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ABSTRACTS

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EL-01

Physiology and Pathophysiology of the Biliary System: A basic science view of cholestasis

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EL-02

Molecular Mechanisms of Transporters for Bile Formation and Related Liver Diseases

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Recent studies revealed that the biliary secretion of bile lipids, such as bile salts, phospholipids and cholesterol, are mediated by several ATP-binding cassette (ABC) transporters. Bile salt export pump (BSEP/ABCB11) is necessary for the biliary secretion of bile salts. Multidrug resistance 3 P-glycoprotein (MDR3/ABCB4) contributes to the biliary secretion of phospholipids, especially phosphatidylcholine, which are essential in the formation of biliary mixed micelles with bile salts. ABCG5/ABCG8 heterodimer mediates the biliary secretion of cholesterol and related compounds from the canalicular membrane of hepatocytes to biliary mixed micelles. Genetic disruptions of these transporters are known to cause severe hereditary disorders; the progressive familial cholestasis type 2 (PFIC2) by BSEP, PFIC3 by MDR3 and sitosterolemia by ABCG5/ABCG8. In the presentation, we would like to introduce the molecular mechanisms of these transporter-mediated processes and related disorders, including hot topics of a canalicular cholesterol importer Niemann-Pick C1-like 1 (NPC1L1) and a biliary cholesterol binder Niemann-Pick C2 (NPC2).

EL-03

PSC and PBC, aetiology, diagnosis and management

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EL-04

Cholangiocarcinoma and Viral Hepatitis

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Viral hepatitis B and C are increasing known to be a risk factor of intrahepatic cholangiocarcinoma, especially in East Asia. Viral hepatitis-associated intrahepatic cholangiocarcinoma is thought to have common disease processes with hepatocellular carcinoma. From 2000 to 2010, 170 patients with intrahepatic cholangiocarcinoma who received detailed pathological assessment and regular follow-up at the National Taiwan University Hospital were selected for this study. Of 170 patients, 69 (41%) were positive for hepatitis B and/or C virus. These patients were younger, were more frequently male, and had elevated serum α-fetoprotein levels as compared with seronegative intrahepatic cholangiocarcinoma patients. Grossly these tumors were mostly of the mass-forming type, and histologically, cholangiolar differentiation was more frequently seen. We identified N-cadherin as an immunohistochemical marker strongly associated with hepatitis virus infection. The prevalence of viral hepatitis in patients with N-cadherin-positive intrahepatic cholangiocarcinoma was 75%, and that in N-cadherin-negative patients was only 37%. N-cadherin-positive patients were younger, had elevated α-fetoprotein, and had no hepatolithiasis. All N-cadherin-positive intrahepatic cholangiocarcinomas were of the mass-forming type. N-cadherin positivity was strongly associated with cholangiolar morphology and lack of carcinoembryonic antigen and MUC2 expression, whereas K-RAS mutations were less frequent. Our results indicate that a subgroup of intrahepatic cholangiocarcinoma characterized by cholangiolar differentiation and N-cadherin expression is strongly associated with viral hepatitis.

EL-05

Cholestasis: the progression from pediatric to adult diseases

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With the improvement in the diagnosis and management of cholestatic liver diseases in past two decades, the life span of pediatric patients with cholestasis has increased. Their long-term outcome and complication deserves attention from both pediatric and adult hepatologists. The onset of genetic cholestasis varies, depending on the disease types, and the severity of mutations/polymorphisms. In some cholestatic diseases, symptoms may subside beyond infancy, with reappearance of symptoms in adulthood, such as benign recurrent intrahepatic cholestasis, Dubin-Johnson syndrome, and citrin deficiency. Some adult patients may present with extra-hepatic symptoms, such as neuropsychiatric symptoms and hyperammonemia in patients with citrin deficiency. Growth delay is usually a problem in patients with cholestasis. Short statue and delayed puberty is frequently seen, and most prominent in patients with progressive familial intrahepatic cholestasis, Alagille syndrome, and primary sclerosing cholangitis. Some pediatric cholestatic diseases are been corrected by surgical intervention, including hepatoportoenterostomy (Kasai operation) for biliary atresia and partial biliary diversion for progressive familial intrahepatic cholestasis. Patients with biliary atresia may have long-term survival after the operation, but some of them may gradually develop liver cirrhosis, recurrent cholangitis, late-onset biliary stricture, cardiopulmonary complication, or chronic hepatic encephalopathy that requires liver transplantation in young adulthood. Hepatocelular carcinoma and cholangiocarcinoma have been reported in patients with underlying cholestasis or genetic polymorphisms of cholestatic genes. The timing to receive liver transplantation in these patients should be well considered before irreversible or fatal complications occur. A continuous

care from childhood to adulthood, and further studies of long-term follow-up for cholestatic patients are anticipated.

EL-06

Genetic causes of cholestasis: not just a paediatric problem

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In the past decades technological advances have expanded our knowledge about the genetic determinants of cholestatic liver diseases. Genetic assays for cholestatic liver diseases can be divided into diagnostic tests for monogenic diseases and assessment of polygenic disease predisposition (susceptibility tests) by genome-wide association studies and next-generation sequencing (Krawczyk et al. Nat Rev Genet 2010). Several cholestatic syndromes are monogenic diseases. However in contrast to a_1-antitrypsin deficiency, genetic tests for most monogenic cholestatic diseases are not 'simple' genetic tests, since in general no hot-spot mutations exist. Hence, genetic testing is based on sequencing of candidate genes. However, Alagille syndrome illustrates that sequencing of exons does not identify all mutations, since some patients carry deletions to be detected by FISH or comparative genome hybridization, or variants of other genes in critical pathways. The two exceptions to this rule are progressive familial intrahepatic cholestasis (PFIC) type 2 (*ABCB11* p.E297G and p.D482G) and cystic fibrosis-associated liver disease (*CFTR* DF508).

Table 1 summarizes the gene defects causing the three PFIC subtypes in children and the corresponding benign recurrent intrahepatic cholestasis (BRIC) syndromes in adults, which are caused by mutations of hepatocanalicular ATP-dependent transporters. BRIC is characterized by acute episodes of cholestasis, jaundice and pruritus triggered by environmental factors (e.g. hormones, drugs, infections). Liver fibrosis has been described in cases of BRIC, indicating a continuum between BRIC and PFIC in some cases. Of note in PFIC1 and PFIC2, the elevation of ALT, bilirubin and bile acids is contrasted by low levels of g-GT (in contrast to PFIC3 and Alagille syndrome); a predominant cholestatic pattern (AP/ALT↑) points to PFIC1, whereas elevated aminotransferase activities (ALT/AP↑) indicate ABCB11 deficiency (PFIC2).

In PFIC3, the observation that the mothers of children suffering from this disease had an increased likelihood for episodes of intrahepatic cholestasis of pregnancy (ICP) provided a first clue that some cases of ICP are caused by *ABCB4* variants. The spectrum of *ABCB4*-associated diseases illustrates that severe homozygous variants causing congenital cholestatic diseases can be described as the 'tip of the iceberg', whereas 'mild' and/or heterozygous variants / haplotypes represent genetic risk factors that together with environmental factors confer an increased risk for cholestasis, biliary fibrosis, or gallstones (Figure 1).

Very recently the first reports have identified causative gene variants for cholestatic syndromes by whole-genome sequencing of index family members (Karlsen et al. AASLD 2011). This technology enables parallel analysis of rare variants in genes for both monogenic and complex diseases and can be used for integrated risk analysis. Whole-genome sequencing is challenging, since not only well-annotated genomic and functional information is required for correct data interpretation, but multidisciplinary teams are needed to provide personalized counseling to patients.

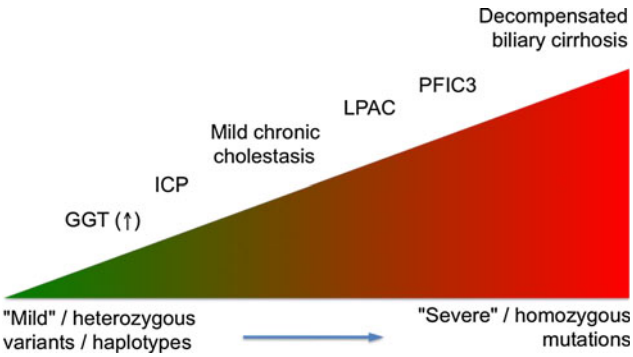

Fig. 1 Gradient of genotype-phenotype correlations in ABCB4 deficiency

ICA-01

The new epidemiology of nosocomial bacterial infections in patients with cirrhosis: therapeutical implications

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ICA-02

Bacterial translocation in cirrhosis: pathophysiology and clinical implications

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Table 1 Genetic and biochemical characteristics of PFIC types 1 - 3 and the associated clinical phenotypes

Type	1	2	3
Gene	(*ATP8B1 FIC1*)	(*ABCB11 BSEP*)	(*ABCB4 MDR3*)
Transport	Phosphatidylserine	Bile salts	Phosphatidylcholine
Phenotypes	Biliary cirrhosis	Neonatal giant cell hepatitis	Biliary cirrhosis with ductular proliferation
	Benign recurrent intrahepatic cholestasis (type 1)	Biliary cirrhosis	PSC-like phenotype
	Extrahepatic manifestations: malabsorption, pancreatitis, deafness, pneumonia	BRIC type 2	ICP
		Intrahepatic cholestasis of pregnancy (ICP)	Low phospholipid-associated cholelithiasis (LPAC)
		Gallstones	HCC
		Drug-induced cholestasis	Cholangiocarcinoma (CCA)
		Hepatocellular carcinoma (HCC)	
g-GT	Low!	Low!	↑
Therapy	(Ursodeoxycholic acid [UDCA]), orthotopic liver transplantation (OLT)	Biliary diversion, (UDCA), OLT	UDCA, OLT

Bacterial translocation (BT) has been defined as the movement of bacteria from the intestinal lumen to mesenteric lymph nodes (MLN), and from there to other territories. Both intestinal bacterial overgrowth and deterioration of the intestinal barrier function are believed to be the main causes of BT in patients with decompensated cirrhosis.

The diagnostic criterion to define BT is the presence of a positive culture of MLN. Indeed the diagnosis of BT in experimental animals does not represent a relevant problem, but it is obviously difficult in patients. The incidence of BT has been rarely described in patients. Probably asymptomatic spontaneous bacteraemia or bacterascites represents unadvertised episodes of BT.

In these last years attempts have been done to develop alternative methods to MLN culture to detect BT, such as measurement of lipopolysaccharide binding protein (LBP), or detection and quantification of bacterial DNA in serum. By means of these methods it can be suggested that BT is present in roughly 40% of patients with cirrhosis and ascites. There is experimental data showing that the presence of bacterial DNA in blood or ascitic fluid is always associated to its simultaneous presence in MLNs. This however may be found in patients with culture-negative MLNs (non-viable BT) or in culture-positive MLNs (BT). There are no differences in the proinflammatory status associated to both pathogenic situations. Therefore, data show that detection of bacterial DNA in a biological fluid may be considered as a surrogated marker of BT. Evidences it exist suggesting that the main reason for BT is intestinal overgrowth of a single bacterial spp.

Bacterial DNA joins to toll-like receptor 9, being followed by the induction of a marked inflammatory response. This fact, in turn may facilitate the development of serious clinical complications, such as hepatorenal syndrome (HRS) or acute-on-chronic liver failure, circumstances that finally shorten the survival of patients.

Selective intestinal decontamination (SID) with norfloxacin almost completely abrogates BT and the associated inflammatory reaction. When used as primary prophylaxis of infections in high-risk patients it reduces the incidence of HRS and improves survival. As secondary prophylaxis also reduces the incidence of new episodes of spontaneous bacterial peritonitis (SBP). However, the continuous use of norfloxacin may induce the development of quinolone-resistant strains in the gut lumen that may finally lead to their overgrowth and translocation. Attempts are being done to find alternatives to norfloxacin in this setting.

BT has been profusely studied in decompensated cirrhosis, but new data show that BT is also common in other settings such as inflammatory bowel disease, acute pancreatitis and morbid obesity. The clinical consequences of this fact may be probably different in each one of these clinical areas.

ICA-03

Bacterial infections: from bench to bedside

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ICA-04

Pathophysiological basis of the use of albumin in the prevention of haemodynamic derangement due to bacterial infections in patients with cirrhosis

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Summary: Albumin was introduced in the treatment of patients with cirrhosis and ascites to increase the reduced plasma oncotic pressure, which, at that time, was thought to be a pivotal factor together with portal hypertension, in the pathogenesis of ascites. The following evolution of the knowledge showed that the renal functional abnormalities in cirrhosis are the final consequence of a reduction of effective circulating volume due to a marked splanchnic arterial vasodilatation. As a consequence, the rationale of the use of albumin in patients with cirrhosis and ascites was completely changed. Albumin is no more used on the basis of the plasma albumin concentration but in clinical situations that are or are going to be a sign of severe reduction of effective circulating volume such as: 1) prevention of post-paracentesis circulatory dysfunction, 2) prevention of hepatorenal syndrome in patients with spontaneous bacterial peritonitis, and 3) treatment of hepatorenal syndrome.

Albumin is very effective in preventing of post-paracentesis circulatory dysfunction and of hepatorenal syndrome in cirrhotic patients with spontaneous bacterial peritonitis. In addition, albumin administration improves survival in patients with spontaneous bacterial peritonitis. In the treatment of hepatorenal syndrome, the use of albumin in combination with vasoconstrictor drugs is essential for the recovery of renal function and to improve slightly survival. Probably these effects can be due not only to its properties as plasma expander but to its several biological effects also. In particular, in the setting of SBP, albumin exerts a positive on cardiac output. Recent experimental data showed that the increase in cardiac output induced by albumin is not only related to its effect on cardiac pre load but also to a cardiac positive inotropic effect. The inotropic effect of albumin in rats with cirrhosis and ascites was related to its effectiveness in counteracting the negative effects of oxidative stress- and TNF-α-induced activation of NF-kB-iNOS pathway and oxidative stress-induced alteration of β-receptor signaling in the cardiac tissue.

It seems easy to foresee that the role of albumin will be once more defined in the near future, as it was almost 30 years ago.

Parole chiave: cirrhosis, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, albumin, effective circulating volume.

"*Mini*" abstract: In the 1950s albumin was introduced in the treatment of patients with cirrhosis and ascites to increase the reduced plasma oncotic pressure. The following evolution of the knowledge showed that ascites is the final consequence of a reduction of effective circulating volume. So, albumin is now used in cirrhotic patients only in clinical situations that are or are going to be a sign of severe reduction of effective circulating volume.

ICA-05

Sepsis in patients with acute on chronic liver failure: new strategies for prevention and treatment

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Acute-On-Chronic Liver Failure (ACLF) is a serious acute insult of liver on an underlying compensated chronic liver disease. ACLF has been defined as acute hepatic insult manifesting as jaundice (serum bilirubin$\geq$5 mg/dL) and coagulopathy (INR$\geq$1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease (APASL criteria). With conservative treatment, the mortality rate is as high as 60%. Liver transplantation remains the only definitive therapy for patients with ACLF, however, is often not feasible. The most important cause of mortality and multi-organ failure is development of sepsis. Sepsis which sets in rather early in patients with ACLF, is partly related to neutrophil dysfunction.

We have recently shown that GCSF therapy could improve the CTP, MELD and Sequential Organ Failure Assessment score (SOFA) score in patients with ACLF. Consecutive patients with ACLF were enrolled and randomized to receive either: G-CSF (5 μg/kg, s/c, 12 doses, Group A) or placebo (Group B) plus standard medical therapy. Forty seven ACLF patients were randomized to Group A (n=23) or B (n=24). Median leucocyte count [21.7 (10.0-40.1) vs. 10.4 (3.6-18.4) $\times$1000/cumm](p<.001) and neutrophil count [18.2(7.0-36.0) vs. 7.1(3.0-16.5) $\times$1000/cumm](p<.001) at wk1 were significantly higher in group A. Sixteen (69.6%) patients in group A and seven (29%) in group B survived; the actuarial probability of survival at day 60 was 66% vs. 26%, p=0.001). The G-CSF therapy resulted in improvement in Gr. A compared to Gr. B in CTP [median Δ -33.3% vs. +7.1% (p=0.001)], MELD [median Δ -15.3% vs. +11.7% (p=0.008)] and

SOFA score [median Δ -50% vs. +50% (p=0.001)]. The probability of development of HRS, new onset HE and sepsis was significantly lower in group A versus B [(19% vs. 71%, p=0.0002), (19% vs. 66%, p=0.001), (14% vs. 41%, p=0.04)] respectively. G-CSF therapy led to a significant increase in the CD34 cell population in the liver at 1 month (27.5% vs. 45%, p=0.01). In conclusion, G-CSF therapy improves survival in patients with ACLF and results in improvement in the CTP, MELD and SOFA score and prevents development of sepsis, HRS, and new onset HE. We also observed that G-CSF therapy led to a significant increase in the CD34 cell population in the liver tissue after 4 weeks of GCSF administration protocol. This important observation gives credence to the role of recruitment of bone-marrow derived cells after GCSF stimulation in patients with ACLF. In fact, the use of GCSF can help bone marrow derived macrophages to migrate and engraft into the liver and help in reducing the hepatic fibrosis and support hepatic regeneration.

PS01-01

IL28B Genotypes Affect Lipid Profiles and Viral Clearance Rate in Chronic Hepatitis C Patients Treated with Pegylated Interferon plus Ribavirin

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Background: The mechanisms by which IL28B genotypes affect CHC outcomes remain unclear.
Since metabolic regulation and interferon response are highly integrated, IL28B genotypes may affect metabolic profiles. We aimed to examine the association of IL28B rs8099917 genotypes with metabolic profiles, and the impact of metabolic profiles on viral kinetic parameters.
Methods: A case–control analysis of subjects with and without chronic HCV infection was performed. The HCV Group consisted of 91 CHC patients treated with pegylated interferon alfa-2a (Peg-IFN) plus ribavirin, and the Control Group consisted of 91 age, sex and body mass index (BMI)-matched subjects without HCV infection. The associations of IL28B rs8099917 genotype with pretreatment metabolic profiles and early viral kinetic parameters were evaluated.
Results: Although HCV patients had significantly lower serum triglyceride, total cholesterol and LDL levels than the controls, IL28B rs8099917 genotypes were associated with serum triglyceride and HDL levels only in HCV patients, but not controls (Table 1). HCV patients with TT genotype had lower serum triglyceride and fasting blood glucose, but higher HDL than those with GT genotype. Compared to HCV genotype 1 patients, the differences in metabolic profiles were more significant in genotype 2 patients. In addition, patients with higher serum TG, higher fasting blood glucose, and lower HDL had a lower viral clearance rate (Table 2).
Conclusions: IL28B genotypes may affect lipid profiles of chronic hepatitis C patients, especially in HCV genotype 2 patients. Patients with higher serum fasting blood glucose, triglyceride, and lower HDL have a lower viral clearance rate during Peg-IFN plus ribavirin therapy.

PS01-02

BOCEPREVIR PLUS PEGINTERFERON/RIBAVIRIN FOR THE TREATMENT OF HCV/HIV CO-INFECTED PATIENTS: INTERIM RESULTS

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Background: Adding boceprevir (BOC) to peginterferon (P) and ribavirin (R) increases SVR among HCV-monoinfected patients. This phase 2 trial investigated efficacy and safety of BOC+P/R in HCV/HIV-coinfected patients.
Methods: Patients with untreated hepatitis C genotype 1 and HIV-RNA < 50 copies/mL were randomized 1:2 to receive P (PEG 2b 1.5 ug/kg/wk)/R (600-1400 mg/day, by weight) + BOC 800 mg TID or P/R + placebo for 44 weeks, after a 4-week lead-in of P/R. Patients were stratified by: cirrhosis/fibrosis (yes vs. no) and baseline HCV-RNA (< 800,000 IU/mL vs
Results: 100 patients were randomized between 11/2009 and 12/2010; 2 patients in the BOC arm did not receive medication; thus, 34 control and 64 experimental patients were treated. The majority were non-cirrhotic (95%), white (82%), male (69%) with median age ~43 years. Most had high baseline HCV-RNA (88%) and HCV genotype 1a (65%). At TW 24, rate of undetectable HCV-RNA was 70% and 34% in the BOC and control arms, respectively. Discontinuations due to adverse events occurred in 14% and 9% of the BOC and control group respectively. Compared to control group, BOC patients were more likely to have headache, pyrexia, decreased appetite, dysgeusia, vomiting, and neutropenia. There were no marked differences in CD4 count or % patients with HIV-RNA <50 copies/mL in the treatment groups.
Conclusions: The addition of BOC to P/R was associated with higher rates of undetectable HCV-RNA at TW 24. The safety and tolerability profile was consistent with that observed in HCV-monoinfected patients.

PS01-03

ITPA gene variant protects against treatment-induced anemia and improves viral clearance by pegylated interferon-alfa and ribavirin therapy in chronic hepatitis C patients

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Background: Inosine triphosphatase (ITPA) deficiency protects against hemolytic anemia in chronic hepatitis C patients receiving ribavirin. Here, we evaluated the clinical significance of ITPA variants in hepatitis C patients who were treated with peginterferon plus ribavirin.
Methods: In this multicenter retrospective cross-sectional study, 474 chronic hepatitis C patients were enrolled who were treated with peginterferon plus ribavirin in 4 geographically different hospitals in Japan. Patients were grouped according to hemoglobin decline of more than 3 g/dl at week 4. Three SNPs within or adjacent to ITPA gene (rs6051702, rs7270101, and rs1127354) were genotyped.
Results: A functional SNP, rs1127354, within ITPA exon was strongly associated with protection against anemia with only one (0.8%) in 129 patients with ITPA minor variant A developed severe anemia ($P = 5.9 \times 10 - 20$). For rs6051702 which had significant association in European-Americans, significant but weak association with severe hemoglobin reduction was found in Japanese ($P = 0.009$). In patients excluding genotype 1b and high viral load, who were treated with 24-week regimen, those with ITPA minor variant A achieved significantly higher sustained viral response rate than those with major variant (CC) (96% vs. 70%, respectively, $P = 0.0066$). A multivariate logistic regression analysis showed that age and the ITPA SNP are significant predictive factors that are associated with treatment responses.
Conclusions: ITPA SNP, rs1127354, is a useful predictor of ribavirin-induced anemia in Japanese patients. Patients with ITPA minor

variant A (~27%) have advantage for peginterferon plus ribavirin-based therapies, due to expected adherence of ribavirin doses, resulting in higher viral clearance rate.

PS01-04

Decrease of Myeloid-derived suppressor cells in the peripheral blood of patients with chronic hepatitis C after 4 weeks of antiviral treatment

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Background: Myeloid-derived suppressor cells (MDSCs), one of the most important regulators of anti-tumor T-cell responses in cancers, has not been reported in hepatitis C virus-related chronic hepatitis. Here we investigated the change of MDSCs and CD4+CD25high regulatory T cells (Tregs) in peripheral blood of HCV patients before and after 4 weeks of administration with PEG-interferon and ribavirin.

Methods: Twenty-five HCV patients administrated with PEG-interferon and ribavirin and 40 sex- and age-matched healthy people as control group were enrolled in this study. Peripheral blood mononuclear cells (PBMCs) were analyzed by multi-color flowcytometry. LIN-HLA-DR-CD11B+CD33+ MDSCs level and relationship with the prevalence of CD4+CD25high regulatory T cells (Tregs) in peripheral blood of HCV patients before treatment and at week 4 of the treatment were analyzed.

Results: Compared with healthy control group (0.460 ± 0.255 %), MDSCs in the peripheral blood of HCV patients before antiviral therapy (0.586 ± 0.462 %) did not increase significantly (t=-1.246, P=0.221). While the $CD4^{+}CD25^{high}$ Treg cell in the peripheral blood of HCV patients before antiviral therapy (2.602 ± 0.876 %) were higher than that of healthy control group (1.827 ± 0.533 %) (t= -4.473, P<0.001). The frequency of circulating MDSCs (4w: 0.161 ± 0.108 %, t=4.865, P<0.001) and $CD4^{+}CD25^{high}$ Treg cell (4w:2.101 ± 0.782 %, t=2.498, P=0.020) decreased significantly after 4 weeks of treatment with PEG-interferon and ribavirin.

Conclusions: PEG-interferon and ribavirin may modulate antiviral immunity in chronic HCV patients by reversing MDSC-mediated immunosuppressionD.

PS01-05

Characterization of Hepatitis C Virus Variants Detected in Vitro and in Vivo after Treatment with ACH-1625, a Potent HCV NS3 Protease Inhibitor

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Background: ACH-1625 is a potent HCV NS3 protease inhibitor in phase 2. In a phase 1 study, administration of ACH-1625 in genotype-1 HCV patients at doses of 200–600 mg BID or QD for

Methods: In vitro selections were performed in cells harboring genotype-1a or 1b replicon. PCR products amplified from patient plasma were sequenced directly or after cloned into plasmids. The role of mutations was evaluated by introducing them into a naive replicon.

Results: Replicons emerged under ACH-1625 selection in vitro carried mutations at residue 155, 156 or 168 of NS3. Virions carrying substitutions at these three loci were also detected in ACH-1625-treated patient plasma but the type of substitutions were more diversified and included ones with the simultaneous substitutions at two of three loci. Notably, detection of these variants was often inversely related to the viral load. Phenotypic analysis showed that various substitutions at these three loci resulted in reduced susceptibility of replicons to ACH-1625 from 5.9 to > 100 fold, but not to other classes of inhibitors, and often led to reduced fitness of replicons.

Conclusions: The same loci, but more diversified substitutions within NS3 protease were uncovered in vivo. These substitutions resulted in a reduced susceptibility to ACH-1625 but not to other classes of inhibitors, warranting combination studies in clinic.

PS01-06

Hepatitis C virus specific T lymphocytes response induced by dendritic cell loaded with novel identified HLA-A2 restricted hepatitis C virus epitopes

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Background: To observe immune-stimulating capacity of dendritic cells (DCs) loaded with the mixture of novel predicted HCV-specific cytotoxic T lymphocyte (CTL) epitopes.

Methods: Bioinformatics to predict HLA-A2 restricted HCV-specific-CTL epitopes and IFN-^-ELIspot detected the stimulating function of epitopes for peripheral blood mononuclear cell (PBMC) from CHC patients and spontaneous clearance. DC from PBMC was incubated in serum-free medium with cytokine cocktail and the phenotypes of DCs were observed by flow cytometry on day 7. Autologous T lymphocytes were cocultured with mature DCs loaded with novel epitopes mixture, Granzyme B(GrB) and IFN-^-ELIspot observed epitope-specific CTLs responses.

Results: We identified nine novel HLA-A2 restricted HCV-specific-CTL epitopes, which stimulated more apparently IFN-^-SFCs (spot forming cells) compared to other epitopes. Four epitopes had the strongest stimulating capability in spontaneous clearance, two in E1, one in NS2 and one in NS3; Five epitopes had a strong stimulating capacity in CHC and spontaneous clearance, but stronger in spontaneous clearance. They were distributed in E2BNS2BNS3BNS4 and NS5 region respectively. We found DC expressed high CD83/CD80/CD86/HLA-DR and low CD14 expression on day 7, and observed that mature DCs loaded with novel epitopes mixture could increase significantly GrB and IFN-^-SFCs compared to single epitope loading, especially IFN-^-SFCs. Even some epitopes mixture could induce more IFN-^ and GrB-SFCs compared to previously reported HLA-A2 restricted HCV-specific CTL epitopes NS3(1073-1081) and NS5(2594-2601).

Conclusions: We identify nine novel HLA-A2 restricted HCV-specific CTL epitopes. DCs loaded with epitopes mixture can induce epitopes specific-CTLs response and significantly IFN-^secretion.

PS02-01

Liver stiffness measurement using acoustic radiation force impulse (ARFI) elastography: a comparison with Fibroscan and influence of necroinflammation

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Background: Acoustic radiation force impulse (ARFI) elastography can assess the degree of liver fibrosis. To evaluate the performance of ARFI elastography in assessing liver fibrosis and compare with the performance of transient elastography using Fibroscan (FS).

Methods: We prospectively analyzed 243 consecutive patients who underwent liver biopsy and ARFI from June 2010 to May 2011. FS was additionally performed in 97 (39.9%) patients.

Results: The mean age of the patients (144 male and 99 female) was 46.7 years. Liver stiffness values using ARFI elastography were significantly correlated with histological fibrosis stage ($R = 0.420$, $P<0.001$). Area under the receiver operating characteristics curves (AUROCs) of ARFI elastography for predicting significant fibrosis.

Conclusions: ARFI elastography is a reliable surrogate marker of liver fibrosis, provided that its relationship with biochemical markers such as ALT level is taken into account.

PS02-02

The levels of tissue inhibitor of metalloproteinases-1 expression are correlated with the degrees of liver fibrosis in patients with chronic hepatitis B

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Background: Increased levels of tissue inhibitor of metalloproteinases-1 (TIMP-1) expression are observed in patients with liver fibrosis. However, the relationship between the levels of TIMP-1 expression and the degrees of hepatic fibrosis in CHB patients is unclear. This study is aimed at investigating the relationship between TIMP-1 expression and liver fibrosis severity in CHB patients.
Methods: A total of 159 CHB with varying degrees of liver fibrosis were subjected to liver biopsy for the analysis of liver fibrotic stages and inflammatory activities. The levels of TIMP-1 in the liver tissues and sera of those patients were determined by immunohistochemistry and ELISA, respectively. The concentrations of serum TIMP-1 in the diagnosis of significant liver fibrosis and liver cirrhosis were determined using the receiver-operating characteristic (ROC) analysis.
Results: Our results indicated that the concentrations of serum TIMP-1 were positively correlated with the levels of TIMP-1 expression in the liver tissues ($r = 0.896$, $P < 0.001$), with the degrees of liver fibrosis in CHB patients ($r = 0.854$, $P < 0.01$), particularly in those with inflammation at grade 1, 2, and 3, and with the grades of liver inflammation in CHB patients, especially in those with fibrosis at stage 1 or without fibrosis ($r = 0.695$, $P < 0.01$). The area under the ROC curve was 0.918 and 0.895 for significant liver fibrosis and early liver cirrhosis, respectively ($P < 0.001$).
Conclusions: Our findings suggest that the TIMP-1 is a valuable biomarker and that the detection of serum TIMP-1 concentrations may be a safe and cost-effective measure for evaluating significant liver fibrosis and early liver cirrhosis in CHB patients.

PS02-03

Transient elastography and simple blood markers in diagnosis of oesophageal varices for compensated patients with hepatitis B virus-related cirrhosis

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Background: To evaluate the usefulness of transient elastography (TE) and simple blood markers in oesophageal varices (OV) diagnosis for patients with hepatitis B virus (HBV)-related cirrhosis prospectively.
Methods: Consecutive patients with compensated cirrhosis and positive HBV surface antigen were enrolled prospectively. At enrollment, aspartate aminotransferase (AST) to alanine aminotransferase ratio (AAR), AST to platelet ratio index (APRI) were recorded and TE (Fibroscan; Echosense; Paris; France) was performed. Two experienced endoscopists assessed OV independently. High-risk OV was defined as small size with red color sign, medium or large size. The diagnostic performances, optimal cut-offs and their validities of TE, APRI, platelet count (PLT) and AAR in OV diagnosis were assessed.
Results: One hundred and twenty-six consecutive patients (male/female: 93/33; mean age: 54.5) with reliable TE results were analyzed. There were good agreements between two endoscopists in assessing presence of OV and high-risk OV (kappa value: 0.82 and 0.96). Forty-eight (38.1%) patients had OV (small: 35; high-risk: 13). There was correlation between TE result and OV size ($r = 0.515$, $p < 0.001$). TE, APRI and PLT were similar however, superior to AAR, in diagnostic accuracies for OV and high-risk OV. In high-risk OV prediction, the negative predictive value was 97%, 98% and 98% with the cut-offs of 21 kPa, 1.24 and 110 ($\times$109/L) for TE, APRI and PLT, respectively.
Conclusions: For compensated patients with HBV-related cirrhosis, TE, APRI and PLT had similar diagnostic performances in OV and high-risk OV diagnosis and were useful to exclude the presence of high-risk OV.

PS02-04

Mest down-regulates Transforming growth factor-beta1 induced hepatic stellate cells activation

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Background: It has been demonstrated that TGF-]1 played a key role in HSCs activation through interaction with]-catenin. This study was designed to elucidate the molecular mechanism involved in the effect of inhibition of]-catenin on TGF-]1 induced HSCs activation.
Methods: HSC-T6 cells were transfected with pEGFP-C1-Mest (Mest, experiment group) and pEGFP-C1- neo (control group), while the normal group received PBS instead of Mest. All cells without the normal group were incubated with 1 ng/ml TGF-]1 for 2 h. At the end of the experiment, the mRNA and protein levels of smad3,]-catenin and \-SMA in cells were analyzed via RT-PCR and western-blot.
Results: Both mRNA and protein levels of]-catenin and \-SMA in HSCs were significantly increased by TGF-]1 in control group compared with normal group, whereas Mest markedly reduced all the above parameters ($p < 0.05$, respectively). Moreover A Mest significantly decreased the cell viability of HSC-T6 cells compared with control group.
Conclusions: Inhibition of Wnt/]-catenin pathway down-regulated the TGF-]1-induced activation of HSCs, which might provide us a new therapeutic approach to liver fibrosis.

PS02-05

Polymorphisms of AZIN1 Rs2679757 and TRPM5 rs886277 are associated with the cirrhosis risk in Chinese hepatitis B patients

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Background: Patients with chronic liver diseases have highly variable rate of fibrosis progression. Host genetic factors contribute significantly to the variable risk. The present study was designed to validate the association of emerging single nucleotide polymorphisms (SNPs) with the cirrhosis risk in Chinese hepatitis B patients.
Methods: A total of 714 Chinese subjects with persistent HBV infection (429 with evident liver cirrhosis and 285 without cirrhosis)

were studied. Fourteen SNPs in ten candidate genes including the seven SNPs built a cirrhosis risk score in previous studies were detected with matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) method, The distribution of each polymorphism was compared between the age-matched cirrhotic and non-cirrhotic subjects.

Results: Rs2679757 polymorphism of the antizyme inhibitor 1 (AZIN1) gene (odds ratio for GG+AG versus AA=1.47, 95% confidence interval=1.08-2.01, P=0.01), and the Rs886277 in the transient receptor potential cation channel subfamily M, member 5 gene (TRPM5) (odds ratio for CC+CT versus TT=1.63, 95% confidence interval=1.20-2.22, P=0.002) were found to be associated with the development and the severity of cirrhosis. Other SNPs were not polymorphic in chinese or had no association.

Conclusions: This study provides the first evidence that the rs2679757 polymorphism in AZIN1 gene and rs886277 in TRPM5 gene were associated with the development and severity of cirrhosis in hepatitis B patients. The emerging SNPs associated with cirrhosis prognosis warrant further clinical validation in other CHB cohorts or ethnic groups, and evoke mechanistic studies to reveal their roles in fibrosis progression.

PS02-06

Terlipressin versus Octreotide as an Adjunct to Endoscopic Variceal Ligation in Acute Esophageal Variceal Bleeding: A Meta-analysis

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Background: Combined pharmacologic (vasoactive agents) and endoscopic therapy remains the mainstay of treatment in acute variceal esophageal bleeding among cirrhotics. Terlipressin, a synthetic vasopressin analog, reduces portal pressure and has been shown to improve variceal bleeding and improve survival compared to placebo. Octreotide, a synthetic somatostatin analogue, shows a similar mechanism and appears to be equivalent to terlipressin in controlling variceal bleeding. Thus, this study aims to compare the efficacy of terlipressin and octreotide in controlling acute bleeding from esophageal varices among cirrhotic patients.

Methods: Cochrane Library, Pubmed, EMBASE, Google Scholar, LILAC databases were searched for randomized controlled trials (RCTs) published until May 2011 comparing the efficacy of terlipressin and octreotide in controlling bleeding from acute esophageal varices. Cross-reference was also done. Using Jadad scale, two independent reviewers evaluated the methodologic criteria of each study while a third reviewer settled any disputes. Analysis was done using odds ratio as measure of effect, Mantel–Haenszel statistical method and fixed-effect model.

Results: Eleven studies were retrieved from the search but only three RCTs were included in this meta-analysis. Pooled data from 472 patients shows a trend towards better control of bleeding in the octreotide group (93.22%, 220/236) compared to terlipressin group (88.55%, 209/236) but this is not statistically-significant (OR 0.53, CI: 0.27 V 1.04, p value 0.07, i2 = 0%).

Conclusions: There is no significant difference between terlipressin and octreotide as an adjunct to EVL in controlling acute variceal bleed. More high-quality studies are needed to establish any superiority.

PS03-01

Effect of nucleos(t)ide analogues therapy on HBsAg, intrahepatic HBV DNA and covalently closed circular DNA levels

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Background: We aimed to study 1) the effects of 1-year nucleos(t)ide analogue (NA) therapy on HBsAg and covalently closed circular DNA (cccDNA) levels; and 2) the possible use of HBsAg reduction as a marker for cccDNA reduction.

Methods: We recruited 124 NA-treated patients with baseline and 1-year sera and liver biopsies. The NAs were categorized into the more potent (entecavir, telbivudine, and clevudine; n = 71) and less potent groups (lamivudine and adefovir; n = 53). cccDNA and HBsAg levels were measured by real-time PCR and the Elecsys HBsAg assay, respectively.

Results: At year 1, there were approximately 5 log(IU/ml), 2 log(copies/cell), and 1 log(copies/cell) reductions in serum HBV DNA, intrahepatic total HBV DNA, and cccDNA, respectively. Only a small reduction of HBsAg (mean: 0.18 log[IU/ml]) was observed. There were no significant differences between the more and less potent NAs in the reduction of HBsAg, intrahepatic total HBV DNA and cccDNA. Although 88/124 (71%) patients had undetectable serum HBV DNA, all had detectable HBsAg and intrahepatic total HBV DNA. Logarithmic reductions of HBsAg and cccDNA correlated weakly ($r = 0.183$, $p = 0.042$). Patients with cccDNA reduction.

Conclusions: Despite the profound serum HBV DNA reduction after 1 year of therapy, reduction in HBsAg level was minimal, and reduction in intrahepatic total HBV DNA and cccDNA was relatively mild. HBsAg reduction may be a potential marker for the monitoring of cccDNA reduction during NA therapy.

PS03-02

Entecavir 1.0 mg Monotherapy or Entecavir plus Adefovir Dipivoxil for Patients with Lamivudine-resistant Chronic Hepatitis B Had Suboptimal Response to Lamivudine plus Adefovir Dipivoxil

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Background: To evaluate the efficacy of entecavir (ETV) 1.0 mg/d or ETV plus adefovir dipivoxil (ADV) in adults with chronic hepatitis B virus (HBV) infection who had previously resisted lamivudine (LAM) and failed with rescue treatment of LAM+ADV.

Methods: 40 patients were enrolled. 14 patients were treated with ETV 1.0 mg/d monotherapy while 26 patients were treated with ETV 0.5 mg/d+ADV 10 mg/d. HBV DNA level, liver function and HBV serology were observed.

Results: There was no statistically significant difference with baseline situation between two groups. HBV DNA level were declined in both groups, but decline in group ETV 1.0 mg were sharper than that in group ETV+ADV. At 24 weeks, there were 28.6% patients achieved HBV DNA < 500 copies/ml in group ETV 1.0 mg, but there were 80.8% patients in group ETV+ADV achieved it. There was statistically significant difference ($q^2 = 8.469$A $P = 0.004$). At 48 weeks, there were still 4 patients achieved HBV DNA < 500 copies/ml in group ETV 1.0 mg, but patients in group ETV+ADV all achieved it. At 24 weeks, ALT level of 42.9% patients in group ETV 1.0 mg were back to normal, but there were 92.3% patients ALT level back to normal in group ETV+ADV. There was statistically significant difference ($q2 = 9.337$A $P = 0.002$). At 48 weeks, there was 1 patient with HBeAg seroconversion in group ETV 1.0 mg while there were 4 patients in group ETV+ADV.

Conclusions: As rescue treatment for patients with chronic hepatitis B who had previously resisted LAM and failed with treatment of LAM+ADV, ETV+ADV was more efficient than ETV 1.0 mg monotherapy, and it can achieve better virological and biochemical response.

PS03-03

Hepatitis B e antigen-positive chronic hepatitis B patients with three- year entecavir therapy: efficacy and predictors

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Background: To evaluate the efficacy of entecavir (ETV) in treatment-naïve hepatitis B e antigen (HBe) positive chronic hepatitis B (CHB) patients and identify factors predictive of favorable treatment outcomes.

Methods: Eligible patients receiving 0.5 mg ETV daily for more than 1 year were enrolled from 6 major hospitals in Taiwan. The primary therapeutic endpoint was HBeAg loss and/or seroconversion.

Results: A total of 248 HBeAg-positive patients (69.4% in men and mean age of 40.6±12.7 years) were recruited and 15.7% of them had cirrhosis. The baseline alanine aminotransferase (ALT) and HBV-DNA levels were 312.7±337.2 U/L and 7.3±1.5 $\log_{10}$ IU/mL, respectively. The median treatment period was 25.3 months (range: 12-69.6). The rates of ALT normalization at year 1, 2 and 3 were 83.1%, 87.9% and 94.9%, respectively. The cumulative rates of HBeAg loss at year 1, 2 and 3 were 20.3%, 38.0% and 48.9% respectively. The rates of undetectable HBV DNA at year 1, 2 and 3 were 52.1%, 78.9% and 82.5%, respectively. Multivariate analysis showed that age > 40 years, baseline ALT > 5 times upper limit of normal and viral load were independent factors associated with HBeAg loss (odds ratio: 0.485, 1.963 and 0.79; 95% confidence interval: 0.267-0.881; 1.103-3.492; 0.638-0.978, respectively).

Conclusions: ETV treatment for 3 years can achieve good biochemical and virologic responses, but modest effect in HBeAg loss and/or seroconversion in Taiwanese HBeAg-positive chronic hepatitis B patients. In addition, age, baseline serum ALT and HBV-DNA levels are independent factors associated with treatment responses.

PS03-04

Factors Associated with Development of HBeAg-Negative Chronic Hepatitis B in Patients with HBeAg-Positive Chronic Hepatitis B Undergoing Peginterferon Alfa-2a Therapy

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Background: HBeAg-positive chronic hepatitis B (CHB) patients can develop HBeAg-negative CHB following the treatment of peginterferon alfa-2a with serum HBV DNA > 10,000 copies/mL despite HBeAg loss. We aimed to identify baseline factors predictive of development of HBeAg-negative CHB following peginterferon alfa-2a therapy.

Methods: One hundred and three HBeAg-positive CHB patients undergoing peginterferon alfa-2a therapy were enrolled. Baseline factors included age, gender, ALT, necroinflammatory grade and fibrosis stage, HBV DNA, quantitative HBsAg, HBV genotype, and mutations in the basal core promoter (BCP, A1762T/G1764A), pre-core region (G1896A), core gene, and pre S2 region as determined by direct DNA sequencing. At 24 weeks off therapy, HBeAg/anti-HBe and serum HBV DNA were measured to assess treatment outcomes.

Results: Thirty-two (31%) patients achieved HBeAg loss at 24 weeks off therapy. Of them, 13%, 18%, and 14% had HBV DNA < 10,000, > 10,000, and > 100,000 copies/mL, respectively. Multiple regression analyses identified serum HBsAg < 3.8 log10 IU/mL (P = 0.015) as the only independent predictor of achieving HBeAg loss and HBV DNA < 10,000 copies/mL. By contrast, similar analyses showed that serum HBV DNA < 7 log10 copies/mL (P = 0.027), necroinflammatory grade A2 and A3 (P = 0.012), and BCP mutations (P = 0.024), were independent predictors of achieving HBeAg loss and HBV DNA > 10,000 copies/mL. Only BCP mutation (P = 0.025) was an independent predictor of achieving HBeAg loss and HBV DNA > 100,000 copies/mL.

Conclusions: Low serum HBV DNA level, higher necroinflammatory grade, and the presence of BCP mutations are independent predictors of developing HBeAg-negative CHB in HBeAg-positive CHB patients undergoing peginterferon alfa-2a therapy.

PS03-05

REP 9AC/REP 9AC': Potent HBsAg release inhibitors that can rapidly elicit durable immunological control of infection in patients with chronic hepatitis B

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Background: HBsAg suppresses host immunity and permits chronicity of HBV infection. REP9AC/REP9AC are nucleic acid-based polymers (NAPs) that block HBsAg release from infected hepatocytes. The current clinical results with REP9AC and a 4th generation NAP (REP9AC) are disclosed.

Methods: Patients with pre-treatment HBV DNA titers between 10^6 and 10^{12} copies/ml were treated by IV infusion. Virologic response was assessed using the Cobas and Architect testing platforms.

Results: (REP9AC): > 99.5% reduction of HBsAg occurred in seven of eight patients within 7 days to 32 weeks of treatment. All responders achieved 3-7 log reductions in HBV DNA. Four responders achieved complete control of their infection with 20-44 weeks of treatment (HBV DNA < 500 cpm). Off treatment, three patients had sustained immunological control of their infection (HBV DNA < 500 cpm, and HBsAg < 10 IU) for 12-24 months. All other patients had partial immunological control of their infection (> 90% reductions in HBsAg and 2-7 log reductions in HBV DNA). Mild pro-inflammatory side-effects accompanied drug administration. RESULTS (REP9AC): REP9AC is more stable with reduced pro-inflammatory activity compared to REP9AC. Interim data show robust HBsAg reductions in all seven patients in the first 10 weeks of treatment. Three patients have already experienced a 3-4 log decline in HBV DNA. Pro-inflammatory side-effects during administration were substantially reduced.

Conclusions: NAPs can affect rapid clearance of HBsAg, allowing restoration of host immunity. These results suggest that NAPs may become an important new tool in the treatment of chronic hepatitis B.

PS03-06

Undetectable HBV DNA at Month 12 of Entecavir Treatment Predicts Long-Term Maintained Viral Suppression and HBeAg Seroconversion in Chronic Hepatitis B Patients

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Background: Long-term outcome data among suboptimal responders to entecavir is limited. We aimed to investigate the predictive value of on-treatment HBV DNA suppression for responses to entecavir.

Methods: This was a retrospective cohort study among nucleos(t)ide analog-naïve HBV-infected patients on entecavir followed up for ≥1 year. Maintained response was defined as undetectable HBV DNA (<20 IU/ml) till the last visit. Virologic breakthrough was defined as an increase of HBV DNA by ≥1 log from the nadir during treatment.
Results: 667 patients (age 52±11, 69% male, 232 HBeAg-positive) followed for 28±12 months were studied. The cumulative probability of maintained response at year 1, 2 and 3 were 70.3%, 79.7% and 83.8%, respectively. On multivariate analysis, undetectable HBV DNA at month 12 was the only independent predictor of maintained response. Month 12 responders had higher probability of maintained response at 3 years (99.4%) than the non-responders (48.0%; $P<0.001$). The cumulative probability of HBeAg seroconversion at year 1, 2 and 3 were 16.9%, 23.1% and 27.6%, respectively. Month 12 responders had higher probability of HBeAg seroconversion at 3 years (36.4%) than the non-responders (15.6%; $P=0.001$). The cumulative probability of virologic breakthrough at year 1, 2 and 3 were 0.2%, 0.9% and 3.3%, respectively. Detectable HBV DNA at month 12 HBV DNA did not increase the risk of virologic breakthrough.
Conclusions: Undetectable HBV DNA at month 12 was associated with higher probability of maintained response and HBeAg seroconversion. The risk of virological breakthrough was low regardless of the month 12 HBV DNA suppression.

TCS01-01

Induction of functional hepatocyte-like cells from mouse fibroblasts by defined transcription factors

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Differentiated cells are epigenetically plastic as they can be reprogrammed into pluripotent stem cells by nuclear transfer or transcription factor overexpression. Recent studies have revealed that overexpression of lineage-specific transcription factors converts differentiated cells into other lineages without reversion to the stem cell state. Here, we induce mouse mesenchymal fibroblasts directly into functional hepatocyte-like (iHep) cells by transduction of three hepatic transcription factors and inactivation of p19Arf. iHep cells show typical epithelial morphology, express hepatic genes and acquire hepatocyte functions. Importantly, using fumarylacetoacetate hydrolase-deficient mice as a liver injury model, transplanted iHep cells repopulate the liver and rescue recipients from death by restoring liver functions. Our study thus provides a novel strategy to generate functional hepatocyte-like cells for liver engineering and regenerative medicine to treat liver diseases.

TCS01-02

Cancer Stem Cells and HCC

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TCS01-03

Principles of Cell Plasticity and the Liver

Scott Swenson
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TCS02-01

Natural history of chronic hepatitis B infection: from clinical to immunological point of view

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HBV infection is usually a self-limited disease in adult. Adequate immune responses could achieve successful anti-HBV immune control though these HBV possess the stealth nature with minimal activation of innate immunity. On the other hand, chronic HBV infection is not a rare outcome for patients infected perinatally. However, most patients with chronic HBV infection will recover without major sequales. Spontaneous HBe seroconversion is the first milestone for immune control of chronic HBV infection. The spontaneous HBeAg seroconversion usually occurs before age of 40 in 90% of cases. HBeAg seroconversion is usually followed by clinical remission and a life-long inactive state with an excellent outcome. Spontaneous HBsAg seroclearance can occur in these patients with a 45% cumulative incidence at the age around 70. Based on these facts that a large proportion of patients with chronic HBV infection could gradually recover with 45% of patients achieving HBs seroconversion at the age of 70, the natural history of chronic HBV infection could be deemed as a long process of successful recovery of anti-HBV immune responses.

However, a portion of patients still suffer from chronic hepatitis characterized by long-term fluctuation of liver damages and unsuccessful immune control of HBV. Why some of these patients with chronic HBV infection could not successfully control this virus and result in chronic hepatitis is still unknown. An exhausted phenotype of HBV-specific CD8+T cells is a hallmark of chronic hepatitis B. However, some evidence had shown a liver damage during the stage of chronic hepatitis might further hamper the recovery of HBV specific immune responses by overshooting the regulatory immune responses like regulatory T cells and anti-inflammatory cytokines. Following these new observations in patients with chronic hepatitis B, a possible strategy for the future immunotherapeutic treatment might aim to rejuvenate the exhausted T cell and to reduce the liver damage at the same time.

TCS02-02

The liver injury during chronic hepatitis B: Is it good or bad for the immunological control of virus?

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The degree of liver injury during chronic hepatitis B is often interpreted as a direct proportional measurement of the presence of active anti-viral specific immunity. We will discuss data derived from work in animal models and in patients with acute and chronic HBV infections, which show that the normality of transaminase levels does not necessarily reflect an absence of HBV-specific T cell immunity. Moreover, we will discuss the importance of the mechanism of the intrahepatic recruitment of non-antigen specific inflammatory cells in HBV control and liver damage.

TCS02-03

Restoration and its clinical significance of host immune responses in chronic hepatitis B with antiviral therapy

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To date, two kinds of drugs are currently used for antiviral therapy in chronic hepatitis B (CHB) patients: nucleotide analogs and interferon. In CHB patients undergoing successful antiviral treatment, three consequent phases may develop: (1) complete virus suppression (viral load drops below detectable level) together with ALT normalization; (2) HBeAg seroconversion; and (3) HBsAg seroconversion. The three processes indeed represent the sequential phases of clinical recovery. Recent studies indicate that the host immune status may play an important role in determining responsiveness to antiviral therapy. In other words, restoration of host immune response during the antiviral treatment is considered to be critical for HBeAg and HBsAg seroconversions. This presentation

will summarized the related advances and their implications in clinic. Since the antiviral immunity of the host not only determines the outcome of HBV infection, it also dictates the clinical efficacy of antiviral therapy including the sustained clearance of HBV and HBsAg seroconversion. Thus, how to obtain efficient restoration of host immune responses against HBV infection has drown much attention. Based on the characteristics of immune responses in CHB patients with antiviral therapy, immunomodulatory strategies aimed at enhancing antiviral immune defects and tempering immune-mediated injury could represent a complementary approach toward a cure for chronic HBV infection.

TCS03-01

Problems of HCC management in India

Yogesh Chawla
Pgimer, Chandigarh

TCS03-02

Viral hepatitis and liver cancer in Korea; an epidemiologic perspective

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Korea is one of the countries where HBV infection was endemic in the past; 11.7% positivity for HBsAg in males, and 9.5% in females in 1986. However, the prevalence of HBsAg has dramatically declined during the last two decades reaching 3.3% in males and 2.7% in females in 2008. An apparent dose-dependent relationship between HBV infection and the subsequent occurrence of HCC has been demonstrated through a reconstructed cohort study in 1991 (n = 369,725, RR = 5.71) and in 2004 (n = 1,283,112, RR = 24.3) in Korea. Recent publication reported that HBV infection was responsible for 23.9% for liver cancer cases and 37.5% of death, and HCV infection for 6% of cases and 9% of deaths in Korea. An epidemiologic study showed adjusted RRs of HBV and HCV mono-infection, and HBV/HCV co-infection were 17.1 (95% CI = 8.4–34.8), 10.4 (95% CI = 4.9–22.1) and 115.0 (95% CI = 32.5–407.3), respectively. Synergistic effect of HBV/HCV coinfection on HCC risk was also observed. Infection with HCV genotype 1b significantly elevated HCC risk (adjusted RR = 33.5, 95% CI = 16.4–68.6). Relationship between cholangiocarcinoma and clonorchiasis has also been demonstrated in some selected area. Through several case–control studies, both vertical transmission via trans-placental route and horizontal transmission were identified as the most important mode of transmission of HBV in Korea. HBV vaccination has been available since 1982, and was first recommended mainly for government employees, soldiers, and students on a voluntary basis in 1985. The national vaccination program for infants and children was launched in 1995. A national vaccination program against vertical transmission for neonates born to mothers with HBV began in 2002. After implementation of the national vaccination program, HBV prevalence in Korean declined from 6∼8% to 2∼3%. Liver is the 4th leading site of cancer in men, and the 7th in women, accounting for 8.8% of cancer cases and 17.7% of cancer deaths in Korea. However, an age-period-cohort analysis showed a significant reduction in liver cancer mortality rate when compared to the period 1991–1994 when the national vaccination program was not implemented (RR = 0.30, 95% CI 0.21–0.44). The fact that the national vaccination program have contributed to the reduction of liver cancer mortality beyond just a natural decrease in Korean children and adolescents has also been demonstrated in 2011. National cancer screening program for 5 leading sites of cancer, including liver cancer, has been launched under the universal coverage by the Korean government in 1999. Accordingly, five-year survival rate of liver cancer has much been improved from 13.2% in 1996–2000 to 23.3% in 2003–2008 in Korea. The poor prognosis and lack of effective therapies for hepatocellular cancer indicate that the development of prevention programs is of critical importance.

TCS03-03

Successful control of hepatocellular carcinoma in Taiwan

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Hepatocellular carcinoma (HCC) has been the first or second leading cause of cancer incidence and mortality for decades in Taiwan. Around 90% of HCC patients were related to chronic hepatitis B (HBV) or C virus (HCV) infection. Primary, secondary and tertiary prevention have been conducted through public health policies and the national health insurance (NHI).

Education for keeping away from risk behaviors, using disposable syringes and needles, and blood donor screening for ALT, HBsAg and anti-HCV were universal precaution for blood-borne transmission. Most of horizontal transmissions of HBV and HCV have been prevented. Prevalence of anti-HCV marked decreased in cohorts born after 1950. Universal hepatitis B vaccination program to newborn has blocked almost all vertical transmission since 1984. Not only HBsAg carrier rate but also HCC incidence declined in the vaccinated cohort. Both HBV- and HCV-related HCC are prospected to become a rare disease in 2040.

The NHI began to reimburse anti-viral treatment for chronic HBV and HCV infection since 2003. Because of effective treatment, decreasing of liver related mortality and morbidity, HCC incidence, and post-resection and ablation recurrence rates of HCC have been reported. The NHI also reimbursed periodical surveillance of patients with chronic HBV and HCV infection. HCC can be detected in its early stage. Early detection and prompt treatment increase the cure rate and prolong survival. This medical care system accelerates the control of HCC.

The successful experience of HCC control in Taiwan is a useful reference for other endemic countries. However, there are still some unresolved issues, such as HB vaccine failure, HBsAg mutation, diseases transmitted through intravenous drug user, medical care to rural endemic area, alcoholic and non-alcoholic fatty liver diseases and so on.

TCS03-04

Epidemiology and disease burden of viral hepatitis in Thailand

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Viral hepatitis is a major public health problem in Thailand. In 2004, chronic liver disease is ranked among the top ten causes of death with the reported incidence of liver cirrhosis and liver cancer (HCC and cholangiocarcinoma) to be 18 and 42 per 100,000 populations, respectively. Among HCC cases, 60–70% of the patients were infected with HBV and 15% with HCV. The seroprevalence rate of HBsAg carriers has declined among children below the age of 20 years due to the high coverage rate of more than 90% of the universal immunization program in the Thai newborns since 1988. In 2004, the carrier rate of Thai children below the age of 15 years was 0.7%. We studied the sequences of Pre S1, Pre S2 and S regions of 147 subjects with positive HBsAg and HBV-DNA. The molecular epidemiological study showed that genotypes C, B and A were accounted for 87.1%, 11.6% and 1.3% of the cases, respectively. The distribution of the HBV antigenic subtypes is adr, adw and ayw with the prevalence of 84.4%, 14.2% and 1.4%, respectively. Pre S mutations were detected in 9.5% of the samples. HCV is classified into 6 major genotypes based on phylogenetic analysis of the genomic sequences. The prevalence of hepatitis C in Thailand is approximately 2.2%. The 3 major genotypes found in Thailand are 3 (3a) 19 (1b), and 6 with the

prevalence of 51%, 26.7% and 6.9%, respectively. Regarding hepatitis A, epidemiological studies have shown that there has been a markedly decrease of the prevalence from hyperendemic to hypoendemic state due to improvement in sanitation and hygiene in Thailand. The incidence of acute hepatitis A is approximately 10–40 per 100,000 populations. Although the prevalence of hepatitis A is decreasing, several outbreaks have occurred due to the decline of protective antibodies. During 2001–2008, many phylogenetic analyses on various HAV isolates obtained from different outbreaks revealed a single sub genotype (genotype 1A) circulating in Thailand. These data on viral hepatitis are crucial for public health surveillance and prevention of the disease. In addition, molecular epidemiological studies can delineate the previous and current routes of transmission. The results of these studies suggest that stringent measures to prevent and control viral hepatitis should be continuously implemented.

TCS04-01

Hepatitis B Vaccination – A global view

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TCS04-02

Cancer Preventive Vaccine—Starting from Hepatitis B Vaccination to Other Cancer

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Prevention of chronic hepatitis B virus (HBV) infection can successfully reduce the incidence of liver cancer. It is the first example of cancer preventive vaccine in human, which proves that prevention of the infection of an infectious agent can prevent its related cancer.

Taiwan has launched the world first universal HBV vaccination program in July 1984. The prevalence of HBV infection in vaccinated birth cohorts have been reduced remarkably to approximately one-tenth of the original prevalence. Furthermore, reduction of the HCC incidence in the vaccinated birth cohorts aged 6–14 years have been demonstrated. Recently, we have further provided evidence that the effect of HCC prevention by HBV vaccination has been extended from childhood to adolescent and gradually into early adulthood.

The risk of developing HCC in vaccinated cohorts was associated with incomplete HBV vaccination; prenatal maternal HBsAg seropositivity; and prenatal maternal HBeAg seropositivity. Failure to prevent HCC results mostly from unsuccessful control of HBV infection by highly infectious mothers. Future strategies to increase the global coverage rate of HBV immunization and to interrupt mother-to- infant transmission may enhance the cancer prevention effect of HBV immunization.

The success of prevention of chronic HBV infection can successfully reduce the incidence of liver cancer. This prevention strategy has been actively conducted in the prevention of cervical cancers in many countries in the world. This example hopefully will be further extended into other infection related cancers in the near future.

TCS04-03

Preventative and Therapeutic Hepatitis C Vaccines: Developments and Challenges for the Future

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HCV infects 3% of the world's population ($\sim$130 million individuals) and causes an estimated 476,000 deaths per year as a result of HCV-associated end-stage liver disease and its complications. An effective preventative vaccine would considerably reduce the number of new infections and thereby reduce the burden on health care systems. However there are many impediments to the development of a vaccine for HCV including the limited availability of animal models to test vaccines.

Viral and host specific factors contribute to viral evasion and present important impediments to vaccine development. Both, innate and adaptive immune responses are of major importance for the control of HCV infection. However, HCV has evolved ways of evading the host's immune response in order to establish persistent infection. For example, HCV inhibits intracellular interferon signalling pathways, impairs the activation of dendritic cells, CD8+ and CD4+ T cell responses, induces T-cell exhaustion and selects escape variants with mutations CD8+ T cell epitopes.

Although the correlates of protective immunity are not entirely known the development of a multi-specific T cell response during acute HCV infection is associated with the spontaneous clearance of infection and may provide a level of protection against reinfection. Reinfection among individuals who are repeatedly exposed to HCV, such as injecting drug users (IDU), however, raises concerns that the development of long-term protective immunity for HCV may not be possible. It is also apparent that neutralising antibody is protective and associated with the rapid clearance of hepatitis C viraemia, although the intricate association of HCV with lipoprotein pathways and receptors adds a further layer of complexity for vaccine design. We know that spontaneous recovery does occur in the setting of a successful immune response against HCV and so the development of an effective vaccine for HCV should be achievable.

Several approaches to HCV vaccine development have now been studied however, the success of these approaches has been limited the delivery of a limited number of protective viral epitopes, the inclusion of incorrectly folded recombinant proteins, the limited humoral and/or cell mediated responses that have been associated with DNA vaccines and insect cell derived VLPs, and the use of adjuvants with relatively poor potency. It is also now apparent that a vaccine inducing strong T cell responses alone may not be sufficient to prevent hepatitis C infection. An effective vaccine will therefore need to produce strong and broadly cross-reactive CD4+, CD8+ T cell and neutralising antibody responses to overcome these factors and be successful in preventing or clearing HCV.

Vaccines in clinical trials include recombinant proteins, synthetic peptides, virosome based vaccines, tarmogens, modified vaccinia Ankara based vaccines and DNA based vaccines. Several preclinical vaccine strategies are also under development and include recombinant adenoviral vaccines, virus like particles and synthetic peptide vaccines. An overview of the vaccine strategies employed, their success to date and future directions of vaccine design will be presented.

TCS05-01

NAFLD and Metabolic Syndrome

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Along with the epidemic of obesity in Asia–Pacific region, the prevalence of NAFLD and the metabolic syndrome also increased significantly. In this presentation, the popular definitions of the metabolic syndrome and its prevalence rate in this region will be reviewed. The pathophysiological connections between NAFLD and the metabolic syndrome and the clinical implications of these connections will be briefly summarized. In brief, both NAFLD and the metabolic syndrome are not a single homogeneous disease entity. In a broader sense, NAFLD could be considered as a part of the metabolic syndrome, because the liver is the major player in the pathogenesis of the metabolic syndrome. The clinical significance of NAFLD, however, is beyond the liver itself. More attention should be directed to some specific metabolic disorders and subsequent vascular damage.

TCS05-02

Clinical diagnosis of NAFLD/NASH

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The rising incidence of obesity and metabolic syndrome has resulted in a dramatic increase in NALFD. NAFLD consists of two clinical entities: simple steatosis, which generally follows a non-progressive course, and NASH, which may progress to cirrhosis. NAFLD patients are usually asymptomatic, so NAFLD is often detected during health checks or clinical visits for other diseases. NAFLD is diagnosed in nonalcoholic subjects with fatty liver and exclusion of other causes of liver disease. Epidemiological studies have shown that alcoholic liver disease can occur when daily alcohol consumption exceeds 20 g in women and 30 g in men. Then nonalcoholic indicates less than these amounts of alcohol consumption. In general practice, detection of fatty liver is performed by ultrasonography, after which computed tomography scanning or magnetic resonance imaging is performed for more objective and quantitative assessment. Unfortunately, these imaging modalities cannot distinguish NASH from NAFLD. Recently, several biochemical markers for predicting NASH or severity of fibrosis have been reported. However, even now, histology is considered the "gold standard" for definitive diagnosis. The principal histological features of NASH are as follows: macrovesicular steatosis, ballooning degeneration, and mixed lobular inflammation. Liver biopsy has several drawbacks: it is an invasive and costly procedure, with the possibility of sampling error and variability in pathologist interpretation. Moreover, given the extremely high prevalence of NAFLD, a liver biopsy is poorly suited as a diagnostic test for NAFLD. These shortcomings and drawbacks of liver biopsy support the urgent need to find noninvasive markers for the assessment of NASH.

TCS05-03

CLINICAL TREATMENT OF NAFLD/NASH

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By ultrasonography or magnetic resonance spectroscopy, rates of NAFLD are now between 15 and 30% in most Asia–Pacific countries, 10-25% have NASH, and 3–5% significant fibrosis or cirrhosis. Most unexplained ALT abnormalities are due to NAFLD, but the relationship with disease severity is weak. Older age, hyperglycemia (or T2D), severe obesity and number of features of metabolic syndrome (hypertension, dyslipidemia) correlate with NASH severity. Clinicopathological scores and several non-invasive markers are good at distinguishing severe fibrosis/cirrhosis from mild/no fibrosis, but limited for distinguishing moderate from mild fibrosis. Thus, if specific medical treatments for NASH were available, liver biopsy would still be indicated. At present, clinical management of patients with NAFLD/NASH is to correct the underlying pathophysiology, which is related to over-weight and insulin resistance. Since up to two-thirds already have T2D (by OGTT or history) or will develop it in follow-up, OGTT testing can now be recommended for all NAFLD patients: the results may assist motivation in the lifestyle program (exercise; dietary adjustments) that are required lifelong after diagnosis. Onset of cardiovascular complications following diagnosis is also high, with implications for general medical work-up and monitoring of blood pressure and lipids by the patients primary care physician. Obesity surgery must be considered for morbidly or treatment-refractory obesity with associated metabolic complications, including NASH: reversal of NASH and possibly fibrosis (controversial) has been described with lap-banding and more invasive obesity surgery. Attention to agents that cause or worsen metabolic syndrome is important: corticosteroids, tamoxifen, anti-depressants and anti-psychotics can contribute to development of NASH. Pharmacotherapy should be aimed at reversing insulin resistance and/or hepatic lipotoxicity, but metformin is ineffective and "glitazones" has been relatively disappointing and are now removed from use in many countries because of feared adverse cardiac and bone outcomes. Agents aimed at the old "second hit" (oxidative stress, cytokines, hepatoprotection) have been disappointing or results are controversial. For example, vitamin E was found to have some efficacy in adults (the "Piven" study) but not in children, and unopposed use of high dose vitamin E is associated with increased cardiac events. Data for pentoxyphylline are insufficient. High dose ursodeoxycholic acid was ineffective in a German study but even higher doses (25–30 mg/kg) lowered ALT in a French study. We and others have found evidence that hepatic cholesterol pools rather than triglyceride or free fatty acids are involved in NASH pathogenesis (lipotoxicity). It is therefore noteworthy that 2 recent open studies of the Nieman Pick-like protein1(NpL1) inhibitor ezetimibe have found some efficacy against NASH; NpL1 is highly expressed on the surface of hepatocytes and is involved with cholesterol reclamation from bile. Ultimately, knowledge about appetite regulation and bodily lipid distribution, and how hepatic lipotoxicity occurs will lead to effective medical therapy to augment the known beneficial effects of lifestyle adjustments.

TCS06-01

Surgical resection

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TCS06-02

Long-term results of surgical treatment of early HCC

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TCS06-03

Curative Therapy for Early-stage HCC: Local ablation update

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Resection, liver transplantation and local ablation are generally considered as curative treatment for early-stage HCC. Local ablation can achieve comparable long-term overall survival as compared with resection. Current local ablation has the advantage of minimal invasiveness and easily repeatable and therefore they can be considered as an option for unresectable or even resectable HCC. Percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), and microwave ablation (MCA) are employed currently. Meta-analysis of randomized controlled studies have shown that RFA is superior to PEI for early-stage HCC owing to more predictable ablation, lower local tumor progression, lower overall tumor recurrence, and higher survival. RFA was comparable to conventional MCA in local tumor progression but a fewer ablation sessions were required by RFA. Therefore, RFA is more widely accepted as the first option of local ablation for most of small unresectable or even resectable HCC ($\leq$3 cm). For HCC with intermediate (3.1 to 5 cm) size, combine RFA with ethanol injection or TACE is superior to RFA alone. Because current RFA devices are effective in HCC $\leq$ 3 cm, recent advances of switching control of RF generator with simultaneous placement of uni-polar or bipolar RF electrodes or MCA with multiple antennas can create a larger ablation in a short time. Preliminary results from some medical centers have shown a larger ablation volume in a shorter time as compared with conventional RFA or MCA.

Data on long-term survival after RFA was very limited. A limited number of studies reported overall survival rates of 80–100% at 1 year, 63–98% at 2 years, 45–67% at 3 years, 74% at 4 years, and 41% at 5 years. Longer survival were commonly observed in sub-groups with early Child-Pugh class, small tumor size, low AFP, low DCP level, well-differentiated tumor, and single tumor number. Two studies particularly showed that RFA could achieve a very good 5-year survival rate (68% reported by Livraghi T et a in Hepatology 2008, and 76% reported by N'Kontchou G et al. in Hepatology 2009) for very early stage operable HCC. Recent studies also show comparable survival rate in very-early stage or early-stage HCC as compared to resection (Hung HH et al., Clin Gastro Hepatol 2011; Wang JH et al., J Hepatol epub) and even comparable recurrence in very-early stage HCC (Hung HH et al., Clin Gastro Hepatol 2011).

In addition to first-line therapy, a recent cohort study also showed the high repeatability of RFA makes it particularly valuable for controlling intra-hepatic recurrences (Rossi S et al., Hepatology 2011). Repeat RFA can achieve a 96% of complete ablation rate and an estimated survival rate as 67% at 3 years and 40% at 5 years.

RFA was also accepted as a bridge therapy for early-stage HCC awaiting liver transplantation. In early-stage HCC, the tumor progression beyond 12 months increased strikingly after RFA, particularly in those of failure of achieving initial complete ablation, baseline AFP above 200 ng/ml and Child-Pugh B status (Fernandes ML, Lin SM et al., Br J Surg 2009). Therefore, prompt for transplantation is required in those with risk factors in early-stage HCC receiving RFA. We also found delay in treatment (>5 weeks) of early-stage HCC using RFA may impact the survival (Chen WT, Lin SM et al., J Surg Oncol 2011).

TCS07-01

A BRIEF HISTORY OF THE ASIAN PACIFIC ASSOCIATION OF THE STUDY OF THE LIVER

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The concept of an Asian Pacific Association for the Study of the Liver (APASL) to represent the region in the International Association for the Study of the Liver (IASL) was conceived during a discussion between Kunio Okuda and Lawrie Powell in 1977. There already existed the American Association for the Study of Liver Disease (AASLD), the European Association for the Study of the Liver (EASL, 1966) and the Latin American Association for the Study of Liver Disease (LAALD, 1968) and there was clearly a need for a corresponding association in the Asian-Pacific region. (The African Association for the Study of the Liver was established in 1982). Shortly afterwards more extensive discussions were held with Seah Cheng Siang (Singapore), Vikit Viranuvatti (Thailand), Cliff Jones (Auckland) and June Halliday (Brisbane). Seah agreed to host a meeting of an enlarged steering committee in Singapore in 1978. This was held at the Shangri La Hotel with some 20 participants well representing the region. There was uniform enthusiasm and support for the Association and a constitution and by-laws were drawn up. Lawrie Powell was nominated as the first President and the first official meeting of the Association was scheduled for 1980 in Auckland, New Zealand to be held in association with the Asia–Pacific Association of Gastroenterology (APGE). Hans Popper accepted an invitation as the international guest lecturer and he and his charming wife Lina participated actively at the meeting and also afterwards in Australia in what proved to be a memorable visit. The Auckland meeting was highly successful and the APASL was firmly launched.

Subsequent meetings were held every two years and the venue rotated around the Asia–Pacific region. The Presidents also rotated such that at least one has been chosen from each of ten different countries within the region. With Professor Shiv Sarin as President the 2004 biennial scientific meeting was held in New Delhi in December 2004. This was the second meeting to be held in India. The APASL meeting has been held twice as a joint meeting with the International Association for the Study of the Liver, in 1982 in Hong Kong and again in 1999 in Fukuoka, Japan. These meetings have brought together members of these affiliated associations from all over the world and were extremely successful. The 2005 meeting was held in Bali, Indonesia in August 2005 and, like the 2004 New Delhi meeting was very popular with over 2000 delegates. The President was Professor L. Lesmana.

The scientific meetings of the APASL have been so popular and successful that the Executive resolved to hold them annually and wherever possible in the month of March to avoid clashes with other international meetings. In March 2006 the meeting held in Manila was with the President Professor Jose Serrano. In March 2007 the annual meeting was held in Japan with Masao Omata as President. The Executive has now scheduled meetings through to 2014 when it will be in Brisbane, Australia. Thus, the annual meeting of the APASL has now grown in size and significance to compare with the annual meeting of the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. These meetings represent the three most significant liver meetings internationally and all are increasingly popular. The Association has also introduced single topic conferences held at least annually and are also very popular.

A further significant development within the APASL was the establishment of the Journal of Gastroenterology and Hepatology in 1985. The founding editors were Kunio Okuda, Lawrie Powell, David Shearman and S.K. Lam. The journal was published by Blackwell Scientific and has continued to flourish with contributions from all parts of the region including numerous articles contributed from other parts of the world. The impact factor of this journal has risen significantly over the past five years.

The Association is particularly keen to attract young investigators in the field. Several prestigious Young Investigator Awards in both clinical and basic sciences are now offered at the meetings. In addition some travel bursaries are offered to young investigators to facilitate their attendance to present their papers. Each annual meeting includes a postgraduate course.

The APASL is thus continuing to fulfil its role as the regional association to foster teaching, research and the dissemination of knowledge in all aspects of diseases of the liver and biliary system. Membership is open to any clinical or basic researcher interested in hepatology.

TCS07-02

The impact of HBV studies in Asia-Pacific region on clinical practice

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Since the discovery of Australia antigen in 1965 and the link of this antigen with hepatitis B in 1967, the antigen has been renamed HBsAg and tremendous advancement in hepatitis B has been achieved in these 4 decades. As the most prevalent region of HBV infection, Asia has actively participated in fighting HBV and its diseases. According to cited reference search using SCI-expanded database (Web of Science®) spanning all years since 1975, around 2.5% of hepatitis B or HBsAg or HBV-related papers each have been cited over 100 times and are thus considered as papers representing research of significant scientific impact or contribution. Of these papers around 17% were conducted in Asia. Based on these papers,

the contribution and impact of the research conducted in Asia include the following: elucidation of the mode and age of HBV transmission and its rate of chronicity; implementation of mass HBV vaccination program with excellent outcomes including prevention of HCC; elucidation of the natural history of chronic HBV infection and coin the terms of three phases (immune tolerant phase, immune clearance phase and residual inactive phase); proof of the concept that HBV is an etiologic agent of HCC; and HBV replication is the driving force while other factors increase the risk of disease progression, including cirrhosis and HCC development. The studies in Asia also contribute greatly in the early detection of HCC and the understanding of HCV superinfection in patients with chronic HBV infection. More importantly, Asian patients play major role in almost all of the pivotal trials of anti-HBV therapy. Studies also helped to improve the therapeutic strategies and enabled experts in this region to issue the world's first hepatitis B guidelines in year 2000, and update the guidelines to its 5th version in 2012.

TCS07-03

The impact of HCV studies in Asia-Pacific region on clinical practice

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HCV (Hepatitis C Virus) was discovered in 1989. Subsequently, how it influenced for the clinics by epidemiological and clinical studies. In particular the influence of the infection is varying from countries to countries. Such as in Japan, 80% of patients with hepatocellular carcinoma (HCC) are infected by HCV. In contrast, many other Asian countries, prevalence of HCV infections among patients with HCC varies from 10 to 20%. Because of this geographic variation, the paper published by the Asian countries varies.

In this session, I will discuss about the influence of the studies on HCV from Asian countries to our daily clinical practices.

TCS08-01

Recent advances in biomarkers for the diagnosis and management of drug-induced liver injury

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Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are very sensitive measures of liver injury and have been used for over 40 years to monitor the liver safety of drugs. However, there are drugs that, when administered at recommended doses, cause ALT/AST elevations but do not cause clinically important liver injury. To search for improved biomarkers of drug-induced liver injury, we have analyzed serial serum samples obtained from healthy adult volunteers treated with recurrent therapeutic doses of acetaminophen or various heparins, treatment regimens that cause marked elevations in serum ALT and AST but have low or no risk for serious hepatotoxicity. We and our collaborators have employed a variety of techniques, including transcriptomics, metabolomics and proteomics to identify biomarkers that may provide insight into the mechanisms underlying these benign and self-limited laboratory abnormalities. Such biomarkers have included cytokeratin-18 fragments (apoptosis), HMGB1 (necrosis) and acetylated HMGB1(innate immune activation). These studies support that therapeutic doses of acetaminophen and heparins cause hepatocyte death, but the mechanisms involved in cell death differ between treatments. Although our studies do not provide an explanation for why these treatments are safe for the liver, they are establishing the serum and blood signatures of benign and self limited liver injury. These signatures will be compared to similar analyses performed on patients with serum ALT/AST elevations due to drugs with serious liver liabilities.

TCS08-02

Drug-induced liver injury in Japan: Is there optimal causality assessment?

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The diagnostic scale proposed at a workshop during DDW-Japan 2004 (Hepatol Res 2005;32:250), which modified the RUCUM score, has been widely used for the diagnosis of drug-induced liver injury (DILI) in Japan. Major modifications of the scale include 1. The item of concomitant drug(s) was omitted. 2. The item of age in the risk factor was excluded. 3. For the item of previous information on hepatotoxicity of the drug, scores were changed either to +1 or 0. 4. Scores of the drug-induced lymphocyte stimulation test (DLST) and eosinophilia ($\geq$6%) were added. In 2008, 1,674 Japanese DILI cases between 1997 and 2006 were surveyed. In total, 721 males and 955 females aged between 12 and 99 years old (an average of 55 years old) were reported (59% hepatocellular type, 20% mixed type and 21% cholestatic type). As for the duration until the onset of liver injury; 59% cases occurred within 30 days and 80% of cases occurred within 90 days after starting drug administration. The distribution of scores of the diagnostic scale of the DDW-Japan 2004 workshop was a follows; 87% were diagnosed as "highly probable", and 11% as "possible", suggesting the usefulness of this diagnostic scale. Percentages of causal drugs were as follows; 14.3% antibiotics, 10.1% drugs for the psychiatry and neurological system, 10.0% dietary supplements, 9.9% anti-inflammatory drugs, 7.5% drugs for the circulatory and respiratory system, 7.1% Chinese herbal drugs, and 6.1% drugs for the gastrointestinal system. Further modification of the scale should be discussed in the future.

TCS08-03

Drug-induced liver injury in Singapore: the burden of herb-induced liver injury

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TCS08-04

Drug-induced liver injury in Taiwan: pharmacogenetic approach to anti-tuberculosis drug-induced liver injury

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Although drug-induced liver injury (DILI) is not the commonest adverse drug reaction (ADR), it is the single most frequent ADR causing drug withdrawal from the market. It also makes the preclinical termination of many developing drugs, and limits the use of some drugs after marketing.

In Taiwan, Drug-Induced Liver Injury Network in Taiwan (DILINT) has been launched, sponsored by Taiwan Food and Drug Administration, since 2011. This is a multi-center collaborative program to collect the clinical data of DILI prospectively and retrospectively from 6 medical centers across the island. The preliminary data showed that anti-tuberculosis drug is the leading discriminated drug (27.8%), followed by herbs (20.5%), and antibiotics (10.0%). The finding that anti-tuberculosis drugs and herbs play major roles in DILI of Taiwan is consistent with that in Mainland China, Hong Kong, Singapore, Korea and many other countries. This spotlights that pharmacovigilance program is urgently needed both in conventional western drugs and herbs.

Assaying functional genetic polymorphisms of the target drug-metabolizing enzymes is one of the mainstreams to detect the susceptibility genetic factors of DILI. Since anti-tuberculosis drug is the leading culprit drug of DILI in Taiwan and many Asian countries, we

have performed a series of pharmacogenetic association studies in this field recently. We found that patients with *N-acetyltransferase 2 (NAT2)* slow acetylator status, *cytochrome P450 2E1(CYP2E1)* wild c1/c1 genotype, *glutathione S-transferase M1(GSTM1)* null genotype, and *manganese superoxide dismutase* (*MnSOD, SOD2*) mutant C allele may have higher risk of anti-tuberculosis drug-induced liver injury. Although these associations need to be verified by other ethnic populations with a larger sample size, this kind of pharmacogenetic or pharmacogenomic approaches disclose the potential of early detection and prevention of DILI induced by some drugs.

A well pharmacovigilance system, including detection of severe DILI, is the hallmark of high standard healthcare. Together with the experiences and insights from the various networks or organizations relevant to DILI, we stand an extraordinary status to combat the crucial and inevitable DILI.

TCS09-01

Prophylaxis and treatment of hepatitis B reactivation in patients receiving chemotherapy

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Reactivation of hepatitis B virus (HBV) infection is a well-known complication during and after anti-cancer therapy. This condition can affect two patient populations: the first, and the most commonly affected, are patients who are seropositive for hepatitis B surface antigen (HBsAg); the other consists of those who are HBsAg-negative but who have prior HBV infection as evident by seropositive status for anti-body to hepatitis B core antigen (anti-HBc), irrespective of their anti-HBs (anti-body to HBsAg) status. While the former diagnosis is supported by raised HBVDNA level in combination with hepatic transaminitis, the latter is also evident by seroreversion with HBsAg reverting from negative to positive status. The clinical course can vary from asymptomatic hepatitis to fulminant hepatic failure that can be potentially fatal. In addition to potent cytotoxic chemotherapy, biological agents that target B- or T-lymphocytes for the treatment of haematological malignancies have increasingly been associated with this condition. In particular, rituximab, a chimeric mouse human monoclonal antibody against CD20+malignant B lymphoid cells, have been found to induce profound and durable B cell depletion and have been associated with severe infections. Prior to the availability of anti-B and anti-T cell therapies, HBV reactivation among patients who are anti-HBc+with or without anti-HBs + have generally been considered to occur infrequently and this tends to run a mild clinical course. However, it has since been reported that HBV reactivation may occur in between 2-25% of anti-HBc+patients who are treated with rituximab, with isolated fatal cases have been reported. For patients who are HBsAg positive, the APASL, AASLD and EASL have recommended the use of prophylactic anti-viral from the start of immunosuppressive anti-cancer therapy. However, with regards to patients who are HBsAg negative with anti-HBc positive, data from rituximab-associated viral reactivation has prompted some to suggest the adoption of prophylactic antiviral approach. While such an approach has not been formally addressed in prospective studies, it may also not be practical in HBV endemic areas, where up to 40–50% of patients with lymphoid malignancies have been reported to have prior HBV infection. Until further data become available, patients who are HBsAg negative/anti-HBc positive receiving rituximab therapy should be closely monitored for HBV reactivation, with prompt administration of anti-viral upon detection of the condition. The identification of risk factors for the development of HBV reactivation may enable clinicians in directing antiviral prophylaxis to appropriate patient subgroup.

TCS09-02

Strategy to prevent hepatitis B reactivation in patients receiving immunotherapy

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Chronic hepatitis B virus (HBV) infection is a major public health and medical concern all over the world. The interaction between host immune response and viruses plays an essential role in the pathogenesis of chronic hepatitis B (CHB). HBV reactivation, manifested as the abrupt reappearance or rise of HBV viral loads in the serum of HBV-infected patients, is a potential complication of immunosuppressants and biological agents. HBV viral load elevation is usually ahead of hepatitis flare. Hepatic decompensation and eventually death is not infrequent once initiation of viral reactivation. Reactivation not only happens in hepatitis B surface antigen (HBsAg)-positive, but also in HBsAg-negative/hepatitis B core antibody (anti-HBc)-positive patients undergoing immunosuppressant therapy. The risk of HBV reactivation is attributed to the viral status and the regimen of immunosuppressants. Currently, immunosuppression and biological agents, such as etanercept (Enbrel), infliximab, adalimumab (Humira), rituximab, are widely adopt in the treatment of rheumatic diseases such as rheumatoid arthritis or systemic lupus erythematosus. Routine serological tests for HBV markers (HBsAg and anti-HBc) are mandatory for all rheumatic patients prior to immunosuppressant or biological treatment. Current HBV treatment guidelines address the importance of antiviral prophylaxis in HBV carriers when receiving finite course of immunosuppressant therapy. However, the treatment duration, when to start and stop the anti-HBV agents, are unsettled in rheumatic patients.

TCS09-03

Do we need prophylactic treatment for patients with HBV related HCC receiving TACE or molecular target therapy?

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HBV reactivation has been shown to occur with chemotherapy for solid cancer, treatment for leukemia especially when rituximab is used, immune modulation using prednisolone or infliximab for autoimmune condition, and after bone marrow and liver transplantation. The reactivation can be transient and clinically silent, but often causes a flare of diseases that can be severe, resulting in acute hepatic failure. The reactivation can occur in situations when the ratio of HBV replication and immune response is altered. If antiviral prophylaxis is not used, the frequency of HBV reactivation in HBsAg positive patients is 20–50% in moderate-intensity chemotherapy, but is over 50% in high-intensity chemotherapy such as lymphoma chemotherapy (which includes rituximab). However, in HBsAg negative patients, the frequency of HBV reactivation is 1–3% in low risk group, but 12–30% in high-intensity chemotherapy using rituximab and steroid containing regimen.

During the treatment of HCC, HBV reactivation is uncommon. However, chemotherapeutic agents during TACE can induce HBV reactivation in patients with HBV related HCC. In our previous RCT, the hepatitis due to HBV reactivation after TACE occurred in 29.7% of 37 controls, 2.8% of 36 patients with lamivudine prophylaxis. With multivariate Cox regression model, a baseline HBV DNA level of more than 10^4 copies/mL was the only independent predictor of hepatitis due to HBV reactivation during chemo-lipiodolization. In prospective study for HBV reactivation risk by viral status and treatment intensity (local ablation therapy vs TAC+adriamycin vs TAC+epirubicin+cisplatin vs TAC-epirubicin+cisplatin+radiation therapy) in 250 HCC patients, 62 (30.2%) patients developed HBV reactivation. Multivariate analysis identified HBV DNA levels $> 10^4$ copies/ml ($P = 0.041$)

and treatment option ($P = 0.001$) to be independent predictors of HBV reactivation. There was a significant trend for increased risk of reactivation with higher intensity of therapy, with hazard ratios of 1.0 for LAT, 2.45 for TAC-ADR, 4.19 for TAC-EC and 10.17 for TAC-EC+RT. The severity of reactivated disease also increased with the growth of treatment intensity (P value for trend <0.05).

In severe acute hepatitis after reactivation, aggressive therapy and discontinuation of cytotoxic chemotherapy has been the mainstay of treatment. Despite the use of lamvudine, HBV associated mortality has been reported in up to 20% of HBsAg positive patients who were treated. It has been suggested that this may be because antiviral administration had not begun until after severe liver impairment had already occurred. In contrast to no-prophylaxis, lamivudine prophylaxis significantly reduced the number of HBV related ALT flares, liver failure, deaths and cessation of chemotherapy in HBsAg positive patients. However the optimal duration of lamivudine prophylaxis has not been defined. Diseases exacerbation can occur after lamivudine is discontinued in patients with high pretreatment HBV DNA levels. Close follow-up of patients with serial serum ALT and HBV DNA monitoring is advised after discontinuation of LAM prophylaxis.

The HBV reactivation didn't occur in 45 HCC patients treated with sorafenib in one retrospective study. So, the impact of sorafenib would be small regarding HBV reactivation after drug trial. However, the clinical experience of HBV related HCC is so limited in the aspect of HBV reactivation. Further clinical studies using new molecular targeting agents are needed.

In conclusion, current clinical experience suggests that high-level viremia and high-level treatment intensity are the major risk factors for HBV reactivation during loco-regional therapy in HCC. Pre-emptive antiviral therapy should be considered in HCC patients with high risk of HBV recurrence.

TCS10-01

Life cycle of HCV and potential target sites for treatment

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Hepatitis C virus (HCV) infection affects approximately 180 million individuals worldwide and is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma. Currently pegylated interferon and ribavirin is the standard of treatment in most parts of the World. The evolution of directly acting anti-virals have ushered in a new era for genotype 1 patients with triple therapy of pegylated interferon, ribavirin and either telaprevir or boceprevir (protease inhibitors). Ongoing drug development strategy has involved targeting several replication steps of the virus and the hope is to see all oral therapies. The drugs that act at various steps of the viral replication could potentially be additive or even synergistic in their anti-viral effects and lead to high SVR rates and with much better tolerability than interferon based regimens.

The replication of hepatitis C virus requires several steps. The initial step involves viral attachment to the hepatocyte, entry and fusion. These steps involve the two envelope glycoproteins E1 and E2 and several HCV receptors that include, among several, glycosaminoglycans, CD81, scavenger receptor B type I, Claudin-1, and LDL receptor. Thus far efforts to neutralize the virus by using monoclonal and polyclonal antibodies have largely been unsuccessful. Efforts to interrupt the cycle through blocking the RNA translation process by antisense oligonucleotides, ribozymes, and specific small molecule inhibitors of HCV IRES function have led to limited success. The next targets have been around the post translational processing of the virus and much work has evolved in this area. The various viral peptidases include NS3/4A, and other downstream junctions that include NS4A-NS4B, NS4B-NS5A, and NS5A-NS5B. Boceprevir and telaprevir are the first HCV NS3/4A protease inhibitors to be approved for the treatment of chronic hepatitis C genotype 1 infection. These drugs must be used in combination with peginterferon plus ribavirin (P/R) to maximize efficacy and prevent the emergence of resistance-associated variants (RAVs).Other protease inhibitors are under development, and more importantly need to be pan-genotypic. The characteristics of NS3/4A protease inhibitors include their moderate to high potency, possibly with multi-genotypic coverage with newer molecules, and an intermediate barrier to resistance. The function of NS5A in the HCV life cycle remains unknown; yet the pipeline of drugs includes NS 5A inhibitors and they are potent, are pan-genotypic and have demonstrated a low barrier to resistance. The NS5B polymerase inhibitors in development are both non-nucleoside and nucleoside inhibitors with variable efficacy across genotypes and variable barriers of resistance. Cyclophilin A is a host protein which is found in the cytosol and it has been reported to exhibit anti-HCV activity in vitro and in chimpanzees. Cyclosporin A acts by antagonizing the effect of cyclophilin B on HCV replication. Synthetic, nonimmunosuppressive analogues of cyclosporine B have been developed and are undergoing evaluation in chronic HCV infection. Lastly, inhibitors of viral assembly include iminosugars that are able to cross cellular membranes and concentrate in the ER where they could competitively inhibit ER-resident alfa-glucosidases, alter envelope proteins glycosylation, and interfere with the assembly of HCV.

TCS10-02

Direct acting antiviral agents for chronic hepatitis C: present status

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Treatment of hepatitis C virus infection has entered a new era with the FDA and EMA approval of the first HCV protease inhibitors, boceprevir and telaprevir, in summer 2011. National and international guidelines have to be updated as triple therapy with a protease inhibitor (PI), pegylated interferon alfa (PEG-IFNa) and ribavirin (RBV) has to be considered as the new standard of care for most patients infected with HCV genotype 1.

Several additional direct acting antivirals (DAAs) targeting different steps in the HCV life-cycle are in clinical development. Based on the experience from treating HIV infections it is likely that a combination of 2-3 different DAAs would be needed to achieve the goal of sustained suppression of HCV replication — depending on the potency and resistance barrier of the respective antiviral drugs. During the last 2 years, first data of phase II trials investigating different IFN-free combination therapies have been presented. The proof of concept that chronic hepatitis C can be cured by combination of DAAs has now been established by treatment with a protease inhibitor and a NS5A inhibitor developed by BMS. In addition, nucleosides or nucleotides inhibiting the HCV polymerase seem to be of particular interest as the resistance barrier is very high and pan-genotypic activity of these drugs has been demonstrated. Recently cure of chronic HCV genotype 2 and 3 infection has been shown with a combination therapy of ribavirin with the polymerase inhibitor PSI-7977.

The long-term goal of novel therapeutic options for hepatitis C virus (HCV) infection should be the development of an easy to apply treatment without side-effects that induces cure within a reasonable time-frame. It might well be that this goal can be achieved already within the next 3–4 years. The optimal treatment duration for individuals patients will remain to be established.

TCS10-03

Future treatment for chronic hepatitis C: IFN or Ribavirin-free regimens

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Current standard-of-care (SOC) for chronic hepatitis C infection is combination of pegylated interferon (PEG) plus ribavirin (RBV) in

HCV genotype 2/3 and combination of pegylated interferon (PEG) plus ribavirin (RBV) plus either boceprevir or telaprevir (triple therapy).

Although triple therapy is associated with improved efficacy, poor tolerability remains an important barrier to treatment uptake. Also, triple therapy will have limited efficacy in patients infected with HCV GT non-1, previous null-responders and those with contraindications to interferon. It is hoped that the combination of multiple DAAs which target different steps of HCV replication should provide interferon-free treatment regimen. In the first proof-of-concept study of IFN-free combination DAA therapy (INFORM-1), 87 patients with HCV genotype 1 infection receive 14 days of meracitabine, a nucleoside polymerase inhibitor, and danaprevir, an NS3/4A protease inhibitor (Gane E, et al. Lancet 2010). This combination achieved profound synergistic antiviral suppression and prevented the emergence of resistance to either compound. Viral kinetic data derived from this study suggested that 8–10 weeks DAA therapy should eradicate HCV infection. In the first study of curative intent, 11 patients received 24 weeks of combination of NS3/4A protease inhibitor (BMS-650032) and NS5A inhibitor (BMS-795002) (Lok A, et al. EASL 2011). Although 7 patients had virologic breakthrough within 2 months, with dual resistance, the remaining 4 patients were cured. Current and planned studies of Interferon-free combination DAA will determine the number of different DAAs, the need for RBV and duration of therapy needed to maximise cure whilst minimising the risk of emergence of multi-resistance, which would jeopardise future retreatment options.

The most promising interferon-free regimen to date is the all-oral combination of the nucleoside polymerase inhibitor PSI-7977 plus ribavirin. In a Phase II study, 40 Genotype 2/3 patients received PSI-7977 plus ribavirin for 12 weeks, plus 12, 8, 4 weeks, or no pegylated interferon (Gane E, et al. AASLD 2011). All patients achieved RVR, EoTR, SVR12 and SVR24. This regimen of PSI-7977 plus ribavirin for 12 weeks is now being studied in global Phase III studies across all genotypes.

In conclusion, combinations of nucleoside polymerase inhibitors with ribavirin or with other DAAs will improve the tolerability and efficacy of antiviral therapy on patients affected with all HCV genotypes.

TCS11-01

The heart in cirrhosis: Pathophysiology & clinical aspects of cirrhotic cardiomyopathy

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In cirrhosis, cardiovascular function is deranged. Although the circulation becomes hyperdynamic, manifested as increased cardiac output and decreased peripheral vascular resistance and arterial pressure, the heart responds abnormally to numerous stimuli/stresses. Cardiac ventricular function under physiological, pharmacological or surgical stress is blunted, with abnormalities of both systolic and diastolic function. This condition is known as cirrhotic cardiomyopathy. Other features of the syndrome include: a) electrophysiological changes in repolarization including prolonged electrocardiographic QT interval and a curious asynchrony in the normally tightly-regulated time interval between the electrical and mechanical onset of systole. b) enlargement or hypertrophy of cardiac chambers, c) markers of cardiac 'distress' such as BNP or pro-BNP and troponin I.

Although these changes when initially described more than 4 decades ago were ascribed to a mild or latent form of alcoholic cardiotoxicity, it is now firmly established that the condition of cirrhosis *per se* is associated with this, as patients and animal models with non-alcoholic cirrhosis show the same pattern or cardiac dysfunction. According to a large series of patients from several global centers, approximately 50% of patients with cirrhosis show some evidence of ventricular dysfunction based on routine echocardiography. Some evidence implicates a significant pathogenic role of this syndrome in the development of acute hepatorenal syndrome after spontaneous bacterial peritonitis and poor outcomes such as increased mortality/morbidity after challenges such as TIPS insertion and liver transplantation. It may also explain the uncommon but mysterious and inexplicable onset of heart failure in the peri- and post-transplantation period in patients with no previous history of heart disease or dysfunction.

Several pathogenic mechanisms have been described including: dysfunction or defects in the cardiac β-adrenergic receptor system, plasma membrane physico-chemical milieu (decreased membrane biophysical fluidity due to an increased cholesterol:phospholipid ratio in the plasma membrane lipid bilayer), membrane calcium channels, and humoral factors such as cytokines, nitric oxide, carbon monoxide and endogenous cannabinoids. These factors can lead to other changes such as increased apoptosis in cardiomyocytes, mediated by the 'exterior' pathway. Recently, we have found an abnormal isoform shift of the main cardiac 'motor' of contraction, the myosin heavy chain (MHC) which forms the major part of the 'thick' myofilament. In the cirrhotic rat, the predominant α-MHC has shifted to a mixed α- and β-MHC profile, which would explain many of the contractile abnormalities in the cirrhotic heart. Many of these pathogenic mechanisms are inter-related and their exact relationship is the subject of ongoing research.

Treatment strategies for cirrhotic cardiomyopathy remain unclear. Fortunately overt heart failure is distinctly uncommon. Repolarization abnormalities such as QT prolongation may respond to β-blockade. Promising avenues of inquiry include cardiac anti-fibrogenic therapies such as angiotensin converting enzyme inhibitors. Cirrhotic cardiomyopathy is a previously underappreciated syndrome with important clinical consequences in patients with cirrhosis, especially given the emergence of liver transplantation as effective therapy for endstage liver disease.

TCS11-02

The kidney in cirrhosis: Hyponatremia and Acute Kidney Injury

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Hyponatremia is common in patients with decompensated cirrhosis and is related to impaired solute-free water excretion secondary to non-osmotic hypersecretion of vasopressin (the antidiuretic hormone), which results in a disproportionate retention of water relative to sodium retention. Hyponatremia in cirrhosis is arbitrarily defined when serum sodium concentration decreases below 130 mmol/L, but reductions below 135 mmol/L should also be considered as hyponatremia, according to recent guidelines on hyponatremia in the general patient population. It is important to differentiate hypovolemic from hypervolemic hyponatremia. Hypovolemic hyponatremia is characterized by low serum sodium concentrations in the absence of ascites and edema, and usually occurs after a prolonged negative sodium balance with marked loss of extracellular fluid. Management consists of administration of normal saline and treatment of the cause (usually diuretic withdrawal). Fluid restriction to 1000 ml/day is effective in increasing serum sodium concentration in only a minority of patients with hypervolemic hyponatremia, but may be effective in preventing a further reduction in serum sodium levels. Treatment with vaptans may be considered in patients with severe hypervolemic hyponatremia (<125 mmol/L). Tolvaptan is licensed in some countries for oral treatment. Conivaptan is only licensed in some countries for short-term intravenous treatment. Rapid increases in serum sodium concentration (>8–10 mmol/day) should be avoided to prevent the occurrence of osmotic demyelination syndrome.

Acute kidney injury (AKI) is common in patients with decompensated cirrhosis (i.e., patients with ascites and/or variceal

hemorrhage). The Acute Kidney Injury Network (AKIN) defined AKI as an abrupt (≤48 hours) reduction in kidney function manifested by either an absolute increase in serum creatinine level of more than 0.3 mg/dL (26.5 μmol/L), or an increase by more than 50% (by a factor of 1.5 from baseline) or a reduction in documented urinary output (<0.5 mL per kilogram of body weight per hour for >6 hours). Once AKI is established, a staging system then defines its severity. Causes of AKI are divided into prerenal, intrarenal, and postrenal factors. Prerenal factors range from obvious renal hypoperfusion in patients with hypotension or hemorrhage to more subtle renal hypoperfusion, such as that seen in patients with cirrhosis and type 1 hepatorenal syndrome (HRS). Postrenal AKI is caused by the blockade of urinary flow. Intrarenal causes of AKI can be divided into diseases of the vasculature, tubulointerstitium, and glomerulus. Patients may have a combination of different types of kidney changes. In cirrhosis, the most common causes of AKI are 'prerenal factors' and ischemic acute tubular necrosis. In other words, renal hypoperfusion can explain most of cases of cirrhosis-associated AKI. Moreover, prerenal AKI is a pre-ischemic state which is reversible if renal perfusion is restored by an appropriate treatment. However, prerenal AKI may progress very rapidly to ischemic ATN in patients with severe hypotension and/or in the absence of or delayed appropriate treatment, with a prolonged decrease in renal perfusion. Management includes treatment of the cause (e.g., terlipressin plus intravenous albumin for patients with type 1 HRS), general care (e.g., avoid use of nepthrotoxic drugs, optimization of extracellular fluid volume), prevention of complications of cirrhosis (e.g., antibiotics to prevent infections), and renal-replacement therapy in some cases.

TC11-03

The Brain in Cirrhosis: Advances in Hepatic Encephalopathy

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Hepatic encephalopathy (HE) is complication of chronic and acute liver dysfunction, with reversible neuropsychiatric manifestations ranging from mild disturbances in cognitive functions, consciousness to coma. The pathogenesis of HE is complex and multifactorial, mainly involves role of circulating gut-derived toxins of nitrogenous compounds, with elevated ammonia in serum and central nervous system. Ammonia causes neurotransmitter abnormalities, astrocyte swelling and brain edema.There is synergistic role of oxidative stress, inflammation and neurosteroids in pathogenesis of HE. Therapeutic options for HE include avoidance and treatment of precipitating factors and ammonia lowering drugs like non-absorbable disaccharides and antibiotics. Non-absobable disaccharides like lactulose and lactitol are considered first line pharmacotherapy of HE. Neomycin, metronidazole and rifaximin are second line drugs for treatment of HE. Rifaximin is as effective as conventional drug therapy with fewer side effects. Lactulose, rifaximin and probiotics have been tried for prevention of HE. Other therapeutic options being investigated are MARS, L-ornithine phenylacetate, sodium benzoate, branched chain amino acids, probiotics, zinc supplementation, acarbose, L-acetyl carnitine, C GMP modulators (sildenafil), anti-inflammatory drugs and gene therapy. Liver transplantation is considered in selected cases with HE.

TCS12-01

Tailored Laparoscopic Approach for HCC

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Laparoscopic liver resection (LLR) is still not a well established treatment modality for hepatocelluar carcinoma (HCC). Moreover, most of reported cases have been limited to the anterolateral segments (segments 2, 3, 4b, 5, 6). The indications on location of the laparoscopic liver resection have previously been limited to easily accessible lesions. Performing laparoscopic liver resection in the posterior and superior parts of the liver has been considered difficult due to inadequate exposure, the poor operative field and the difficulty with parenchymal dissection. However, there are several attempts that laparoscopic liver resection was performed as open surgery in terms of indications and operative methods. Flexible endoscopy, high definition imaging and various kinds of equipments for parenchymal transection have been helpful for advanced technique. As the patients with HCC have concomitant liver cirrhosis or chronic liver disease, there is high probability of liver dysfunction after liver resection. Therefore, it is necessary to perform organ sparing liver resection, so called tailored approach for the patients with HCC. The type of resection also may depend on the remaining liver's functional capacity. Yet for safer laparoscopic liver resection, the patient positioning and trocar placement should be individualized according to the tumor's location.

Tailored liver resection can be possible with the use of Glissonian approach. For example, S5 segmentectomy, the Glissonian pedicle to S5 was isolated.

TCS12-02

Laparoscopic anatomical resection for HCC: Indication and technique consideration

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Background: The introduction of laparoscopic liver resection has a great impact on liver surgery especially in the treatment of HCC. Anatomical liver resection appears to be superior to non-anatomical liver resection in operative and oncological results. The aim of the present study was to describe the procedure of laparoscopic anatomical liver resection and to review a single institution's experience of laparoscopic liver resection (LLR) including totally laparoscopic liver resection (TLLR) and laparoscopy-assisted liver resection (LALR) as a minimally invasive surgery for HCC.
Methods: Anatomical liver resection was performed by Glissonian approach either with TLLR or LALR. Between May 1997 and December 2010, 212 patients underwent LLR for hepatocellular carcinoma (HCC) (75 patients), liver metastases (92), cholangiocellular carcinoma (CCC) (3), carcinoid (1), benign liver lesions (16), and living donor (25). Operations included 119 TLLR (96 wedge resections, 17 left lateral sectionectomies, 4 major anatomical hepatectomy, two S5 subsegmentectomy), 93 LALR (2 right trisectionectomy, 16 right hepatectomy, 17 left hepatectomy, 3 central bisectionectomy, 5 right anterior sectionectomy, 8 extended right posterior sectionectomy, 25 donor hepatectomy, and others). Nineteen percent of TLLR, 100% of LALR, and 67% (141/212) in total, were anatomical liver resection.
Results: Median operating time was 161, 324 min, and blood loss, 57, 546 ml for TLLR, LALR, respectively. One TLLR was converted to a LALR. Only ten patients (4.7%) experienced postoperative complications, 4 patients (1.9%) showed bile leakage, and 6 patients (2.8%) developed wound infections. Overall 5-year survival for HCC was 65%.
Conclusions: Laparoscopic anatomical liver resection can be performed safely for HCC. Procedures vary from hybrid to pure technique and seem to offer at least short-term benefits in selected patients. The number of anatomical resections has increased as our experience increases.

TCS12-03

Laparoscopic Surgery VS Traditional Surgery for HCC: Indication and Technique Consideration

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Background: Recent accumulating reports has suggested that the laparoscopic liver resection can offer advantages over conventional liver resection in term of less hospital stay, intraoperative blood loss and ascites. As to HCC, it is still controversial due to problems of hemostasis during liver resection, the oncological integrity and tumor seeding under CO2 pneumopritoneum. Additionally, the long term oncological results of laparoscopic liver resection for HCC remained an issue of debate.
Here we presented to study and the feasibility, safety, and long term results of laparoscopic liver resection of HCC and analyze the outcomes of laparoscopic liver resection compared with open liver resection for HCC by case-matched analysis for tumor size, type of resection, degree of liver cirrhosis, type of resection, and tumor location (including segments 7 and 8).
Method: We started to performed laparoscopic hepatectomy since October 2001. Between October 2001 and December 2010, 447 patients with HCC received liver surgery by a single surgical team, at the Taipei Medical University related Hospital. Fifty-four laparoscopic cases were performed.
Initially the patients selection was strictly at: 1. Liver function was Child A or B status. 2. Tumor location: S2,3,4.5,6,7 in the subcapsular area. 3. Tumor does not invaded major vessel or billary tree. 4. Tumor size was less than 6 cm in diameter. The tumor size and location was given in consideration in the patient selection criteria. In contrast, 37 patients HCC had an open procedure became compared group which were reviewed from the images studies and assumed as a candidate of laparoscopic liver resection.
Results: The results was shown below: (Tables 1, 2, 3, 4 and 5)

Table 1 The basic and clinical characteristics of laparosocpic and open groups

	L-group (54)	O-group (37)
Age (yrs)	59.0 (35-82)	59.3 (31-79)
Gender (female/male)	11/43	12/25
BMI	24.3 (18.5-30.2)	25.5
HepatitsB/C/B+C/no BorC	45/6/1/3	23/11/1/3
Co-morbidity	12	9
Child status A/B	49/5	36/1
ASA I/II/III	40/13/1	26/9/2
Hand assisted technique	27	
Liver cirrhosis +/-	38/16	30/7

Table 2 Tumor locations and the procedures of resection in open and laparoscopic groups

	L-group (54)	O-group (37)
Tumor location		
II and III	23	5
IV	1	8
V	6	7
VI	14	7
VII	8	9
VIII	2	1
Operative procedure		
Partial hepatectomy	28	19
Left lateral segmentectomy	19	3
One segmentectomy	6	9
Rt or Lt hemihepatectomy	1	6

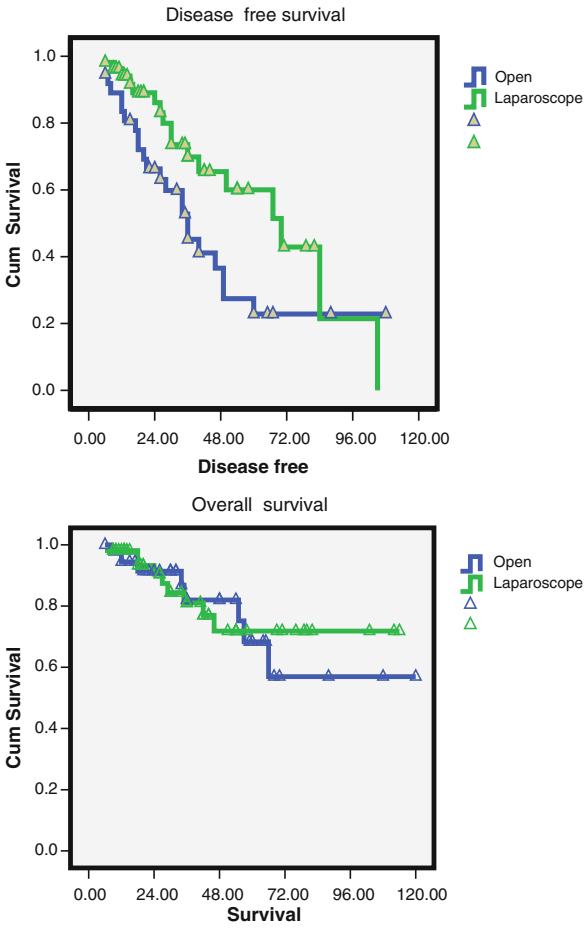
Table 3 The perioperative results of laparoscopic and open group

	L-group (54)	O-group (37)
Surgical duration (min)	141.9 (60-240)	193.4 (110-270)
Blood loss (ml)	359 (30-1500)	579.7 (0-2000)
Hospital stay (days)	7.3 (4-17)	10.3 (6-22)
Conversion	3 (5.5%)	
Transfusion	6 (11%)	8 (21%)
Complications	7 (13%)	5 (13%)
Intraoperative bleeding	4	0
Bile leakage	2	1
Prolong ascites	3	5

Table 4 The resection specimen of laparoscopic and open group

	L-group (54)	O-group (37)
Tumor size (cm)	3.4 (1.1-14.0)	3.7 (1.2-11)
Tumor < 3 cm	22	25
Specimen (cm)	10.3 (3.0-19.0)	9.7 (3.2-20)
Resection margin (cm)	1.7 (0.1-4.0)	1.2 (0-3.0)
Resection margin < 1 cm	16	15

Table 5 Disease-free and survival of the open and laparoscopic groups



Conclusion: This study showed that laparoscopic liver resection for HCC is feasible and safe in selected patients with good surgical results including a shorter postoperative hospital stay, shorter operating time, less intraoperative bleeding, and there is no oncological compromise with similar outcomes in terms of l survival when compared with open surgery.

TCS13-01

The impact of cirrhosis/portal hypertension research in Asia–Pacific region

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TCS13-02

The impact of HCC research in Asia-Pacific region

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TCS13-03

The impact of research on haemochromatosis and liver transplantation in the asia-pacific region

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Many recent advances in clinical hepatology have emanated from basic and clinical research conducted within the Asia-Pacific region. In particular, Australia and New Zealand centres have made important contributions to current knowledge have been in the areas of iron overload and liver transplantation.

Disorders of iron homeostasis that result in excess cellular and systemic iron may be associated with the production of reactive oxygen radicals that cause damage to cell membranes, DNA and proteins. The liver is the principal iron storage site in the body and is therefore susceptible to iron-induced tissue injury often resulting in progressive fibrosis, cirrhosis and ultimately hepatocellular carcinoma. The classic example of iron overload disease is *HFE*-hereditary haemochromatosis (*HFE*-HC) and genetic studies conducted in Australian subjects localised the genetic defect in this condition to a precise region on chromosome 6p. Following the cloning of *HFE,* Australian researchers quickly confirmed that a single gene polymorphism was responsible for the majority of cases of hereditary haemochromatosis and the population prevalence in Caucasian subjects for the C282Y mutation was approximately 1: 200-300 subjects. However it also became apparent that up to 20% of patients with iron overload did not carry the characteristic C282Y mutation, and mutations in other genes controlling iron metabolism were described in patients from Australian and other Asian Pacific Countries. Unlike *HFE*-HC, the non-HFE hereditary haemochromatosis syndromes are not confined to subjects of Caucasian descent, but rather have been identified in Asian populations where mutations in transferrin receptor 2 (*TFR-2*) seem to be the most common. Whether the liver was the principal site of the underlying pathophysiological defect in HC was a focus of intense interest and a large study involving liver transplant programs in Australia, New Zealand and the United Kingdom supported that hypothesis. Subsequently, it was demonstrated that hepcidin, a small molecule principally derived from the liver is the key regulator of iron homeostasis. Bridle et al showed that *HFE*-HC was characterised by a low hepcidin state and this observation collectively explained the inappropriate increase in iron absorption, the demonstrated increase in intestinal iron transport genes and the pathological increase in tissue iron concentration in the liver and other organs seen in HC. Of later interest has been studies investigating the interactions between alcohol, iron and steatosis as well as the role of iron as a co-toxin in other forms of liver injury. Fletcher et al showed that an alcohol intake greater 60 grams/day greatly increased the risk of cirrhosis in *HFE*-HC. Similarly, Powell et al demonstrated that steatosis was common and increased the risk of progressive fibrosis in *HFE*-HC. Australian investigators have shown an important effect of iron on the gene expression of enzymes involved in lipid metabolism, and Tan et al recently demonstrated that *Hfe* $^{-/-}$ mice fed a high fat diet develop marked steatohepatitis and fibrosis and a concomitant reduction in hepcidin gene expression. There is also conclusive evidence that alcohol ingestion reduces hepcidin gene expression and facilitates intestinal iron absorption. The associated increase in liver iron concentration may amplify the underlying alcoholic liver injury. Increased liver iron stores are common in end stage liver disease as shown in studies from the Queensland Liver Transplant Service. Recent evidence suggests that patients with advanced liver disease have an inappropriately reduced serum hepcidin concentration which may be an important pathogenic factor in cirrhosis associated iron loading. This may have clinical implications since the same group have recently shown elevated serum ferritin concentration is an important predictor of mortality for patients awaiting liver transplantation and other groups have shown elevated iron stores pre-transplant are associated with increased post-transplant mortality.

Countries within the Asia Pacific region have high liver-related mortality rates because of endemic HBV and HCV infection. Liver transplantation has become the accepted treatment for both end-stage liver disease and early liver cancer. Since the first successful liver transplant was performed in the Asia-Pacific at Princess Alexandra Hospital in Brisbane in 1985, more than 50,000 liver transplants have been performed in Asia-Pacific region, and 5 year survival rates now approach 90%. Unfortunately, deceased donation rates remain low in Asia Pacific, for cultural and infrastructural reasons. The increasing gap between demand and supply has driven the expansion of the donor pool to include "marginal donors" within Asia-Pacific.

The first successful live donor liver transplant was performed by Russell Strong, again at Princess Alexandra Hospital, in 1989 – a left lobe donated by a parent into a child. Since then, a number of innovative procedures have been developed in Asia-Pacific to allow safe live donor liver transplantation for adult recipients, which reduce the risk of small-for-size syndrome. These include surgical techniques which either increase functioning allograft mass (extended left lobe, right lobe, or dual left lobe grafts from 2 donors) or reduce portal venous inflow (retaining MHV with Rt lobe; portocaval shunts). Last year, an estimated 3000 live-donor liver transplants were performed in the Asia-Pacific, with outcomes comparable to deceased donor programmes.

Many of the important advances in the transplantation for HBV have come from the Asia-Pacific region, where rates of HBV infection remain endemic in both the donor and recipient populations. Almost 50% of organ donors in Asian and more than 10% in Australia and NZ have had previous exposure to HBV (HBsAg neg/anti-HBcore+). Recipients of livers from these donors are at a high risk of *de* novo HBV infection. Several Asian studies have demonstrated that this risk becomes negligible if the recipient of an anti-HBcore+ liver receives long-term prophylaxis with either lamivudine or HBIG or if the recipient has documented protective immunity prior to transplant (anti-HBs>100 IU/mL).

Chronic hepatitis B is the most common indication for elective liver transplantation in Asia-Pacific, whilst acute-on-chronic hepatitis B is the most common indication for emergency liver transplantation. Although the high-dose intravenous hepatitis B immunoglobulin strategies used by European and US transplant centres may prevent overall recurrence rate by 60%, this is prohibitively expensive and is less effective in HBV DNA positive candidates, who are more prevalent in Asia. This has driven the development of HBIG sparing strategies within the Asia-Pacific. The Australasian multicentre study demonstrated that substitution of high-dose intravenous HBIG dose by low-dose intramuscular HBIG was safe and effective, with <5%

HBV recurrence at a cost of only 10% that of the European/US high-dose HBIG protocol. Many of these patients receiving post-transplant LAM/HBIG entered a second study where half were randomised to substitute adefovir (ADV) for HBIG. This study showed that conversion to LAM/ADV provided equivalent protection against recurrent HBV infection, but with better tolerability and less cost compared to LAM/HBIG. Finally, in a recent prospective open-labelled study, the Australasian Liver Transplant group evaluated combination LAM/ADV started pretransplant at the time of listing. This regimen was universally effective, well tolerated and removed the need for post-transplant HBIG, further reducing the cost of prophylaxis.

Finally, the Australasian Liver Transplant group has published many studies into the natural history of recurrent HCV infection, identifying several baseline and post-transplant host and viral predictors of rapid fibrosis progression.

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Infections in the Etiology of Human Cancers

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During the past century a number of chemical and physical risk factors for human cancers have been identified. Only relatively recently, mainly during the past 30 years, infectious agents have been identified as important human carcinogens. Besides a larger number of viral infections identified as risk factors for divergent and in part highly prevalent human cancers, also bacteria and parasites play a significant role. The bacterium *Helicobacter pylori* represents a major cause of gastric cancer, parasitic infections cause bladder (*Schistosoma haematobium*) and liver cancers (*liver flukes*).

Remarkable differences exist in the mechanism of cancer induction between individual potentially carcinogenic iinfections. Some viruses (*High risk papillomaviruses*, *Epstein-Barr virus*, *Kaposi' sarcoma virus*, *Merkel cell polyomavirus* and *human T-lymphotropic retrovirus* act as direct carcinogens. Here persistence and expression of specific viral oncogens are required for the maintenance of the malignant phenotype of the infected cells. Replication incompetence emerges as a major factor for the carcinogenic function of this group of agents. Other infections contribute to malignant transformation indirectly, e.g. *human immunodeficiency viruses* by immunosuppression, commonly followed by the activation of other latent potentially tumorigenic viruses. Alternatively, induction of chronic inflammations, resulting in the production of oxygen and nitrogen radicals seems to result in random genetic and epigenetic modifications of the host cell genome with the eventual outcome of malignant growth. The number of required geneic or epigenetic modifications in host cell genes seems to determine the long latency periods between primary infection and cancer occurrence, frequently covering several decades.

Although we can presently link more than 20% of the global cancer incidence to infectious events, some data will be summarized suggesting a role of infectious agents in additional common human cancers.

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Hepatitis B Viral Factors and Clinical Outcomes of Chronic Hepatitis B: Asian Perspective

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Abstract

Hepatitis B virus (HBV) infection is an important health problem and the major cause of chronic hepatitis, cirrhosis as well as hepatocellular carcinoma (HCC) worldwide, especially in the Asia-Pacific region. The natural history of chronic HBV infection can be divided into 4 dynamic phases in HBV carriers who acquire the virus early in life. In general, the frequency and severity of hepatitis flares in the immune clearance or reactivation phase predict disease progression in HBV carriers, and early HBeAg or HBsAg seroconversion typically confers a favorable outcome. In contrast, late or absent HBeAg seroconversion after multiple hepatitis flares accelerates the progression of chronic hepatitis to cirrhosis. Recently, several hepatitis B viral factors predictive of clinical outcomes have been identified. For example, serum HBV DNA level at enrollment is the best predictor of adverse outcomes (cirrhosis, HCC and death from liver disease) in adults with chronic HBV infection. However, in HBeAg-negative patients with a low viral load (<2000 IU/mL), serum HBsAg level >1000 IU/mL increases the risk of HCC. In addition, HBV genotype C, basal core promoter (BCP) mutant and pre-S deletion mutant are associated with increased risk of HCC development. In contrast, combination of serum HBsAg < 10 IU/mL and HBV DNA <2000 IU/mL can predict HBsAg loss over time in HBeAg-negative patients with HBV genotype B or C infection. In conclusion, hepatitis B viral factors such as serum HBsAg level, viral load, genotype and mutants have already been clarified to influence disease progression of chronic hepatitis B in our region. Further studies are needed to investigate the pathogenic mechanisms of each viral factor.

TSA-01

The U.S. Drug Induced Liver Injury Network

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Drug Induced Liver Injury (DILI) remains the major adverse drug event that leads to termination of clinical development programs and regulatory actions including failure to approve for marketing, restricted indications, and withdrawal from the marketplace. The type of DILI that is most problematic is idiosyncratic meaning that only a very small fraction of treated patients are susceptible to the liver injury. Current preclinical models, even humanized ones, do not reliably identify molecules that have this liability and, conversely predict liabilities in molecule that are in fact quite safe for the liver. The best models to study DILI are probably the people who have actually experienced it.

The U.S. Drug Induced Liver Injury Network (DILIN) supported by the National Institutes of Health has created a registry of over 1,000 patients who have experienced DILI. Subjects are followed longitudinally to define natural history of DILI. Biospecimens including DNA, serum, plasma and urine are been collected from each subject, and identify links are maintained for allow re-contact of each subject for enrollment in additional studies.

Genome wide association analyses and whole exome/whole genome sequencing of certain DILI cases is well underway and appear promising in identifying risk factors. Serum biomarker analyses including proteomics, metabolomics and microRNA analysis have also yielded promising results.

DILIN is serving as a model research program for similar efforts around the world, including in Asia.

TSA-02

Global control of viral hepatitis: An Asian-Pacific perspective

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TSA-03

Natural History of Chronic Hepatitis B REVEALed: Update in 2012

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