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CMV in transplant recipients
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CMV has long been described as the Achilles heel of organ transplantation. CMV may produce direct effects such as fever, and end-organ damage, such as retinitis and colitis. CMV is also thought to produce indirect effects such as rejection, diabetes, and perhaps even graft atherosclerosis (in heart transplant recipients). Advances in viral diagnostics, plus the availability of ganciclovir and valganciclovir, however, have made CMV less fearsome than it used to be. In this lecture, we will review the data on both the prophylactic and pre-emptive modes of CMV prevention in organ transplant recipients, and ask ourselves if the technology that is now enabling us to measure host immunity to CMV has a role in clinical management.

Drug design and development against EV71 and other enteroviruses
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Enteroviruses are a family of single stranded, positive sense RNA virus of Picornaviridae. Although most of the enterovirus-associated diseases are mild and asymptomatic, some member in the family can cause severe diseases and death, especially in the young and immunocompromised. Enteroviruses are the leading cause of aseptic meningitis which in turn is the most common central nervous system infection. Enterovirus 71 (EV71), for example, is an important pathogen besides polioviruses of the family. It is emerging as the most significant neurotropic enterovirus in some area of the world in outbreaks and epidemics. This virus circulates in US, and 26% of the adults tested in a study had antibody. EV71 was the leading cause of infectious diseases in China in 2010. The outbreaks of EV71-associated diseases have been reported in the United States, Australia, Sweden, Japan, Bulgaria, Hungary, Malaysia, and other countries. It has been associated with a variety of clinical diseases, including hand, foot and mouth disease, herpangina, aseptic meningitis, encephalitis, poliomielitis-like paralysis, and even fatal pulmonary edema or hemorrhage. Enterovirus-associated disease can be both acute and chronic. The chronic diseases include dermatomyositis, polymyositis, dilated cardiomyopathy, and diabetes mellitus. There is an urgent need to develop therapeutics against EV71 in particular, and enteroviruses in general.

Upon infection, a polyprotein is translated from the single open reading in the genome of an enterovirus, which is processed into mature proteins by virally encoded proteinases. These proteinases are not only vital to the propagation of the virus but important factors in limiting host defense against the virus infection as well. We carry out structure-based screening, design, and development of inhibitors against the enterovirus infection using the proteinases as the targets. The lead compounds were generated after hits were identified by virtual screening, structure characterization, and medicinal chemistry. The lead compounds were improved by iterations of structure-based design, chemical synthesis, and functional assay. The resulting inhibitors are shown to be capable of inhibiting virus replication and restore host functions.

More and more coronaviruses after the SARS epidemic: human coronavirus HKU1 and other coronaviruses
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The recent SARS epidemic has boosted global interest in the discovery of novel human and animal coronaviruses. The number of coronavirus species with complete genomes available has increased from nine in 2003 to about 30 in 2011, of which nine, including human coronavirus HKU1 (Betacoronavirus subgroup A), SARS-related Rhinolophus bat coronavirus (Betacoronavirus subgroup B), Rhinolophus bat coronavirus HKU2 (Alphacoronavirus), three bat coronaviruses of two novel subgroups (C and D) in Betacoronavirus, and three avian coronaviruses which constitute a proposed novel genus (Deltacoronavirus) were sequenced by our laboratory. Recently, we have also developed a comprehensive database, CoVDB (http://covdb.microbiology.hku.hk), of annotated coronavirus genes and genomes, for rapid and accurate batch sequence retrieval, the cornerstone and bottleneck for comparative gene or genome analysis. With the increasing amount of genomes available and the user-friendly database, easy comparative genome analysis and more specific blast search results can be generated for efficient downstream analysis.

Management of the complications of liver cirrhosis
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Liver cirrhosis is defined as development of regenerative nodules surrounded by fibrous septa in response to chronic liver injury. This leads to vascular remodeling and giving rise to portal hypertension and end stage liver disease. Liver transplantation is the only treatment which improves both longevity and quality of life in patients with uncompensated liver cirrhosis. However every patient with compensated liver cirrhosis is not eligible for transplantation and it is not available for majority of the patients. Our current understanding of natural history, pathophysiology and treatment of complication has resulted in improved management quality of life and life expectancy in patients with compensated liver cirrhosis. Median survival of patients with compensated cirrhosis is 12 years while that of decompensated patients is reduced to 2 years. Approximately 5 to 7% of the patients change from compensated stage to decompensated stage. Portal hypertension (PH) is a universal consequence of cirrhosis responsible for most of the complications like esophageal varices, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome and hepatic encephalopathy. PH in cirrhosis is defined by hepatic venous pressure gradient (HVPG) more than 5mm of mercury. HVPG is indirect measure of portal pressure. Now it is clear that HVPG more
than 10 is significant PH above which the complications like variceal bleed and ascites develop. Currently proposed classification of cirrhosis is based on the degree of PH and associated clinical features. Development of ascites, variceal bleed and hepatic encephalopathy is considered to be decompensated cirrhosis. PH results from increase in the intrahepatic resistance which has dynamic and fixed components and it is coupled with increase in the portal blood flow. Therapeutic interventions which can reduce the HVPG like non-selective beta blockers and Transjugular intrahepatic portosystemic shunt (TIPS) can be helpful in combating complications of cirrhosis. And they have been shown to improve survival. Bacterial infection is common in cirrhosis with one month mortality of 30%. Oral prophylactic antibiotics or bowel decontamination have shown to improve long term outcome in patients with decompensated cirrhosis. Malnutrition is common in all patients with cirrhosis. Now it is clear there is no need of restricting the proteins in these patients. In fact nutritional therapy can improve survival, reduce the rate of infections, stay in ICU and hospital, and reduce post operative complications. Screening for hepatocellular carcinoma (HCC) can pick up very early disease and survival can be improved in these patients by offering curative treatment. Therapeutic modalities can reverse the cirrhosis. These modalities according to the etiology are (1) abstinence for alcoholic cirrhosis, (2) antiviral therapy for hepatitis B, (3) immunosuppression for autoimmune hepatitis, (4) relieving biliary obstruction in patients with secondary biliary cirrhosis, (5) antiviral therapy for hepatitis C and (6) relieving obstruction in patients with Budd Chiari syndrome. Future therapies like antifibrotic, antiangiogenic and anti coagulants may have potentials reducing fibrosis, reversing cirrhosis. Stem cell therapy may be helpful in patients with liver cirrhosis.

**PL-001** USP18 stimulates HCV production in vitro: a novel mechanism for HCV resistance to interferon therapy

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**Background:** The molecular mechanisms of interferon resistance in almost 50% of the HCV infected patients remain unclear. We have previously identified that upregulation of interferon stimulated genes (ISGs), such as Interferon Stimulated Gene15 (ISG15) and Ubiquitin Specific Protease 18 (USP18) in hepatocytes, predicts treatment failure. Moreover, silencing USP18 potentiates IFN anti-HCV activity and increased expression of ISG15 promotes HCV production. In this study we investigate the role of USP18 in HCV production.

**Methods:** We studied the effect of over-expression of wild type (catalytically active) USP18 or an enzymatically inactive mutant form of USP18 on HCV RNA replication and viral production in JFH1 culture system. Levels of various ISGs and of the critical miRNA 122 were assessed by real-time PCR, and surface expression of the key HCV entry receptor, CD81, were quantified by FACS.

**Results:** Over-expression of wild type and mutant USP18 increases HCV production at baseline (without IFN) and blunts the anti-HCV activity of IFNa by itself in the 122 system. While neither ISG expression nor miRNA 122 levels were unaffected by overexpression of USP18, whether in the presence or absence of IFNa, surface expression of CD81 was increased following USP18 over-expression in HuH7.7 cells.

**Conclusions:** These data indicate that USP18 overexpression leads to increased HCV production independent of its catalytic activity, and in concert with increased surface expression of CD81. Thus, USP18, one of the ISGs increased in chronic HCV infection, stimulates HCV production and likely contributes to treatment failure by promoting HCV cell entry and blunting IFN anti-HCV activity.

**CS016.3** New concept in nomenclature, classification and diagnosis of liver failure

Y.M. Wang*. Chongqing, China

Abstract not available

**CS016.4** Treatment strategy developments of hepatitis B with liver failure

Z.L. Gao*. Guangzhou, China

Abstract not available

**Free Paper Presentation 1: Hepatitis C**

Friday, July 15, 2011, 15:30–17:00
Meeting Room 310

**DL-001** Clinico-epidemiological profile of patients with hepatitis C virus infection seen in private practice clinics in Metro Manila

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**Background:** Hepatitis C virus (HCV) infection is a major public health problem worldwide. In the Philippines, there are few published data on the clinico-epidemiological profile of patients with HCV infection.

**Methodology:** Out-patient charts of patients seen from October 2005 to November 2010 in private practice clinics of 3 gastroenterologists were reviewed. All patients with a positive anti-HCV and/or HCV-RNA were included. Clinical and epidemiologic information were collected and analyzed.

**Results:** Of 49 patients included, 27 (55%) were males. Mean age at diagnosis was 48.3 years. 26 patients had HCV genotype data – genotype 1 in 16 (61%) patients, genotype 2 in 8 (31%), genotype 4 in 2 (8%). The most common risk factor was blood transfusion before 1990 identified in 18 (37%) patients. Other risk factors identified: injection drug use (IDU) 7 (14%), hemodialysis (HD) 7 (14%), unknown 11 (23%), others 5 (12%). At presentation, 17 (35%) patients had advanced HCV-related liver disease – 13 cirrhosis only and 4 hepatocellular carcinoma (HCC). Among 37 evaluable treatment-naive patients, 16 (43%) were ineligible for treatment with advanced HCV-related liver disease (69%) as the most common reason.

**Conclusion:** In this study, blood transfusion before 1990, IDU, and HD were the most common risk factors for HCV infection. Many patients had advanced liver disease precluding eligibility for therapy. Screening for HCV among those with a history of blood transfusion before 1990, IDU, and HD may help identify HCV-infected patients early allowing institution of antiviral therapy to prevent progressive liver disease.

**DL-002** Could furoxanstatin affect the sustained virological response in chronic hepatitis C virus treatment?

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**Background:** Hepatitis C viral (HCV) infection is the leading cause of death due to liver disease. Additional agents are...