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BASIC SCIENCE DISCOVERIES YIELD PROGRESS IN HEPATOLOGY

- **Advances in virology translate into new promising drugs to combat Hepatitis C**
- **Clarification of oncogenic pathways aids liver cancer research**
- **Stem cells of potential benefit in liver transplantation**
- **Systems biology helps to solve complex liver diseases**

Milan, April 26th, 2008 – At today's sessions of the 43rd Annual Meeting of the European Association for the Study of the Liver (EASL), experts reported advances in basic research that have important implications for the eventual treatment of people with chronic liver diseases.

The goal of basic or "fundamental" biomedical science is to gain knowledge and understanding for its own sake, without reference to a particular practical problem. "Translational" science transforms basic knowledge into practical terms. "Applied" research, such as "clinical trials," takes the discoveries of basic research even further and uses them to solve specific, clearly defined medical problems. Basic, translational, and applied research are each necessary to progress in medicine, including Hepatology.

In virology, for example, notable progress has been made in clarifying the structure of the Hepatitis C virus (HCV), leading to the development of new experimental drugs such as protease inhibitors and polymerase inhibitors, drugs that inhibit virus production. Some of these drugs have been extensively tested and some are currently in phase II trials. Based on results to date, it is clear that these drugs can be highly effective in combination with pegylated Interferon and Ribavirin. Phase III trials are planned.

Important basic science advances in genetics and systems biology have also been reported, offering potential progress for strategies to treat hepatocellular carcinoma (HCC). Using genomics and microarrays to determine gene expression, scientists have discovered that there are different biological pathways – called "oncogenic pathways" -- that result in HCC. This discovery corrects a past, widely held but mistaken assumption that all cases of HCC arise from a single type of disease process. On the basis of the new discovery, researchers can now classify and explore differing subtypes of HCC, as well as designing and experimentally testing targeted treatments for patients based on their respective cancer subtype. According to Professor Michael Trauner, Professor of Medicine and Molecular Hepatology at the Medical University, Graz, Austria, "It is extremely interesting to look at different gene expression profiles of patients with the same disease and realize that there are different clusters which may be associated with differentially aggressive disease. For example, in the field of cancer, varying gene expression profiles are linked to better and worse prognoses for hepatocellular carcinoma." In addition to genetic signatures, new protein and metabolic markers are also being developed to detect cancer at an early stage among patients considered at risk. Most importantly, new drugs are now available that are able to target signal transduction cascades which, under pathological conditions, help tumor cells to grow and proliferate. These novel drugs include multikinase inhibitors such as Sorafenib,

which has recently been shown to delay progression of HCC. Additional small molecules targeting tumor cell proliferation will be available for clinical trials in the near future.

A third area in which basic science offers the potential for clinical progress in hepatology is in the use of embryonic stem cells for liver repair. One of the major limitations for the development of liver cell therapy programs is the shortage of human hepatocytes. Many laboratories have therefore focussed on stem cells as a renewable source of hepatocytes (although extensive liver tissue formation/replacement has not yet been achieved with either adult or embryonic stem cells). Immortalized hepatocytes could engraft, proliferate and correct a disease phenotype of a recipient liver, but safety issues (e.g. tumor formation) still remain a concern. To date, in the laboratory, stem cells have been found to differentiate into hepatocyte-like cells and other liver cell types and used to restore liver function in mice with liver failure. For some researchers, this is a potential treatment that, if successfully applied to humans, will allow correction of inborn errors of metabolism or allow patients to live long enough for a donated organ to become available. Some scientists believe that stem cells might even enable the liver to completely heal itself so a transplant is no longer needed. In Professor Trauner's view, although the latter application is interesting, its success may be limited due to severe disturbances of liver architecture in advanced liver diseases such as cirrhosis, which limits the function of newly transplanted cells. However, in the future, stem cells perhaps could also be used to reverse fibrous scars in liver cirrhosis.

A fourth promising area is the application of systems biology -- which focuses on interactions in biological systems -- to clinical problems in hepatology. As such, the systematic exploration of RNA, protein and metabolic profiles in hepatitis, fatty liver and cancer may help to identify patients at particular risk for developing severe forms of these diseases, help to predict prognoses, and may unravel potential therapeutic targets in individual patients. This approach brings us a major step toward personalized, individualized medicine with better prediction of individual prognosis and better selection of the best therapy for each individual patient.

About EASL

The European Association for the Study of the Liver (EASL) aims to promote investigation into liver disease and improve the treatments that currently exist for these conditions. The association, through its annual meetings, seeks to inform and educate both the scientific community as well as society in general about the increasing occurrence of liver diseases along with the importance of understanding these conditions in order to treat and prevent them. Since its creation in 1966, the EASL congress has been hosted in 20 different European countries. Currently the association has over 1400 members and the annual congress attracts over 6000 delegates from over 65 countries each year.

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For more information:
Carolina Annand / Karine Elkobbi / Melisa Corrigan
Carolina.annand@eurorscg.com / karine.elkobbi@eurorscg.com / melisa.corrigan@eurorscg.com
Tel. +33 617 43 03 38 / +33 6 61 17 44 77 / 328 411 01 38
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