Hepatitis Weekly

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Editor's Choice

Expanded Reporting

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Editor's Choice . . . August 2, 2004

Carol Kohn, ELS(D), Board Certified Diplomate Editor in the Life Sciences, Editor-in-Chief
Susan Hasty, Publisher
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Hepatitis C Virus Screening

Trak-C offers rapid screening for hepatitis C virus core antigen

2004 AUG 2 - (NewsRx.com) -- Trak-C offers rapid screening for hepatitis C virus core antigen.

"A new, sensitive enzyme immunoassay has been developed for detecting and quantifying total hepatitis C virus (HCV) core antigen in anti-HCV positive or negative sera ('trak-C', Ortho Clinical Diagnostics, Raritan, NJ). The purpose of this study was to evaluate the performance of trak-C as an additional laboratory diagnostic marker of viremia. The performance was compared to HCV-RNA detection in the 'screening' of sera from a large heterogeneous population of hospitalized patients and outpatients," scientists in Italy report.

"Six hundred and eighteen anti-HCV negative sera, 405 anti-HCV positive/HCV-RNA negative sera, 604 anti-HCV positive/HCV-RNA positive sera and 67 anti-HCV negative sera containing antigens or antibodies potentially interfering with the performance of the assay were analyzed. Supplemental HCV antibody testing was performed using a commercial strip immunoblot assay. HCV-RNA was investigated using a qualitative commercial assay," wrote P. Valcavi and colleagues, University of Parma, Microbiology Section.

"A quantitative commercial reverse transcriptase-polymerase chain reaction (RT-PCR) was used for the analysis of selected samples. Sensitivity and specificity values were 94.7% and 100%, respectively. The latter was also confirmed when anti-HCV negative samples containing potentially interfering antigens/antibodies were examined. Sensitivity below 100% was probably due to an antigenemia below the detection limit of trak-C."

"Besides, because 65.6% of HCV-RNA positive/trak-C negative samples presented specific antibodies against all four RIBA antigens, the hypothesis was raised that, in some cases, the dissociation step efficiency could be sub-optimal," researchers explained.

"In conclusion, trak-C seems suitable for identifying HCV infection on large based populations. It is a rapid to perform, reliable and specific assay that can be adapted to any laboratory setting."

Valcavi and colleagues published their study in *Journal of Medical Virology* (Evaluation of a total hepatitis C virus (HCV) core antigen assay for the detection of antigenaemia in anti-HCV positive individuals. J Med Virol, 2004;73(3):397-403).

For additional information, contact P. Valcavi, University Parma, Microbiology Sect, Department Pathology & Laboratory Med, Via Gramsci 14, I-43100 Parma, Italy.

The publisher's contact information for the *Journal of Medical Virology* is: Wiley-Liss, Division John Wiley & Sons Inc., 111 River St., Hoboken, NJ 07030 USA.

The information in this article comes under the major subject areas of Hepatitis C Virus, Hepatology, Immunology, Infectious Disease, Medical Devices, and Virology.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

Immunology

Human immunodeficiency virus fosters hepatitis C virus replication

2004 AUG 2 - (NewsRx.com) -- Human immunodeficiency virus fosters hepatitis C virus replication.

According to recent research from the United States, "hepatitis C virus (HCV) was found to replicate in monocytes/macrophages particularly in patients with human immunodeficiency virus type 1 (HIV-1) infection. This study was undertaken to determine whether HIV facilitates HCV infection of native human macrophages in vitro. Monocytes/ macrophages were collected from healthy donors infected with HIV M-tropic molecular clone, and then exposed to HCV-positive sera."

"Presence of positive and negative HCV RNA strands was determined with a novel strand-specific quantitative real-time reverse transcription-polymerase chain reaction (RT-PCR). Preceding as well as near-simultaneous infection with HIV made the macrophages more susceptible to infection with HCV; in particular, an HCV RNA-negative strand was detectable almost exclusively in the setting of concomitant HIV infection," reported T. Laskus and colleagues, Mayo Clinic, Division of Transplantation Medicine.

"Furthermore, HCV RNA load correlated with HIV replication level in the early stage of infection. The ratio of positive to negative strand in macrophages was lower than in control liver samples. HIV infection was also found to facilitate HCV replication in a Daudi B-cell line with engineered CD4 expression.

"It seems that HIV infection can facilitate replication of HCV in monocytes/macrophages either by rendering cells more susceptible to HCV infection or by increasing HCV replication. This could explain the presence of extrahepatic HCV replication in HIV-coinfected individuals," researchers concluded.

Laskus and colleagues published their study in *Blood* (Human immunodeficiency virus facilitates infection/replication of hepatitis C virus in native human macrophages. Blood, 2004;103(10):3854-3859).

For additional information, contact J. Rakela, Mayo Clinic, Division Transplantation Med, Dept. of Med, SC Johnson Bldg Sj3, Scottsdale, AZ 85259 USA.

Publisher contact information for the journal *Blood* is: American Society of Hematology, 1900 M Street. NW Suite 200, Washington, DC 20036 USA.

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Transplant Medicine

Sequential therapy treats recurrent hepatitis C after liver transplantation

2004 AUG 2 - (NewsRx.com) -- Sequential therapy treats recurrent hepatitis C after liver transplantation.

"Hepatitis C virus (HCV) infection invariably recurs after liver transplantation (LT), and sequels of chronic hepatitis of the graft are a significant cause of morbidity and mortality," researchers in Switzerland report.

"In an uncontrolled trial, 31 patients with histologically confirmed hepatitis C after LT received, sequentially, ribavirin (10 mg/kg body weight q.d.) for 12 weeks, followed by ribavirin at the same dose q.d. plus interferon-alpha (IFN-alpha) [3 million units three times a week (3 MU TIW)] for another 48 weeks. Based on an intent-to-treat analysis, the percentages of patients with undetectable HCV RNA in their serum were 0%, 38.7% and 45.2% after 12, 36 and 60 weeks of therapy, respectively," said E. Giostra and colleagues, University Hospital of Geneva, Division of Gastroenterology and Hepatology.

"A sustained virological response, as defined by undetectable serum HCV RNA 24 weeks after the end of treatment, was observed in 9/31 patients (29%). Sustained responders had a significant improvement of their liver inflammatory activity score (p=0.025), but not of their liver fibrosis score."

"The chances of sustained virological response correlated with the length of treatment, but not with the HCV genotype or baseline HCV RNA level," investigators noted.

"In conclusion, patients with recurrent hepatitis C after LT might benefit from ribavirin/IFN-alpha therapy, provided that the treatment is tolerated for a sufficient duration of time," they said.

Giostra and colleagues published their study in *Transplant International* (Ribavirin/interferon-alpha sequential treatment of recurrent hepatitis C after liver transplantation. Transplant Int, 2004;17(4):169-176).

For additional information, contact F. Negro, University Hospital Geneva, Division Gastroenterology & Hepatology, Rue Micheli Du Crest 24, CH-1211 Geneva, Switzerland.

Publisher contact information for the journal *Transplant International* is: Springer-Verlag, 175 Fifth Avenue, New York, NY 10010 USA.

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Viremia

Core antigen tests predict patient response to hepatitis C virus therapy

2004 AUG 2 - (NewsRx.com) -- Core antigen tests predict patient response to hepatitis C virus therapy.

According to a study from France, "a new quantitative marker of hepatitis C virus (HCV) viremia based on the detection of the core antigen of the virus has recently become commercially available in Europe. The usefulness of this test was examined for the management of patients treated with pegylated interferon/ribavirin. One hundred twenty-eight pegylated interferon/ribavirin treated patients were studied."

"Serum samples were available at baseline, week 4, and week 12 time-points, respectively. Core antigen was quantified using the trak-C assay (Ortho Clinical Diagnostics, Raritan, NJ). For all genotypes at week 4, the positive and negative predictive values of HCV core antigen were 81.4 and 92.9%, respectively, while at week 12 they were 67.9 and 100%, respectively," P. Pradat and colleagues, Hotel-Dieu, Department of Hepatology reported.

"These predictive values varied substantially according to viral genotype. Among patients with a negative core antigen level (<1.5 pg/ml) at week 12, only 33% of those who were positive at week 4 achieved a sustained virological response whereas 85% of those who were already negative did ($p<0.001$)."

"The core antigen assay may be used at week 4 and week 12 to distinguish patients who will achieve a sustained virological response from those who will relapse/breakthrough. This assay is a new reliable alternative for early prediction of virological non-response in patients treated with pegylated interferon/ribavirin," study authors indicated.

Pradat and colleagues published the results of their research in *Journal of Medical Virology* (The predictive value of core antigen testing for the management of hepatitis C patients receiving pegylated interferon/ribavirin treatment. J Med Virol, 2004;73(3):392-396).

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Virology

Spontaneous clearance is common with hepatitis C virus genotype 3 infections

2004 AUG 2 - (NewsRx.com) -- Spontaneous clearance is common with hepatitis C virus genotype 3 infections.

According to recent research published in the *Journal of Medical Virology*, "treating acute hepatitis C with interferon alpha prevents chronicity in nearly all cases when therapy is initiated within 3 months after infection. However, 15%-50% of untreated patients may clear the hepatitis C virus (HCV) spontaneously. Therefore, factors are needed to identify patients prior to therapy who have a higher or lower risk for developing a chronic course to avoid unnecessary treatment."

"The role of the HCV genotype for spontaneous recovery from acute hepatitis C has been discussed controversially. In the year 2002, all 1176 new incoming prisoners in a Northern German prison for young men (age 16-24) were screened for anti-HCV antibodies and 92 tested positive. Ninety-eight percent of these reported i.v.-drug abuse for a median of 32 months prior to imprisonment," reported M. Lehmann and colleagues, Hannover Medical School, Gastroenterology Hepatology and Endocrinology.

"HCV-RNA negative individuals (21%) were serotyped and HCV-RNA positive patients were genotyped. The prevalence of HCV genotype 3 was significantly higher among individuals who had cleared HCV spontaneously as compared to chronically infected patients (86% vs. 38%; p=0.002). Ninety-three percent of individuals exposed to HCV genotype 1 but only 63% of individuals exposed to genotype 3 experienced a chronic course of the infection (p=0.006). Thus, acute infection in young Caucasian men with HCV genotype 3 leads more often to spontaneous clearance than infection with HCV genotype-1."

"Considering also the high chance of successful treatment of chronic HCV genotype 3 infection with pegylated-interferon in combination with ribavirin, we suggest not to treat acute hepatitis C genotype 3 infection early but rather to wait at least 3 months after the onset of symptoms when chronicity becomes likely," investigators recommended.

Lehmann and colleagues published their study in *Journal of Medical Virology* (High rate of spontaneous clearance of acute hepatitis C virus genotype 3 infection. J Med Virol, 2004;73(3):387-391).

For additional information, contact H. Wedemeyer, Med Hochsch Hannover, Abt Gastroenterology Hepatology & Endokrinol, Carl Neuberg Str 1, D-30625 Hannover, Germany.

The publisher's contact information for the *Journal of Medical Virology* is: Wiley-Liss, Division John Wiley & Sons Inc., 111 River St., Hoboken, NJ 07030 USA.

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Expanded Reporting . . . August 2, 2004

Carol Kohn, ELS(D), Board Certified Diplomate Editor in the Life Sciences, Editor-in-Chief
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Alcoholism

Microarray analysis identifies changes in liver gene expression

2004 AUG 2 - (NewsRx.com) -- Microarray analysis has been used to identify alcohol-induced changes in hepatic gene expression.

"The mechanisms underlying alcoholic liver disease are not fully understood. It has been established that alcohol interferes with transcriptional and translational regulatory steps of cell function," scientists in Kentucky explained. "To understand such an effect, assessment of alcohol-induced changes in the simultaneous expression of a large number of genes may prove very useful."

With this in mind, I.V. Deaciuc and colleagues at the University of Louisville conducted a study "to test a large number of genes (approximately 8,700) for possible changes in expression induced by alcohol alone or in addition to treatment with lipopolysaccharide (LPS), a putative mediator of alcohol effects on the liver."

"Male rats were fed an alcohol-containing liquid diet (Lieber-DeCarli) for 14-15 weeks, injected with *Escherichia coli* LPS (0.8 mg/kg), and killed 24 hours later," according to the report. "Blood samples were taken for determination of plasma liver enzyme activity, and liver samples were obtained for histologic evaluation and total RNA extraction."

"Total RNA was analyzed for gene expression (Rat Toxicology U34 Array; Affymetrix, Santa Clara, CA). Of 8,740 genes on the microchip, 2,259 were expressed in the liver," published data indicated. "Seven hundred ninety-eight genes underwent significant changes induced by either alcohol or LPS, but listed in this article are only those that significantly increased or decreased expression twofold or more."

"Application of DNA microarray technology to the study of alcohol-induced liver injury generated novel theoretical and experimental approaches to alcohol-induced liver injury," the researchers concluded.

Deaciuc and coauthors published their study in *Alcohol* (Microarray gene analysis of the liver in a rat model of chronic, voluntary alcohol intake. Alcohol, 2004;32(2):113-127).

Additional information can be obtained by contacting I.V. Deaciuc, University of Louisville, Department of Medicine, School of Medicine, Division of Gastroenterology/Hepatology, 550 South Jackson St., Louisville, KY 40202 USA.

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The information in this article comes under the major subject areas of Alcoholism, Disease Associations, Genomics & Genetics, Gastroenterology, Hepatology and Medical Devices.

Breast Cancer

Tamoxifen metabolite R-isomer forms more DNA adducts in liver cells

2004 AUG 2 - (NewsRx.com) -- A tamoxifen metabolite R-isomer forms more DNA adducts in liver cells.

"The antiestrogenic drug tamoxifen forms DNA adducts in rat liver through two genotoxic metabolites, a-hydroxytamoxifen and alpha-hydroxy-N-desmethyltamoxifen. These have now each been resolved into R- and S-enantiomers.

"The work with a-hydroxytamoxifen was published earlier [Osborne, et al, (2001) Chem. Res. Toxicol. 14, 888-893]. Here, we publish results with a-hydroxy-N-desmethyltamoxifen," wrote scientists in the journal *Chemical Research in Toxicology*.

"We prepared the derivative N-ethoxycarbonyl-N-desmethyltamoxifen-alpha-S-camphanate, separated it into two diastereoisomers and hydrolyzed them to give (+)- and (-)-alpha-hydroxy-N-desmethyltamoxifen. The configuration of the (-)-isomer was shown to be S- by degradation of the above ester to a derivative of (-)-2-hydroxy-1-phenyl-1-propanone, which has already been shown to have S-configuration," M.R. Osborne and coworkers reported.

"The two enantiomers have the same chemical properties and were equally reactive toward DNA in vitro at pH 6. However," scientists said, "on treatment of rat hepatocytes in culture, R-(+)-alpha-hydroxy-N-desmethyltamoxifen gave 10 times as many DNA adducts as the S-(-)-isomer."

"This suggests that the R-isomer more readily undergoes sulfate conjugation to generate a reactive carbocation that attacks DNA," Osborne concluded.

Osborne and colleagues published their study in *Chemical Research in Toxicology* (Stereoselective metabolic activation of alpha-hydroxy-N-desmethyltamoxifen: The R-isomer forms more DNA adducts in rat liver cells. Chem Res Toxicol, 2004;17(5):697-701).

Additional information can be obtained by contacting M.R. Osborne, Institute of Cancer Research, Section of Molecular Carcinogenesis, Brookes Lawley Building, 15 Cotswold Rd., Sutton SM2 5NG, Surrey, England.

The publisher of the journal *Chemical Research in Toxicology* can be contacted at: American Chemical Society, 1155 16th St., NW, Washington, DC 20036 USA.

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Chronic Hepatitis C

Key hepatitis C-virus proteins rule interferon resistance mechanisms

2004 AUG 2 - (NewsRx.com) -- Key hepatitis C-virus proteins rule interferon resistance mechanisms.

"Typically, a biphasic decay of viremia can be observed during the first few weeks of interferon-based treatment in patients with chronic hepatitis C. The mathematical and statistical analysis of viral kinetics enables the estimation of individual kinetic parameters. Especially, the infected cell loss, the degradation rate of free virus, and an efficiency factor on blocking viral production can be estimated," scientists writing in the journal *Zeitschrift Fur Gastroenterologie* report.

"Furthermore, mathematical models of viral kinetics have the potential to reveal mechanisms of antiviral therapy. The lower sustained virologic response rates in several patient populations are reflected by impaired kinetic parameters. Besides host-specific and treatment-related differences, especially hepatitis C virus genotype strongly correlates with initial and long-term virologic responses," according to E. Herrmann and colleagues, University Clinical Center of the Saarlandes.

"Reasons for virologic response or non-response to interferon-based therapy for individual patients are unknown. Beside host-specific and treatment-related causes it is assumed that HCV is able to specifically evade the antiviral actions of interferon. So far, three HCV proteins [envelope (E)2, non-structural (NS) protein 3/4A, and NS5A protein] have been associated with interferon resistance mechanisms."

"However, within the E2 (HVR2, CD81 binding domains, PePHD) and NS3/4A proteins no specific mutations in correlation with virologic response to interferon-based antiviral therapy were observed. For the NS5A protein, mutations within the interferon sensitivity determining region (ISDR) and the complete NS5A protein may be of importance for virologic treatment response in patients infected with genotype HCV-1a/b isolates," researchers concluded.

Herrmann and colleagues published their study in *Zeitschrift Fur Gastroenterologie* (Hepatitis C-virus - Virus kinetics and resistance mechanisms. Z Gastroenterol, 2004;42(5):387-396).

Additional information can be obtained by contacting C. Sarrazin, University Klinikum Saarlandes, Klin Innere Med 2, Kirrberger Str, D-66421 Homburg, Germany.

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Diagnostics

Tests for hepatitis C virus infection show variable complementarity

2004 AUG 2 - (NewsRx.com) -- Tests for hepatitis C virus infection show variable complementarity.

"We localized hepatitis C virus (HCV) C-100 protein in liver biopsies of 15 patients with chronic hepatitis C using immunohistochemistry. The results were compared to serum, tissue extract analysis of HCV RNA and in situ reverse transcriptase-polymerase chain reaction (RT-PCR) described in a previous study," scientists writing in the *European Journal of Histochemistry* report.

"HCV was detected in 80% of the sera tested, in 40% of the tissue extracts and in 80% and 60% of the tissue sections tested by immunohistochemistry and in situ RT PCR respectively," stated L. Benkoel and colleagues, University of the Mediterranean, INSERM.

"Compared to the serum positive cases, 83% and 67% of the cases were respectively positive with immunohistochemistry and in situ-RT PCR and 41% were positive with tissue extract detection. Compared to the tissue extract positive cases, 25% and 50% of the cases were respectively positive with immunohistochemistry and in situ RT-PCR. Finally, 75% of the cases positive by immunohistochemistry were also positive by in situ RT-PCR."

"These results underline the complementarity of the different methods for the precise diagnosis of hepatitis C," researchers said.

Benkoel and colleagues published their study in *European Journal of Histochemistry* (Immunohistochemical detection of C-100 hepatitis C virus antigen in formaldehyde-fixed paraffin-embedded liver tissue. Correlation with serum, tissue and in situ RT PCR results. Eur J Histochem, 2004;48(2):185-190).

Additional information can be obtained by contacting L. Benkoel, University Mediterranee, INSERM, U Physiopathol Cellules Epitheliales 559, Faculty Med, 27 Blvd. Jean Moulin, F-13385 Marseille 05, France.

The publisher of the *European Journal of Histochemistry* can be contacted at: Luigi Ponzio E Figlio, Via D da Catalogna 1, 3, 27100 Pavia, Italy.

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Drug Delivery

Microparticles prolong the effect of glycyrrhetic acid in the liver

2004 AUG 2 - (NewsRx.com) -- Microparticles prolong the effect of glycyrrhetic acid in the liver.

"The microparticles (MPs) of an anti-hepatotoxic drug, glycyrrhetic acid (GLA), were prepared using poly(DL-lactic acid-co-glycolic acid) as a drug carrier, and their in-vitro properties, biodistribution and therapeutic effects were investigated," investigators in Japan report.

"The MPs showed a particle diameter distribution of 1.0-1.4 mcm and a drug content of approximately 10% (w/w). In the in-vitro release in a mixture of methanol and phosphate-buffered saline pH 7.4 (3:7, v/v), slow release was observed after an initial burst release of approximately 30% (w/w). After i.v. administration of MPs in normal mice, GLA was mainly distributed to the liver," according to H. Takahashi and colleagues, Hoshi University, Department of Drug Delivery Research.

"After i.v. administration in normal mice, the MPs maintained a much higher liver concentration than did GLA solution, and the plasma concentration also tended to be higher for MPs than for GLA solution. As to therapeutic effect, the liver was damaged by repeated injection of carbon tetrachloride (CCl[4]) in mice every 48 hours (h), and the drugs were administered intravenously as a single dose 3 h after the first injection of CCl[4]."

"At 10 mg GLA eq. Kg(-1), the MPs significantly suppressed the plasma level of glutamic pyruvic transaminase for at least 141 h after administration, while GLA solution did not become significantly effective within 45 h post-administration. MPs are suggested as a possible useful system to prolong the therapeutic effect of GLA," researchers concluded.

Takahashi and colleagues published their study in *Journal of Pharmacy and Pharmacology* (Glycyrrhetic acid-loaded microparticles: liver-specific delivery and therapeutic potential against carbon tetrachloride-induced hepatitis. J Pharm Pharmacol, 2004;56(4):437-444).

For additional information, contact H. Onishi, Hoshi University, Department Drug Delivery Research, Shinagawa Ku, 2-4-41 Ebara, Tokyo 1428501, Japan.

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Drug Development

Astilbin seizes control of tumor necrosis factor to abate liver injury

2004 AUG 2 - (NewsRx.com) -- Astilbin seizes control of tumor necrosis factor to abate liver injury.

According to recent research published in the *Journal of Pharmacy and Pharmacology*, "the aim of this study was to evaluate the effect of astilbin on concanavalin A (Con A)-induced hepatitis, a T cell-dependent model of liver injury. Con A administration resulted in a severe liver injury in mice, with a strong increment in spleen cell adhesion and liver infiltration of T cells, as well as in tumor necrosis factor (TNF)-alpha production."

"Against this liver injury, astilbin significantly inhibited the elevation in transaminase activity, reduced the TNF-alpha production, and improved the histological changes, including inflammatory infiltration, hepatocyte necrosis, and degeneration and Kupffer cell hyperplasia," wrote J. Wang and colleagues, Nanjing University, School of Life Sciences.

"In addition, astilbin inhibited the adhesion of spleen cells and purified T lymphocytes isolated from the liver-injured mice to fibronectin, laminin and type IV collagen. Moreover, the adhesion of human Jurkat T cells to endothelial cell line ECV-304 was also inhibited by astilbin."

"These results suggest that the improvement of the T cell-mediated liver injury by astilbin may be related to the reduction in TNF-alpha production and in T cell adhesion to extracellular matrices and endothelial cells," researchers concluded.

Wang and colleagues published their study in *Journal of Pharmacy and Pharmacology* (Astilbin prevents concanavalin A-induced liver injury by reducing TNF-alpha production and T lymphocyte adhesion. J Pharm Pharmacol, 2004;56(4):495-502).

For additional information, contact Q. Xu, Nanjing University, School Life Science, State Key Laboratory Pharmaceutical Biotechnology, 22 Han Kou Rd., Nanjing 210093, Peoples R China.

The publisher's contact information for the *Journal of Pharmacy and Pharmacology* is: Royal Pharmaceutical Society Great Britain, 1 Lambeth High St., London SE1 7JN, England.

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Hematologic Disease

Hepatitis C virus associates with thrombocytopenia formation

2004 AUG 2 - (NewsRx.com) -- Hepatitis C virus associates with thrombocytopenia formation.

"Chronic hepatitis C virus (HCV) infection has also been associated with the development of several extrahepatic alterations, including thrombocytopenia, and a variety of pathogenic mechanisms are reported to be implicated in this hematological abnormality. Different studies have succeeded in detecting HCV in platelets with discrepant results. Moreover, most of the studies on HCV-associated thrombocytopenia have failed to provide data concerning the infecting genotype, a factor with prognostic implication in chronically HCV-infected patients," scientists in Brazil report.

"To determine whether thrombocytopenia is an extrahepatic alteration dependent on particular HCV genotypes, and to assess the relationship between thrombocytopenia and detection of HCV-RNA (positive strand) in platelets from patients with chronic HCV infection, 106 anti-HCV+/HCV-RNA+ patients (57 thrombocytopenic and 49 non-thrombocytopenic) were prospectively studied," said A.J. deAlmeida and colleagues, University of Rio de Janeiro, Hematology Unit.

"The infecting genotype was analyzed from sera by using direct nucleotide sequencing of the polymerase chain reaction (PCR) products from core region. Genotypes 1a, 1b, and 3a were more prevalent in our patients, and no association between these genotypes and thrombocytopenia was observed (p=0.891)."

"HCV-RNA was detected in platelets by reverse transcriptase (RT)-nested PCR in the 5' non-coding region with a higher frequency (60%) in thrombocytopenic patients than in non-thrombocytopenic subjects (35%, p=0.017), suggesting that HCV is directly involved in the process that, at least in part, leads to thrombocytopenia," researchers concluded.

deAlmeida and colleagues published their study in *Annals of Hematology* (Hepatitis C virus-associated thrombocytopenia: a controlled prospective, virological study. Ann Hematol, 2004;83(7):434-440).

For more information, contact A.J. deAlmeida, University Rio de Janeiro, Hematology Unit, Med Clinical B, School of Medicine & Surgery, Department General Med, Gaffree & Guinle University Hospital, Rio De Janeiro, Brazil.

Publisher contact information for the journal *Annals of Hematology* is: Springer-Verlag, 175 Fifth Avenue, New York, NY 10010 USA.

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Hematology

Hemophagocytic syndrome can erupt after liver transplantation

2004 AUG 2 - (NewsRx.com) -- Hemophagocytic syndrome can erupt after liver transplantation.

According to a study from Spain, "The hemophagocytic syndrome is defined as a proliferation of phagocytic macrophages in the bone marrow, lymph nodes and spleen. Clinically, it is characterized by fever and pancytopenia. We present here a case of hemophagocytic syndrome after liver transplantation in a 63-year-old man who had undergone transplantation for autoimmune hepatitis."

"One month after liver transplantation, he developed ascites, fever and progressive pancytopenia. Bone marrow biopsy showed proliferation of non-neoplastic histiocytes, demonstrating phagocytosis of hemopoietic cells. No infectious or neoplasm-associated disease was found. Several kinds of treatment were attempted, but the course was fatal," according to L. Llado and colleagues, Bellvitge Hospital, Department of Surgery.

"The hemophagocytic syndrome is uncommon after liver transplantation, but this diagnosis has to be kept in mind in cases of pancytopenia of unknown origin," researchers cautioned.

Llado and colleagues published the results of their research in *Transplant International* (Hemophagocytic syndrome after liver transplantation in adults. Transplant Int, 2004;17(4):221-223).

For additional information, contact J. Figueras, Bellvitge Hospital, Department Surgery, Liver Transplant Unit, C-Feixa Llarga S-N, Barcelona 08907, Spain.

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Hematology

Novel human platelet septin SEPT8 is interaction partner of SEPT4

2004 AUG 2 - (NewsRx.com) -- The novel human platelet septin SEPT8 is an interaction partner of SEPT4.

"Septins are a family of GTP-binding proteins, which are essential for active membrane movement such as cytokinesis and vesicle trafficking. In non-dividing cells (such as platelets and neurons) septins are implicated in exocytosis. Platelets from a SEPT5 knockout mouse showed an altered serotonin secretion and platelet aggregation, suggesting that SEPT5 is involved in secretion in platelets," investigators in Germany report.

"Septins form complexes consisting of multiple septin polypeptides," said Susanne Blaser and colleagues at University Hospital Freiburg. "Using the yeast two-hybrid system we had demonstrated that SEPT5 partners with SEPT8. The aim of this study was to identify other interaction partners of the human platelet septin SEPT8. Using the yeast two-hybrid system with SEPT8 as bait protein, we identified the human septin SEPT4 as an interaction partner of SEPT8. The interaction between SEPT4 and SEPT8 was confirmed by immunoprecipitation. Expression analysis revealed that SEPT4 is also expressed in human platelets."

"Thus, SEPT4 is the third described platelet septin besides SEPTS and SEPT8," stated Blaser and her collaborators. "Transmission electron microscopy of platelets revealed that SEPT8 and SEPT4 are localized surrounding alpha-granules (as it had been shown for the septin SEPT5) suggesting that the three septins may be components of the septin complex in platelets and contribute in such a way to platelet biology. Activation of platelets by agonists resulted in the translocation of SEPT4 and SEPT8 to the platelet surface indicating a possible functional role of these proteins in platelet granular secretion."

Blaser and her coauthors published their study in *Thrombosis and Haemostasis* (The novel human platelet septin SEPT8 is an interaction partner of SEPT4. Thromb Haemost, 2004;91(5):959-966).

For additional information, contact Barbara Zieger, Department of Pediatrics and Adolescent Medicine, University Hospital Freiburg, Mathildenstrasse 1, D-79106 Freiburg, Germany. E-mail: zieger@kikli.ukl.uni-freiburg.de.

The publisher of the journal *Thrombosis and Haemostasis* can be contacted at: Schattauer GmbH-Verlag Medizin Naturwissenschaften, Holderlinstrasse 3, D-70174 Stuttgart, Germany.

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This article was prepared by Hepatitis Weekly editors from staff and other reports.

Hepatitis A Vaccine

Live and inactivated hepatitis A vaccines induced immunity in children

2004 AUG 2 - (NewsRx.com) -- Live attenuated and inactivated hepatitis A vaccines induced anti-HAV immune responses in children.

"The immunogenicity of a live attenuated HAV vaccine and an inactivated HAV vaccine was compared. Altogether 117 children were vaccinated with either the inactivated or the live attenuated vaccine. Children were bled at months 1, 6, 7, 12, and 24, and the anti-HAV total IgG antibody and IgG subclass profile were assessed," researchers in China report.

"In both vaccinated groups, the geometric mean titer (GMT) of anti-HAV peaked 7 months after the initial dose and declined during the following months," said Xuan-Yi Wang and colleagues at Fudan University. "The IgG subclass profiles in both vaccinated groups were highly restricted to IgG1 and IgG3. Both vaccines have been shown highly effective in preventing viral hepatitis A in former studies."

Wang and associates published their study in *Vaccine* (Immune responses of anti-HAV in children vaccinated with live attenuated and inactivated hepatitis A vaccines. Vaccine, 2004;22(15-16):1941-1945).

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The information in this article comes under the major subject areas of Hepatitis A Vaccine, Hepatitis A Virus, Hepatology, Vaccine Development, Vaccine Efficacy, Immunology, and Immunotherapy.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

Hepatitis A Vaccine

Methods predict hepatitis A vaccination in men who have sex with men

2004 AUG 2 - (NewsRx.com) -- Scientists have developed methods predictive of hepatitis A vaccination in a sample of men who have sex with men.

According to recent research published in the journal *Health Education Research*, "Studies continue to show that the majority of men who have sex with men (MSM) in the U.S. remain unvaccinated against the hepatitis A virus (HAV). Such limited vaccination coverage is a missed opportunity to prevent disease. This study was designed to develop reliable and valid theory-based quantitative measures to understand beliefs and attitudes regarding HAV vaccination among MSM."

"A convenience sample of 358 patrons of two gay bars in Birmingham, Alabama, completed a theory-based questionnaire," stated Scott D. Rhodes and Ramiro Arceo at Wake Forest University in the U.S. "Data were randomly split into two groups. Exploratory factor analysis (EFA) was performed on the first split-half sample to identify factor structure using standard principal component analysis. Confirmatory factor analysis (CFA) was performed on the remaining half sample using structural equation modeling."

"EFA revealed five scales measuring beliefs about HAV vaccination, including: perceived barriers and benefits associated with HAV vaccination; perceived severity and susceptibility related to hepatitis A infection; and perceived self-efficacy to complete the two-dose vaccine series," reported Rhodes and Arceo. "CFA revealed acceptable absolute model fits for four scales and excellent comparative model fits for all five scales. Multivariable analysis further validated the scales."

The researchers concluded, "Although the results should be tested further, these findings propose standardized measures that may be useful in assessing the beliefs and attitudes of MSM towards HAV vaccination to guide intervention design and evaluation."

Rhodes and Arceo published their study in *Health Education Research* (Developing and testing measures predictive of hepatitis A vaccination in a sample of men who have sex with men. Health Educ Res, 2004;19(3):272-283).

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The publisher's contact information for the journal *Health Education Research* is: Oxford University Press, Great Clarendon Street, Oxford OX2 6DP, England.

The information in this article comes under the major subject areas of Hepatitis A Vaccine, Hepatitis A Virus, Hepatology, Men's Health, and Virology.

Hepatitis B Vaccine

Deficit in dendritic cell-T cell interaction crucial in hepatitis B

2004 AUG 2 - (NewsRx.com) -- A selective functional deficit in dendritic cell-T cell interactions is a crucial mechanism in chronic hepatitis B virus infection.

"A defect in specific T cell immunity has long been assumed to be the central mechanism of persistent Hepatitis B virus (HBV) infection. Recent studies on HBV transgenic mice have suggested. However, that functional deficit of dendritic cells (DC) was an underlying cause for the T cell dysfunction," investigators in China report.

"The functions of monocyte-derived DC were determined by studying 75 subjects that included chronic hepatitis B patients with low or high HBV load; antibody to hepatitis B surface antigen (anti-HBs)-positive individuals who had recovered completely from previous acute HBV infection; healthy donors who had received hepatitis B vaccination and were anti-HBs positive; and immunologically naive to HBV or the vaccine individual," said B. J. Zheng and collaborators at Fudan University, the University of Hong Kong, and Queen Elizabeth Hospital in Hong Kong. "Impaired interactions between monocyte-derived DC and T cells were shown in chronic HBV infection patients, especially in those with active virus replication."

The researchers reported, "The dysfunctions included: failure of DC to increase human leukocyte antigen (HLA-II), B7 expression and interleukin-12 secretion in responses to hepatitis B surface antigen (HBsAg); defective induction of T cell proliferative response to HbsAg; and failure to activate T cells to produce cytokines and (iv) deficit in the induction of antigen specific cytotoxic T lymphocytes (CTLs). In vitro treatment of DC with tumor necrosis factor-alpha improved HLA-II and B7 expression, as well as Th cell and CTL responses."

"It is concluded that defective DC-T cell interactions may account for the specific T cell immune defects in chronic HBV infection," stated the scientists. "Immunotherapy that aims at restoring DC functions could offer a new opportunity for effectively managing persistent HBV infections."

Zheng and associates published their study in the *Journal of Viral Hepatitis* (Selective functional deficit in dendritic cell - T cell interaction is a crucial mechanism in chronic hepatitis B virus infection. J Viral Hepatitis, 2004;11(3):217-224).

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The publisher of the *Journal of Viral Hepatitis* can be contacted at: Blackwell Publishing Ltd., 9600 Garsington Road, Oxford OX4 2DG, Oxon, England.

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Hepatitis C Virus

CHMP recommends approval of shorter course of PegIntron/Rebetol therapy

2004 AUG 2 - (NewsRx.com) -- Schering-Plough Europe reported the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency has issued a positive opinion recommending approval of a shorter 24-week course of PegIntron (peginterferon alfa-2b) and Rebetol (ribavirin) combination therapy for patients chronically infected with hepatitis C virus (HCV) genotypes 2 or 3.

PegIntron is currently approved in the European Union (EU) for a 48-week course of therapy. Infection rates for HCV genotypes 2 and 3 vary by geography and account for approximately 30-50% of HCV infections among European patients.

The CHMP recommendation serves as the basis for a European Commission approval. A commission decision will result in marketing authorization with

unified labeling covering the shorter 24-week course of PegIntron and Rebetol combination therapy for genotypes 2 and 3 that will be valid in the current EU 25 member states as well as in Iceland and Norway.

The positive opinion recommending the labeling change for PegIntron and Rebetol is based largely on results of a clinical study published in the June 2004 issue of the *Journal of Hepatology* investigating the safety and efficacy of a shorter, 24-week course of individualized, weight-based PegIntron and Rebetol combination therapy compared with an historical control of 48 weeks of treatment.

In the study, patients infected with chronic hepatitis C genotypes 2 or 3 were treated effectively with only 24 weeks of PegIntron and Rebetol combination therapy, with 81% of patients overall (93% for genotype 2 and 79% for genotype 3) achieving a sustained virologic response (SVR). SVR is defined as the sustained undetectability of HCV 6 months following the end of treatment and was the study's primary endpoint. The study also showed that the overall safety profile of the 24-week PegIntron and Rebetol treatment regimen was improved compared with that of the historical control of patients treated for 48 weeks and receiving <10.6 mg/kg of ribavirin daily.

"The results of this clinical study clearly demonstrate that shorter treatment durations can be effective for specific hepatitis C patient groups," said Robert J. Spiegel, MD, chief medical officer and senior vice president of medical affairs, Schering-Plough Research Institute. "The study also showed that the shorter treatment regimen was better-tolerated by patients as compared with a 48-week historical control group."

PegIntron and Rebetol combination therapy for chronic hepatitis C was approved in the European Union in March 2001. PegIntron had previously received centralized marketing authorization in the EU and is marketed as a monotherapy in cases of intolerance or contraindication to ribavirin for the treatment of adult patients with chronic hepatitis C.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

Hepatitis C Virus

HCV screening for drug users/transfusion patients only is most cost-effective

2004 AUG 2 - (NewsRx.com) -- Hepatitis C virus screening for drug users and transfusion patients only is the most cost-effective.

According to recent research published in the journal *Gastroenterologie Clinique Et Biologique*, "Hepatitis C viral infection (HCV) is a frequent and severe disease; screening strategies to-date remain insufficient." The objective of this study was to "assess the efficiency of HCV screening of high-risk groups among patients consulting general practitioners."

"A cost-effectiveness analysis was performed involving general medicine screening practices recorded during a survey of 127 practitioners (10,041 patients) conducted in 1997. A reference strategy, defined as HCV screening for illicit drug users and transfused patients, and five extended strategies, where the screening population was broadened to include other risk groups as well, were considered," V. Josset and colleagues wrote.

"Average cost and marginal cost-effectiveness ratios were determined for each extended strategy and compared with those observed for the reference strategy. The sensitivity of HCV screening to funding modalities, HCV seroprevalence and proportion of HCV high-risk groups among patients attending general practitioners was studied," Josset continued.

"The reference strategy was the most cost-effective method irrespective of the funding modality considered. Fixed practitioner payment was the least efficient funding modality. The average cost of one positive test was sensitive to variations of HCV seroprevalence in the high-risk group as well as the proportion of high-risk patients among the general practitioners' patients," reported investigators.

The authors concluded, "Extension of hepatitis C screening to risk groups other than transfused patients and illicit drug users implies a substantial increase in healthcare costs as well as social consensus for such expenditures."

Josset and colleagues published their study in *Gastroenterologie Clinique Et Biologique* (Efficiency of hepatitis C virus screening strategies in general practice. Gastroen Clin Biol, 2004;28(4):351-357).

For additional information, contact V. Josset, CHU Rouen, DESP, 1, Rue Germont, F-76031 Rouen, France.

The publisher's contact information for the journal *Gastroenterologie Clinique Et Biologique* is: Masson Editeur, 21 Street Camille Desmoulins, Issy, 92789 Moulineaux Cedex 9, France.

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This article was prepared by Hepatitis Weekly editors from staff and other reports.

Hepatitis C Virus

History of intravenous drug use strongest predictor for HIV/HCV coinfection

2004 AUG 2 - (NewsRx.com) -- A history of intravenous drug use is the strongest predictor for HIV/HCV coinfection.

"The declining incidence of AIDS-related opportunistic diseases among people with HIV infection has shifted the focus of clinical management to prevention and treatment of comorbidities such as chronic liver disease. The increased risk of hepatitis C virus (HCV)-related advanced liver disease in people with HIV infection makes early HCV diagnosis a priority.

"To assess HCV prevalence and predictors of HIV/HCV coinfection, we have conducted a retrospective analysis of people enrolled in the CAESAR (Canada, Australia, Europe, South Africa) study, a multinational randomized placebo-controlled study of the addition of lamivudine to background antiretroviral therapy," researchers in Australia report.

"The impact of HCV on HIV disease progression was also examined. Anti-HCV antibody testing on 1649 CAESAR study participants demonstrated a HIV/HCV coinfection prevalence of 16.1%, which varied from 1.9% in South Africa to 48.6% in Italy," wrote J. Amin and coworkers.

"The strongest predictor of HIV/HCV coinfection was HIV exposure category (p<.0001), with odds ratios (ORs) compared to homosexual as follows: injecting drug use (IDU), 365 [95% confidence interval (Cl): 179-742]; transfusion or blood products, 32.2 (95% Cl: 15.2-67.6); homosexual and IDU, 22.9 (95% CI: 8.5-62.1). The prevalence of HIV/HCV was low (3.7%) among homosexual men without reported IDU.

"Other predictors of HIV/HCV coinfection were alanine aminotransferase (ALT), country of residence, ethnicity and stage of HIV disease," continued Amin. "A history of IDU or ALT (<=)40 U/L at baseline had a positive predictive value (PPV) of 35%, negative predictive value (NPV) of 96%, sensitivity of 82% and specificity of 71% for HIV/HCV coinfection.

"HIV disease progression was similar in HIV monoinfected and HIV/HCV coinfected patients."

"People with HIV and a history of IDU or elevated liver function tests should be targeted for HCV testing. The low prevalence of HIV/HCV coinfection among homosexual men without a history of IDU suggests low efficiency of sexual HCV transmission," the authors concluded.

Amin and colleagues published their study in *HIV Medicine* (HIV and hepatitis C coinfection within the CAESAR study. HIV Med, 2004;5(3):174-179).

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Publisher contact information for the journal *HIV Medicine* is: Blackwell Publishing Ltd., 9600 Garsington Rd., Oxford OX4 2DG, Oxon, England.

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Hepatocellular Carcinoma

Kinectin splicing in HCC characterized

2004 AUG 2 - (NewsRx.com) -- Kinectin splicing has been characterized in tissue from HCC patients.

"To extend the search for hepatocellular carcinoma (HCC)-associated antigens with immunogenicity for clinical applications," scientists in China "constructed a cDNA expression library using resected human HCC tissue sample and screened it by serological analysis of recombinant cDNA expression library (SEREX) with autologous and allogeneic sera."

"A total of 24 distinct antigens were isolated and kinectin was the antigen most frequently identified," reported H.C. Wang and coauthors at Peking University.

They found that "kinectin was alternatively spliced at four sites," and "obtained all eight theoretical forms of variant, six by SEREX and two by RT-PCR, from the different splicing combinations of the last three sites," published results indicated. "In addition, the splicing patterns of four sites were analyzed. Variant containing D2 was overexpressed in cancerous tissues and this alteration may be tumor-associated."

"The four splicing sites, the variants generated by alternative splicing, and the humoral immune response in HCC patients, may help to analyze the role of kinectin in human HCC cell biology," the researchers concluded.

Wang and colleagues published their study in *Biochemistry and Cell Biology - Biochimie Et Biologie Cellulaire* (Multiple variants and a differential splicing pattern of kinectin in human hepatocellular carcinoma. Biochem Cell Biol, 2004;82(2):321-327).

For additional information, contact W.F. Chen, Peking University, Health Science Center, School of Basic Medical Science, Department of Immunology, 38 Xue Yuan Rd., Beijing 100083, China.

The publisher's contact information for the journal *Biochemistry and Cell Biology - Biochimie Et Biologie Cellulaire* is: National Research Council Canada, Research Journals, Montreal Rd., Ottawa, Ontario K1A 0R6, Canada.

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Hepatocellular Carcinoma

PIN1 overexpression/beta-catenin gene mutations distinct oncogenic events in HCC

2004 AUG 2 - (NewsRx.com) -- PIN1 overexpression/beta-catenin gene mutations are distinct oncogenic events in hepatocellular carcinoma.

"The peptidyl-prolyl-isomerase, PIN1, upregulates beta-catenin by inhibiting its interaction with APC. Beta-catenin accumulation occurs in about 70% of hepatocellular carcinoma (HCC), of which only 20% are due to beta-catenin mutations. The role of PIN1 in beta-catenin upregulation in HCC was investigated," scientists writing in the journal *Oncogene* report.

PIN1 was "overexpressed in more than 50% of HCC. All cases with PIN1 overexpression also showed beta-catenin accumulation, with 68% of cases showing concomitant beta-catenin and cyclin D1 accumulation," wrote R. Pang and coauthors.

Researchers continued, "PIN1 was shown to contribute to beta-catenin and cyclin D1 overexpression directly by in vitro cell-line transfection experiments."

"Finally," Pang concluded, "we showed that PIN1 overexpression and beta-catenin gene mutations appeared to be mutually exclusive events, leading to beta-catenin accumulation in HCC."

These results showed that PIN1 overexpression leading to beta-catenin accumulation might be a critical event in hepatocarcinogenesis and that PIN1 is a potential target for therapeutic intervention in HCC," wrote R. Pang

Pang and colleagues published their study in *Oncogene* (PIN1 overexpression and beta-catenin gene mutations are distinct oncogenic events in human hepatocellular carcinoma. Oncogene, 2004;23(23):4182-4186).

Additional information can be obtained by contacting Y.L. Kwong, University of Hong Kong, Queen Mary Hospital, Department of Medicine, Division of Hematology/Oncology, Hong Kong, Peoples R China.

The publisher of the journal *Oncogene* can be contacted at: Nature Publishing Group, Macmillan Building, 4 Crinan St., London N1 9XW, England.

The information in this article comes under the major subject areas of Hepatology, Liver Cancer and Genomics & Genetics.

Hepatology

TWEAK expression may play a central role in liver cancer proliferation

2004 AUG 2 - (NewsRx.com) -- TWEAK expression may play a central role in liver cancer proliferation.

According to a study from Japan, "tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) is a member of the TNF family whose transcripts are expressed in various human tissues. Since TWEAK has a variety of biological activities, we investigated TWEAK sensitivity, expression, and physiological role in human hepatocellular carcinomas (HCCs). Tweak receptor was detected in four kinds of HCC cells."

"TWEAK significantly promoted cell proliferation and induced nuclear factor-kappaB activation in all HCC cells. Surprisingly, we found that HCC cells constitutively express TWEAK. In addition, soluble TWEAK was detected in culture medium. We found that TWEAK also promotes cell proliferation and induces the secretion of interleukin (IL)-8 and monocyte chemoattractant protein (MCP-1) in human umbilical vein endothelial cell," T. Kawakita and colleagues, Mie University, School of Medicine reported.

"Finally, culture medium from Sh-Hep1 cells incubated with anti-TWEAK antibody significantly inhibited endothelial cell tube formation.

"In conclusion, these results indicate that TWEAK might play a critical role in HCC cellular proliferation using both autocrine and paracrine mechanisms, and modulate tumor-related angiogenesis," Kawakita and coauthors advised.

Kawakita and colleagues published the results of their research in *Biochemical and Biophysical Research Communications* (Functional expression of TWEAK in human hepatocellular carcinoma: possible implication in cell proliferation and tumor angiogenesis. Biochem Biophys Res Commun, 2004;318(3):726-733).

For additional information, contact K. Shiraki, Mie University, School of Medicine, Department Internal Medicine 1, Tsu, Mie 5148507, Japan.

The publisher of the journal *Biochemical and Biophysical Research Communications* can be contacted at: Academic Press Inc. Elsevier Science, 525 B St., Ste. 1900, San Diego, CA 92101-4495 USA.

The information in this article comes under the major subject areas of Hepatology, Liver Cancer, and Oncology.

Immunology

Hepatitis C virus core binding to T cell gC1qR impairs Lck and Akt activation

2004 AUG 2 - (NewsRx.com) -- Hepatitis C virus core binding to T cell gC1qR impairs Lck and Akt activation.

According to recent research from the United States, "complement plays a pivotal role in the regulation of innate and adaptive immunity. It has been shown that the binding of C1q, a natural ligand of gC1qR on T cells inhibits their proliferation. Here, we demonstrate that direct binding of the hepatitis C virus (HCV) core to gC1qR on T cells leads to impaired Lck/Akt activation and T-cell function."

"The HCV core associates with the surface of T cells specifically via gC1qR, as this binding is inhibited by the addition of either anti-gC1qR antibody or soluble gC1qR. The binding affinity constant of core protein for gC1qR, as determined by BIAcore analysis, is 3.8 x 10(-7) M," reported Z.Q. Yao and colleagues, University of Virginia, Department of Microbiology.

"The specificity of the HCV core-gC1qR interaction is confirmed by reduced core binding on Molt-4 T cells treated with gC1qR-silencing small interfering RNA and enhanced core binding on GPC-16 guinea pig cells transfected with human gC1qR. Interestingly, gC1qR is expressed at higher levels on CD8+ than on CD4+ T cells, resulting in more severe core-induced suppression of the CD8+-T-cell population."

"Importantly, T-cell receptor-mediated activation of the Src kinases Lck and ZAP-70 but not Fyn and the phosphorylation of Akt are impaired by the HCV core, suggesting that it inhibits the very early events of T-cell activation," researchers concluded.

Yao and colleagues published their study in *Journal of Virology* (Direct binding of hepatitis C virus core to gC1qR on CD4+ and CD8+ T cells leads to impaired activation of Lck and Akt. J Virol, 2004;78(12):6409-6419).

For additional information, contact Y.S. Hahn, University Virginia, Department Microbiology, HSC Box 801386, Charlottesville, VA 22908 USA.

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Immunology

Immunoglobulin GM genotype heightens susceptibility to hepatitis C infection

2004 AUG 2 - (NewsRx.com) -- Immunoglobulin GM genotype heightens susceptibility to hepatitis C infection.

"Hepatitis C virus (HCV) is a major health problem, affecting over 170 million people worldwide. HCV causes a wide spectrum of liver disease, varying from persistent to asymptomatic infection. To evaluate the role of immunoglobulin (Ig) GM and KM genes in HCV infection, 191 HCV-infected Thai subjects were studied," investigators in Thailand report.

"These included 43 individuals with transient HCV infection and 148 individuals with persistent chronic HCV infection. The controls consisted of 134 healthy individuals. Several GM and KM alleles were determined by polymerase chain reaction-based methods," wrote S. Vejbaesya and colleagues, Mahidol University, Siriraj Hospital.

"The frequency of G1M(f) homozygotes was lower (52.4% vs. 64.2%, p=0.03) and the frequency of G1M(z) homozygotes was higher (10.5% vs. 3.7%, p=0.02) in patients than the respective frequencies in controls."

"These results suggest that GM genotypes make a significant contribution to the risk of acquiring HCV infection," scientists concluded.

Vejbaesya and colleagues published their study in *Journal of Medical Virology* (Immunoglobulin GM and KM genotypes in hepatitis C virus infection. J Med Virol, 2004;73 (3):384-386).

For additional information, contact S. Vejbaesya, Mahidol University, Siriraj Hospital, Faculty Med, Department Transfusion Med, 2 Pranok Rd., Bangkok 10700, Thailand.

The publisher of the *Journal of Medical Virology* can be contacted at: Wiley-Liss, Division John Wiley & Sons Inc., 111 River St., Hoboken, NJ 07030 USA.

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Legal Issues

Safety needle devices maker settles antitrust suit against Becton Dickinson

2004 AUG 2 - (NewsRx.com) -- Retractable Technologies, Inc., (AMEX:RVP) announced that it has settled its longstanding federal antitrust suit against Becton Dickinson (BD) for $100 million in cash.

After legal fees and other expenses the company will receive the majority of these proceeds. The lawsuit, which was originally filed in a Texas state court in 1998, was scheduled to go to trial in federal court in Texarkana, Texas, with testimony slated to begin July 12.

"This is a major victory for Retractable Technologies, Inc. and healthcare workers in the U. S. and around the world," said Thomas J. Shaw, president and CEO.

"In our view, the substantial amount of this settlement vindicates our allegations that BD has blocked our life-saving technology from being used in American and overseas medical facilities, thereby endangering the lives of thousands of healthcare workers who have suffered accidental needlestick injuries, and millions more patients who have contracted deadly diseases such as HIV/AIDS and hepatitis C through needle reuse. Such injuries are preventable using Retractable's VanishPoint safety needle devices," continued Shaw.

"Accidental needlestick injuries and the reuse of conventional disposable syringes are widely regarded as being major causes of transmission of HIV/AIDS and other blood-borne diseases, especially in the developing world.

Shaw added, "While we are confident we would have prevailed at trial, we decided to settle because any resulting verdict and judgment would have been subject to the delays associated with an appeal. With this settlement behind us, we will be in a strong position to market our products to customers in the U.S. and overseas by stressing the superior safety, reliability, and cost-effectiveness of our products."

As part of the settlement with BD, each company released the other from causes of action based on conduct up to the settlement date. In May 2003, Retractable settled with the other three original defendants in the federal antitrust case for cash and other consideration. Those defendants were Novation and Premier Inc., the two largest hospital group purchasing organizations (GPOs), and Tyco International, the second largest U.S. needle device manufacturer.

Retractable Technologies, Inc. (AMEX:RVP) is a maker of safety needle devices.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

Mergers and Acquisitions

Acquisition of Integrity Healthcare Services complete

2004 AUG 2 - (NewsRx.com) -- Priority Healthcare Corporation (NASDAQ:PHCC) announced that it has closed the acquisition of Integrity Healthcare Services.

Integrity Healthcare Services is a specialty infusion pharmacy with 23 branches in 16 states.

"We are excited about our acquisition of Integrity Healthcare," said Steve Cosler, president and chief executive officer of Priority Healthcare. "In addition, we are pleased with the positive response we have received about the transaction from several of our key payor, physician and manufacturer customers."

Integrity Healthcare provides comprehensive programs for patients, payors, and physicians across a number of disease states and conditions including cancer, growth deficiency, hepatitis C, RSV, infections, nutrition deficiency, autoimmune diseases, neurologic disorders, and respiratory and cardiac conditions.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

Proteomics

Several new proteins are implicated for causing fatty liver

2004 AUG 2 - (NewsRx.com) -- Several new proteins are implicated for causing fatty liver.

According to a study from the Netherlands, "the inbred HcB19 mouse strain expresses a truncated form of thioredoxin interacting protein and is phenotypically characterized by fatty liver and elevated plasma triglycerides and very low density lipoprotein (VLDL). Recently, these mice have been proposed as an animal model for familial combined hyperlipidemia. The aim of the present study was identification of hepatic proteins specifically associated with the presence of fatty liver."

"Eighteen differential proteins were detected in whole-liver homogenate from HcB19, or the parental strain C3H, using 2D electrophoresis, and 11 of those were successfully identified by mass spectrometry. Five of the identified differential proteins were mitochondrial, two peroxisomal, two cytosolic, and two secretory," wrote M.M.J. van Greevenbroek and colleagues, Maastricht University, Cardiovascular Research Institute of Maastricht.

"Four differential proteins were novel in the fatty liver proteome [i.e., aconitase, succinate dehydrogenase, propionyl CoA carboxylase alpha chain (PCCA), and 3-hydroxyanthranilate 3,4 dioxygenase (3HAAO)]. Of these, PCCA and 3HAAO are of particular interest because of their known functions in nicotinic acid metabolism (3HAAO) and ketogenesis (PCCA)."

"We have newly identified several differential proteins in the hepatic proteome of mice with fatty liver, including PCCA and 3HAAO, and confirmed differential expression of previously reported proteins. These individual proteins, PCCA and 3HAAO, can be important in development of fatty liver or in the expression of hyperlipidemia," researchers suggested.

van Greevenbroek and colleagues published their study in *Journal of Lipid Research* (Identification of novel molecular candidates for fatty liver in the hyperlipidemic mouse model, HcB19. J Lipid Res, 2004;45(6):1148-1154).

For more information, contact M.M.J. van Greevenbroek, Maastricht University, Cardiovascular Research Institute Maastricht, Laboratory Molecular Metab & Endocrinol, UNS 50 Box 14, POB 616, NL-6200 MD Maastricht, Netherlands.

Publisher contact information for the *Journal of Lipid Research* is: American Society Biochemistry Molecular Biology Inc., 9650 Rockville Pike, Bethesda, MD 20814-3996 USA.

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Stem Cell Research

FGFs enriches embryonic liver cultures for hepatic progenitors

2004 AUG 2 - (NewsRx.com) -- Fibroblast growth factors enrich embryonic liver cultures for hepatic progenitors.

According to recent research from the United States, "Fibroblast growth factors (FGFs) play an important role in hepatic induction during development. The aim of our study was to investigate the effect of exogenous FGFs on ex vivo liver development. We begin our analysis by examining FGF signaling during early mouse liver development."

"Phospho-FGF receptor (Tyr653/654) was detected in embryonic day 10 (E10) to E12 livers only. Next, E10 livers were cultured in the presence of FGF1, FGF4, or FGF8 for 72 hours and examined for histology, proliferation, apoptosis and differentiation," S.S. Sekhon and coworkers reported.

"FGFs, especially FGF8, promoted sheet-like architecture, cell proliferation and survival as compared to the control. All FGFs induced a striking increase in the number of c-kit and alpha-fetoprotein-positive progenitors, without altering albumin staining.

"However these progenitors were CK-19-positive (biliary and bipotential progenitor marker) only in the presence of FGF1 or FGF4 and not FGF8. FGFs also induced beta-catenin, a stem cell renewal factor in these cultures," said investigators.

The authors concluded, "The presence of activated FGFR indicates a physiological role of FGF during early liver development FGF1 and FGF4 enrich the embryonic liver cultures for bipotential hepatic progenitors.

"FGF8 promotes such enrichment and induces a one-step differentiation toward a unipotential hepatocyte progenitor. Thus, FGFs might be useful for enrichment and propagation of developmental hepatic progenitors."

Sekhon and colleagues published their study in *American Journal of Pathology* (Fibroblast growth factor enriches the embryonic liver cultures for hepatic progenitors. Am J Pathol, 2004;164(6):2229-2240).

For additional information, contact S.P.S. Monga, University of Pittsburgh, School of Medicine, Department of Pathology, S421-BST, 200 Lothrop St., Pittsburgh, PA 15261 USA.

Publisher contact information for the *American Journal of Pathology* is: American Society Investigative Pathology, Inc., 9650 Rockville Pike, Bethesda, MD 20814-3993 USA.

The information in this article comes under the major subject areas of Hepatology and Stem Cell Research.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

Transplant Medicine

Washington state authorizes liver transplants at medical center

2004 AUG 2 - (NewsRx.com) -- Swedish Medical Center received approval from the Washington State Department of Health for its Certificate of Need application to establish a new adult liver transplant program on Swedish's First Hill Campus in Seattle, Washington. The first procedures could be done within the next several months.

Currently, the University of Washington Medical Center has the liver transplant program to serve adults in Washington, Alaska, Montana and Idaho.

"For various reasons, current available services haven't been able to meet the demands of our region. So, many individuals have either had to leave the area for a liver transplant or simply not had the option of receiving one," said William Marks, MD, PhD, medical director Swedish's Organ Transplant Program and Laboratory for Transplantation Biology.

A significant number of livers donated by Northwest residents are being sent now to other regions of the country for transplantation. According to LifeCenter Northwest, the region's organ procurement organization, over the past four years more than 100 transplantable livers have been exported from the Northwest to other states.

Liver transplantation is a technically difficult procedure and demands specially trained, multi-disciplinary team surgeons, medical specialists, transplant nurses and other specialty support services such as pharmacy and social services. The average hospital stay for liver transplant patients is 10 to 16 days, and they typically require a great deal of pre- and post-operative care.

According to the American Liver Foundation, more than 25 million Americans are affected by some form of liver or biliary disease. There are approximately 18,000 people on the waiting list for a liver transplant.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

Viral Proteomics

Hepatitis C virus core protein amino acids hold the key to viral localization

2004 AUG 2 - (NewsRx.com) -- Hepatitis C virus core protein amino acids hold the key to viral localization.

According to published research from Japan, "hepatitis C virus (HCV) core protein is suggested to localize to the endoplasmic reticulum (ER) through a C-terminal hydrophobic region that acts as a membrane anchor for core protein and as a signal sequence for E1 protein. The signal sequence of core protein is further processed by signal peptide peptidase (SPP). We examined the regions of core protein responsible for ER retention and processing by SPP."

"Analysis of the intracellular localization of deletion mutants of HCV core protein revealed that not only the C-terminal signal-anchor sequence but also an upstream hydrophobic region from amino acid 128 to 151 is required for ER retention of core protein," noted K. Okamoto and colleagues, Osaka University, Research Center for Emerging Infectious Diseases.

"Precise mutation analyses indicated that replacement of Leu(139), Val(140), and Lett(144) of core protein by Ala inhibited processing by SPP, but cleavage at the core-E1 junction by signal peptidase was maintained. Additionally, the processed E1 protein was translocated into the ER and glycosylated with high-mannose oligosaccharides.

"Core protein derived from the mutants was translocated into the nucleus in spite of the presence of the unprocessed C-terminal signal-anchor sequence. Although the direct association of core protein with a wild-type SPP was not observed, expression of a loss-of-function SPP mutant inhibited cleavage of the signal sequence by SPP and coimmunoprecipitation with unprocessed core protein.

"These results indicate that Leu(139), Val(140), and Leu(144) in core protein play crucial roles in the ER retention and SPP cleavage of HCV core protein," they concluded.

Okamoto and colleagues published their findings in *Journal of Virology* (Intramembrane proteolysis and endoplasmic reticulum retention of hepatitis C virus core protein. J Virol, 2004;78(12):6370-6380).

Additional information can be obtained by contacting Y. Matsuura, Osaka University, Research Center Emerging Infection Diseases, Microbial Diseases Research Institute, 3-1 Yamadaoka, Suita, Osaka 5650871, Japan.

The publisher of the *Journal of Virology* can be contacted at: American Society for Microbiology, 1752 N St. NW, Washington, DC 20036-2904 USA.

The information in this article comes under the major subject areas of Hepatitis C Virus, Hepatology, Proteomics, and Virology.

This article was prepared by Hepatitis Weekly editors from staff and other reports.

Hepatitis Weekly

Events Calendar . . . August 2, 2004

Carol Kohn, ELS(D), Board Certified Diplomate Editor in the Life Sciences, Editor-in-Chief
Susan Hasty, Publisher
CW Henderson, Editor Emeritus & CEO

New Listings

*** September 5-9, 2004**, BILBAO - GUGGENHEIM MUSEUM, **"ISCHS, 12th International Symposium on Cells of the Hepatic Sinusoid: Pathogenic Implications and Therapeutical Targets in Liver Disease."** Information: Univ. of Basque County, Prof. Fernando Vidal-Vanaclocha, Barrio Sarriena s-n, E-48940 Leioa, Viscaya, Spain, Countryphone: +34, Tel: (94) 601 56 91, Fax: (94) 464 89 66, E-mail: xii-ischs-2004@lg.ehu.es, http://www.ehu.es/XII-ischs-2004.

*** November 11-13, 2004**, GREIFSWALD, **"1st International Alfred Krupp Kolleg Symposium on Stress, Behaviour, and Immune Response."** Information: Univ. Greifswald, Prof. C. Schuett, Immunologie und Transfusionsmed., Sauerbruchstrasse, D-17487 Greifswald, F.R. Germany, Countryphone: +49, Tel: (03834) 86-54 68, Fax: (03834) 86-54 90, E-mail: schuett@uni-greifswald.de, http://www.medizin.uni-greifswald.de/immun/sbi2004.

*** June 23-25, 2005**, CANCUN - HILTON CANCUN BEACH & GOLF RESORT, **"LASSAM, 1st Latin American Congress of the Latin American Society for the Study of the Aging Male."** Information: Grupo Destinos, LASSAM 2005, Mexico, E-mail: lassam2005@grupodestinos.com.mx, http://www.latinmale.org.

Previous Listings

August 7-12, 2004, PINE MOUNTAIN, GEORGIA - CALLAWAY GARDENS RESORT, **"FASEB Summer Research Conference on Integrative Approaches to Understanding Obesity and its Metabolic and Clinical Consequences."** Information: FASEB Summer Research Conference, OSMC, 9650 Rockville Pike, Bethesda, MD 20814-3998, USA, Countryphone: +1, Tel: (301) 634-7010, Fax: (301) 634-7007, E-mail: jlevin@faseb.org, http://src.faseb.org.

August 22-28, 2004, TORINO, TURIN, **"IPS 2004, 20th Congress of the International Primatological Society."** Information: Centro Congressi Internazionale, Via Cervino, 60, I-10155 Torino, Italy, Countryphone: +39, Tel: (011) 244 69 11, Fax: (011) 244 69 00, E-mail: ips2004@congressiefiere.com, http://www.IPS2004.unito.it.

October 9-11, 2004, FREIBURG - HISTORISCHES KAUFHAUS, **"IMLI 2004, Immune-Mediated Liver Injury: From Basic Science to Future Therapies - EASL Monothematic Conference."** Information: Univ. Mainz, Ansgar W. Lohse, Medizin 1, Langenbeckstrasse 1, D-55131 Mainz, F.R. Germany, Countryphone: +49, Tel: (06131) 17-71 04, Fax: (06131) 17-27 28, E-mail: lohse@mail.uni-mainz.de, http://www.imli2004.de.