



## ***New HCV Therapies: What Does the Future Hold?***

by Robert Gish, M.D. and Laura Miyashita

Combination therapy with PEG-interferon and ribavirin has emerged as the best current treatment for chronic hepatitis C (HCV) infection, and is now more widely available due to the U.S. Food and Drug Administration's (FDA) approval of Schering's Peg-Intron in August 2001, and approval of Roche's Pegasys expected this year.

"The overall sustained response rate to PEG-interferon with ribavirin is about 55%," says Robert Gish, M.D., medical director of California Pacific's Liver Disease Management & Transplant Program. He adds, "Research shows that genotype 2 or 3 and a baseline viral load of less than 3.5 million copies/ml are the most useful factors in predicting a positive response to combination therapy prior to treatment."

While combination therapy is more likely than interferon monotherapy to lead to dose reductions or discontinuation, researchers are exploring the use of adjuncts such as erythropoietin and filgrastim that can help maintain patients at full dose. The most common cause for dose reduction is hemolytic anemia caused by ribavirin, and these drugs are thought to help manage such side effects.

### **A Hepatitis Vaccine?**

A recent trend in HCV research has centered upon developing vaccines capable of protecting one from chronic infection or modifying its course. This research is difficult, however, because of the virus' composition:

- HCV is highly susceptible to mutation, making it difficult for antibodies to provide long-term protective immunity;
- The virus can avoid being detected by the immune system;
- The body's neutralizing antibodies (specific CD4 and CD8 T-cells) are not efficiently produced;
- The virus replicates poorly in cell cultures.

Although there are many HCV variations, one part is the same in all: the 5 prime untranslated region, or UTR. Scientists have learned how to add



*Yume Phung (left) leads researchers in exploring new treatments for viral hepatitis in California Pacific's Hepatitis and Immunology Research Lab.*

molecules, called "antisense" molecules, to this region of the virus, which can prevent it from replicating itself and make it unable to cause disease. Early clinical trials have recently begun to evaluate the safety of this approach in humans.

### **Other Areas of Research**

**Ribozymes** Another approach uses a normal cell enzyme called a ribozyme. Ribozymes are RNA molecules that one can modify to attach to and break a specific RNA sequence, such as the one the HCV virus must make to replicate itself and cause disease. Ribozyme phase II trials are underway.

**Thymus-derived Proteins (Cytokines)** Two crude thymus extracts, thymosin fraction 5 and thymosin alpha 1, are cytokines. These cytokines are derived from proteins found in the thymus gland and appear to be able to change one's response to HCV infection. More than 20 countries have approved Thymosin alpha 1 (Thymalfasin, Zadaxin™) for treatment of patients with viral hepatitis, and it is in U.S. trials for patients who did not respond to standard interferon ribavirin treatment.

**Viral Replication Proteins** Extensive research of the HCV genome has identified various HCV protein products involved in viral replication,

*HCV THERAPIES, continued back page*

## Contents

2

Study Finds Variant Forms of Autoimmune Liver Disease Occur Commonly

2

California Transplant Donor Network Appoints Robert Osorio, M.D. to Medical Director

3

Liver Team Expands with Addition of New Hepatologist and Surgeon

3

New Liver Allocation System in Effect

# Study Finds Variant Forms of Autoimmune Liver Disease Occur Commonly

Identification of Variant Syndromes Critical to Classifying New Disease Entities

by Robert Gish, M.D. and Laura Miyashita



Robert Gish, M.D. and California Pacific's Research Team evaluated 109 patients with autoimmune liver disease and found that 20% had overlap symptoms.

**A**utoimmune liver disease is an important and often underestimated cause of liver cell inflammation and destruction, as well as biliary tract injury. Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are the three main chronic liver diseases with a presumably autoimmune background.

Commonly, overlap syndromes ("variant forms") in autoimmune liver disease occur, but are too often incorporated into the conventional categories mentioned above. Such overlap syndromes include:

- AIH/PBC: mixed characteristics of autoimmune hepatitis and primary biliary cirrhosis
- Autoimmune Cholangitis (AC): Infiltration of polymorphonuclear leukocytes beyond the portal tract with bile duct injury and abnormal ERCP

To determine the frequency of overlap syndromes, California Pacific's Hepatology Research Program evaluated 109 patients with autoimmune liver disease and classified them according to score. The team modified the International Autoimmune Hepatitis Group's scoring system of autoimmune

liver disease subtypes to include differentiation of histologic lesions (classifying them as nonexistent, mild, moderate, severe or cirrhotic).

"Our research showed that the aggregate frequency of variant syndromes among the 109 patients is 20%," says Robert Gish, M.D., study investigator. He explains, "Although we obtained extensive clinical histories from all patients, there weren't any distinguishing demographics between those with AIH/PBC and those with classical AIH Type 1 as both groups were similar in regards to age (mid-50s), gender (predominantly female) and race (Caucasian)."

The high prevalence of overlap syndromes found in California Pacific's research suggests that the occurrence of such variants may have been previously underestimated. This makes identification of variant syndromes in the clinical setting critical, with biopsy strongly indicated to diagnose autoimmune liver disease.

To firmly establish overlap syndromes as actual autonomous diseases, a greater number of patients must be evaluated in a standardized manner. Particularly, patients with chronic autoimmune liver disease should be thoroughly examined for variant syndromes. While previous studies have shown that variant syndromes exhibit an unpredictable response to conventional monotherapy (such as corticosteroids), it is likely that refinements in the recognition and classification of variant syndromes will improve the prognosis of patients afflicted with these syndromes, thus opening the door for better treatment options. ∞

## California Transplant Donor Network Appoints Robert Osorio, M.D. to Medical Director

By Laura Miyashita



Robert Osorio, M.D.  
Surgical Director

**R**obert Osorio, M.D., surgical director of California Pacific Medical Center's Liver Disease Management & Transplant Program, was appointed to serve a one-year term as Medical Director of California Transplant Donor Network, effective January 2002.

California Transplant Donor Network, the organ procurement organization (OPO) for the Bay Area, helps patients in Northern and Central California and Northern Nevada receive organ and tissue transplants. As Medical Director, Dr. Osorio will oversee all medical aspects of the Network's activities. Among his duties include chairing the Network's Medical Affairs Committee and review-

ing practices for allocating organs in accordance with national (UNOS) guidelines.

"We're pleased to have Dr. Osorio's expertise regarding medical criteria for organ donation," says Phyllis Weber, executive director of California Transplant Donor Network. "His experience and leadership will also help guide our Medical Affairs Committee and organ recovery staff."

In addition to his appointment as medical director, Dr. Osorio will continue his positions as surgical director and vice-chairman of California Pacific's Department of Transplantation. ∞

# Liver Team Expands with Addition of New Hepatologist and Surgeon

By Laura Miyashita

California Pacific's Liver Disease Management & Transplant Team welcomes new physicians to our team:

**Maurizio Bonacini, M.D.**, joined the Medical Center in January of this year after serving as associate professor of clinical medicine at University of Southern California. Dr. Bonacini oversees the care of liver disease and transplant patients, both in San Francisco and at outreach sites throughout Northern California. A hepatologist, Dr. Bonacini received his training at University of Southern California's Liver Unit, Booth Memorial Medical Center (affiliated with New York University Medical Center), and Universite Catholique de Louvain (Brussels, Belgium).

Dr. Bonacini is widely published and his research interests include HCV and HIV coinfection, liver fibrosis and progression in HCV patients, and HBV and liver disease in minorities. Dr. Bonacini speaks Spanish, Italian and French.

**Assad Hassoun, M.D.** also recently joined California Pacific as a kidney, pancreas and liver transplant surgeon. Previously, he was Director of the Pancreas Transplant Program at Scripps Clinic-Green Hospital in La Jolla, Calif. Dr. Hassoun received his medical training at University of Minnesota Hospital and Clinic, the Brookdale University Hospital Medical Center (Brooklyn, N.Y.), Bo-Ali Seena Hospital (Kazween, Iran) and Medical City Hospital (Baghdad, Iraq). He has an M.D. from University of Mosul Medical College in Mosul, Iraq. Dr. Hassoun has also served as Clinical Instructor of Surgery at University of Minnesota Hospital and Clinic. He speaks both Arabic and Persian.

Drs. Bonacini and Hassoun are both available for lectures on a variety of topics relating to new therapies and surgical options for liver disease and transplantation. For further details or a topic listing, contact Sandy Swenson, outreach education coordinator, at (415) 600-1417 or via email at [swensos@sutterhealth.org](mailto:swensos@sutterhealth.org).



Maurizio Bonacini, M.D., hepatologist



Assad Hassoun, M.D., kidney, pancreas and liver transplant surgeon

## New Liver Allocation System in Effect

### MELD System Ranks Patients by Disease Severity

by Robert Osorio, M.D. and Laura Miyashita

On February 27th, California Pacific Medical Center and the nation's transplant centers began using a new system for categorizing adult liver transplant patients. Known as the Model for End-Stage Liver Disease, or MELD, this new scoring classification replaces the previous Child-Turcotte-Pugh (CTP) system.

The MELD system, developed by researchers and clinicians at the Mayo Clinic in Rochester, Minn., estimates a patient's risk of mortality while on the transplant waiting list. Patients are prioritized for liver allocation based upon an assigned numerical score. Points are calculated based on:

- Creatinine
- Bilirubin
- Prothrombin time/INR

"With the MELD scoring system, we can better categorize patients based on the severity of their illness," says Robert Osorio, M.D., surgical director of California Pacific's Liver Disease Management & Transplant Program. "Rather than primarily basing patients' scores on their time on the waiting list, the MELD system uses verifiable medical criteria and should direct organs to patients most in need of transplantation."

MELD scores range from 6 (less ill) to 40 (gravely ill), and replace the previous Status 2A, 2B and 3 categories. The Status 1 category remains in effect. For transplant centers in Northern California, the average MELD score for patients undergoing transplantation is 20.

In cases of hepatocellular carcinoma, familial amyloidosis, hepatopulmonary syndrome, portopulmonary hypertension, polycystic liver disease and biliary stricture syndrome, a special provision will add extra points that reflect the medical severity of these illnesses. For example, depending on the tumor(s) size in cases of liver cancer, patients will be assigned a score according to the chart below. For organ distribution, any ties between patients with the same MELD score will be determined by waiting time.

MELD Score Provisions for Hepatocellular Carcinoma

Criteria	MELD Score Assigned
Patients with T1 disease: a single nodule that is ≤ 1.9 cm.	24
Patients with T2 disease: a single nodule that is 2.0 to 5.0 cm in size, or up to 3 multiple nodules, all ≤ 3.0 cm.	29

#### MELD Score Calculation

The UNOS computer system assigns each patient awaiting liver transplantation a MELD score based on the following calculation:

$$\text{MELD Score} = 0.957 \times \text{Log}_e(\text{creatinine mg/dL}) + 0.378 \times \text{Log}_e(\text{bilirubin mg/dL}) + 1.120 \times \text{Log}_e(\text{INR}) + 0.643$$

As an example, a patient with cirrhosis caused by hepatitis C virus who has a serum creatinine concentration of 1.2 mg/dL, a serum bilirubin concentration of 4.2 mg/dL and an INR value of 1.9, the risk score would be calculated as follows:

$$\text{MELD Score} = (0.957 \times \text{Log}_e(1.2) + 0.378 \times \text{Log}_e(4.2) + 1.120 \times \text{Log}_e(1.9) + 0.643) \times 10 = 21$$

Following calculation, one's MELD score is rounded to the tenth decimal place and then multiplied by 10. Therefore, in the example above, the patient would be assigned a risk score of 21.

translation and packaging. Each of these protein products is a potential target for antiviral therapy and testing for activity against HCV occurs as they are produced.

**Other Emerging Agents** Alpha glucosidase inhibitors and similar medications have an apparent ability to inhibit viral packaging. New ribavirin-like products such as VX497, Levovirin and Viramidine may also have a role in expanding combination therapy for HCV. ∞

## Gastroenterology Conference Planned for July 12 - 13

California Pacific and the American Liver Foundation will present a two-day conference for medical professionals on July 12 - 13, 2002. The conference, "Emerging Treatments for Liver Disease and GERD," will be held in San Francisco's Sir Francis Drake Hotel and will examine various viewpoints on issues such as hepatitis B and C treatment, HIV and HCV coinfection, hepatocellular carcinoma, and a comparison of GERD techniques. For further details, contact Sandy Swenson at (415) 600-1417 or via email at [swensos@sutter-health.org](mailto:swensos@sutter-health.org).

### HCV Therapies in Research

Category:	Ribozyme	Thymus-derived Proteins	Cytokines	Emerging Antiviral Agents	
				Targeting Viral Replication	Targeting Other Viral Production Mechanisms
<b>Name:</b>	Ribozymes	Thymosin alpha 1	Interleukin-10 Interleukin-2 Interleukin-12 Gamma-interferon	Helicase Protease RNA dependent RNA polymerase	Alpha glucosidase inhibitors VX497 Levovirin Viramidine
<b>Status:</b>	Phase II clinical trials beginning	In combination trials in U.S. for patients who didn't respond to standard interferon ribavirin treatment	Interleukin 2 and 12 have not shown any significant antiviral activity Gamma-interferon entering clinical trials as anti-fibrotic agent	Testing by drug developers occurs upon production	Clinical trials starting



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