric CLIF-SOFA score to identify patients at high risk of short-term mortality.** In addition to organ failures, they identified serum sodium as an independent predictor of mortality. This important study, with further validation will allow better characterization of ACLF in children.

HEPATOCELLULAR CARCINOMA (HCC)

Leveraging *ARID1A* deficiency, statin therapy for HCC prevention,

AT-rich interactive domain-containing protein 1A (also known as BAF250; encoded by *ARID1A*) is a component of the ATP-dependent chromatin-remodeling complex, which may act as a tumor suppressor gene. *ARID1A* is frequently mutated in HCC. However, it remains unknown how the *ARID1A*–encoded protein suppresses HCC development and whether *ARID1A* deficiency could be exploited for therapy. These questions were addressed by Hu *et al.*, mainly by using mouse models of HCC and cell lines. Their results reveal that ***Arid1a*-deficiency activates angiopoietin 2-dependent angiogenesis and promotes HCC progression.** Interestingly, loss of *Arid1a* in HCCs confers sensitivity to angiopoietin 2 blockade and sorafenib treatment.

That statin therapy prevents HCC development in individuals at risk of this cancer is unknown. Kim *et al.* conducted a nationwide, nested case-control study using data from the National Health Insurance Service Physical Health Examination Cohort 2002-2013 in the Republic of Korea with the aim to investigate the risk of HCC after statin use in the whole general population and evaluated the effects of preexisting diabetes and cirrhosis on that risk. A total of 1,642 HCC cases were matched to 8,210 control individuals from 514,866 participants. They found that the adjusted odds ratio (OR) for HCC was 0.44 (95% confidence interval [CI], 0.33 to 0.58), in statin users vs. non-users. Moreover, among patients with diabetes, the adjusted OR for HCC was 0.28 (95% CI, 0.17 to 0.46), in users vs. non-users. Among patients with cirrhosis the

adjusted OR was 0.39 (95% CI=0.26-0.60), in users vs. non-users. Therefore, **statin use may have a beneficial inhibitory effect on HCC development, particularly in patients with diabetes or cirrhosis, who are at high risk for HCC.**

The use of contrast enhanced ultrasound (CEUS) for the diagnosis of HCC in cirrhosis was questioned for the risk of false positive diagnosis in case of cholangiocarcinoma. The American College of Radiology has recently released a scheme called CEUS-Liver Imaging Reporting And Data System (CEUS LI-RADS®), classifying lesions at risk for HCC investigated by CEUS. In this scheme, the expected diagnostic pattern of HCC, termed LR-5, corresponds to arterial phase hyperenhancement (rim or globular excluded) followed by late (≥60 seconds) and mild degree of washout. Although of great potential interest, the CEUS LI-RADS proposal has not yet been validated so far. This is why Terzi *et al.* aimed to validate CEUS LI-RADS® scheme for the diagnosis of HCC. A total of 1006 nodules in 848 patients with chronic liver disease at risk for HCC collected in 5 Italian centers were retrospectively analyzed. They show that the **CEUS LI-RADS® class LR-5 is highly specific for HCC, enabling its use for a confident noninvasive diagnosis.**