



## SPOTLIGHT ON Hepatology and Gastroenterology Research

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## The Future of Western Treatments for Hepatitis B and C

### Research Seeks to Inhibit Virus Replication Long-Term

by Robert Gish, M.D. and Laura Miyashita

Despite current treatment advances, a great need exists for more effective and safer antiviral agents for hepatitis B and C. Worldwide, more than 80% of people infected with the hepatitis B virus (HBV) and 40% of people infected with the hepatitis C virus (HCV) do not respond (achieve long-term viral clearance) to Western therapies. These statistics clearly illustrate the need for new treatments to obliterate these global diseases.

#### Hepatitis B

"Therapies currently in use for hepatitis B include interferon, adefovir and lamivudine," explains Robert Gish, M.D., medical director of California Pacific's Liver Disease Management & Transplant Program. He adds, "In addition to these therapies, clinical trials are underway to research potent inhibitors of HBV replication, including HepaVir-B, FTC, emtricitabine, LD4FC, entecavir, clevidine, L-dT, nucleoside/nucleotide analogue combinations and PEG interferon, among others."

#### **Interferon efficacy being re-addressed**

Now that more potent, longer-acting, pegylated interferons are available, researchers are studying their effect on HBV and in combination with oral agents. Historically, interferon-alpha treatment (four months of 5 million units/day injection therapy) has showed a 30%-40% HBeAg loss, approximately 10% HBsAg loss and long-term improvements in natural history without HBV mutations. Interferon therapy is most effective in patients with:

- low-level HBV DNA (100,000 – 40,000,000);
- elevated ALT (>100 IU/mL);
- immunocompetence (HIV negative or absence of organ transplant);
- hepatic compensation; and
- acquisition of infection in adulthood.

#### **Lamivudine helps reduce HBV DNA**

In head-to-head comparisons, lamivudine and interferon show similar efficacy. Unlike interferon, however, lamivudine is taken in daily oral doses of ≥100 mg, requires longer-duration therapy and is associated with the emergence of viral variants at about 20% per year of therapy.

In Phase III, prospective, controlled clinical trials among North American, European and Asian



patients with HBeAg and elevated ALT, 12 months of lamivudine therapy was associated with:

- almost universal suppression of hybridization-assay-detectable HBV DNA;
- approximately 30% HBeAg loss;
- approximately 16%-18% HBeAg seroconversion;
- sustained ALT normalization in approximately 40%-50%;
- liver histologic improvement in approximately 50%.

Hepatitis B e antigen loss/seroconversion achieved during therapy is maintained in approximately 70%-80% over the immediate months and up to >2 years after therapy.

#### **Adefovir offers new option for HBV patients**

In September 2002, the U.S. Food and Drug Administration approved adefovir dipivoxil, which blocks the replication of HBV in the body. Adefovir, marketed under the name Hepsera® by Gilead Sciences, is indicated for treatment of chronic HBV in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. Administered as a daily oral 10 mg tablet, adefovir offers a new, primary therapy option for patients as well as a treatment for those who have become resistant to lamivudine, failed interferon, or who can't tolerate their side effects. Adefovir, like lamivudine, must be dose-adjusted for renal insufficiency.

# Development of California Pacific's Molecular Virology Lab Expands Hepatitis Research

by Laura Miyashita

To better understand the relationship between the hepatitis C virus (HCV), its transmission and the body's response mechanisms, California Pacific Medical Center developed a Molecular Virology Lab in 2001. The lab, under the direction of Hepatologists Natalie Bzowej, M.D., Ph.D. and Ed Wakil, M.D., is involved in numerous hepatitis C trials, with future plans to explore hepatitis B and HCV/HIV co-infected patients.

## Current Studies

**HCV Quasispecies:** "By looking at a short piece of the HCV sequence, we are reviewing the relationship between pairs with lateral versus vertical transmission of HCV, as well as transmission in patients with blood transfusion," explains Yume Phung, virology lab manager. Phung explains, "Some pairs showed a similarity in the virus, and we are currently finalizing the data for publication."

**Hepatocyte in Culture Serum:** In collaboration with the University of Washington, California Pacific is involved in a study using serum samples which contain HCV to infect a hepatocyte primary cell line. Our role is to track the HCV over time and examine viral mutations in the absence of the immune system. This study will ultimately help researchers in understanding the pathway of infection and replication of HCV in hepatocytes in vitro.



Virology lab researchers examine the relationship between treatment response and HCV genotypes in various patient categories.

## Interferon Treatment and Viral

**Quasispecies:** This research, which began in late 2002, investigates the relationship between treatment response and HCV genotypes in three categories of patients: those who respond to interferon therapy, relapsers and non-responders. With such information, researchers may better predict one's outcome to interferon therapy.

## Future Projects

### Tumor Markers for Hepatocellular

**Carcinoma:** California Pacific, in collaboration with UCSF and Stanford, has submitted a grant to the National Institutes of Health to look at tumor markers of HCV-related hepatoma. This research could ultimately lead to the discovery of specific serum markers in

tissue from which an improved diagnostic test for liver cancer could be developed. Hepatoma is the fourth most common malignant tumor worldwide and in the past three decades, the number of diagnosed cases per year of liver cancer has increased five-fold. A diagnostic test would help detect liver cancer early on in HCV patients and could thus lead to improved outcomes.

**NKT-Cell Research:** As the virology lab expands to include immunology research, California Pacific investigators plan to examine the role of immune cells (specifically the NKT-cell) in fighting viral hepatitis. Growing evidence has shown that the NKT cell, part of the immune system's *innate response*, represents one of the first lines of defense against viral hepatitis. "California Pacific's Research Team wants to study this cell population and the signals (cytokines) they generate in human liver tissue," explains Hepatologist Ed Wakil, M.D. He adds, "By increasing understanding of how the immune system fights viral hepatitis, hopefully we can develop new strategies to the enhance immune response."

## Gastroenterology Clinical Trials Seeking Enrollment

Following is a listing of our gastroenterology research trials open for enrollment. If you or a patient are interested in any of these studies, please contact the coordinator listed for further details.

### Irritable Bowel Syndrome

A randomized, double-blind, placebo-controlled, parallel-group, multicenter study to assess the efficacy and safety of repeated treatment with Tegaserod 6 mg twice a day and a placebo in female patients with irritable bowel syndrome with constipation (IBS-C)

**Study Purpose:** Evaluate how well Tegaserod can relieve the symptoms of IBS when given at a dose of 6 mg twice a day to patients with constipation- predominant irritable bowel syndrome. Tegaserod will be given for one month and then stopped. If IBS symptoms reappear after treatment is stopped, a second four-week treatment will be given. In addition to testing how well the drug works, the safety

and tolerability of Tegaserod will be evaluated during both parts of the study.

**Contact: Danielle Hauptman, R.N.**  
(415) 600-1155 or [hauptmd@sutterhealth.org](mailto:hauptmd@sutterhealth.org).

### Crohn's Disease

Adilimumab Versus Placebo in Subjects with Crohn's Disease

**Study Purpose:** Examine how Adilimumab affects patients with confirmed Crohn's Disease.

**Contact: Danielle Hauptman, R.N.**  
(415) 600-1155 or [hauptmd@sutterhealth.org](mailto:hauptmd@sutterhealth.org).

### Colon Evaluation

Prospective comparison of air contrast barium enema (ACBE), computed tomographic colonography (virtual colonoscopy) and colonoscopy for evaluation of the colon.

**Study Purpose:** Compare two X-ray tests

(barium enema and virtual colonoscopy) to colonoscopy for examining the colon. An air contrast barium enema is an X-ray of the lower intestines (colon) taken after a patient is given a white dye (barium) through the rectum and a picture of the intestine is created. Virtual colonoscopy is a special type of X-ray that uses a computer to provide a more detailed look at the colon.

**Contact: Danielle Hauptman, R.N.**  
(415) 600-1155 or [hauptmd@sutterhealth.org](mailto:hauptmd@sutterhealth.org).

### Upper Abdominal Pain

The clinical utility of endoscopic ultrasound (EUS) in upper abdominal pain

**Study Purpose:** To determine the sensitivity of EUS to identify relevant lesions in comparison to routine upper endoscopy (EGD) and transabdominal ultrasound (US).

GASTROENTEROLOGY CLINICAL TRIALS,  
continued on page 3

# New Study Uses Sacral Nerve Stimulation for Fecal Incontinence

by Laura Miyashita

With an aging population, the incidence of fecal incontinence in the United States continues to rise, with one study by the National Center for Health Statistics revealing a 45% prevalence of fecal incontinence among nursing home residents. While not confined to the aging population, fecal incontinence is an embarrassing problem meriting further investigation by researchers.

At California Pacific, physicians are evaluating a new procedure for fecal incontinence—sacral nerve stimulation for bowel control. “We are very excited about our involvement in this study, which is a promising therapy for reducing or eliminating fecal incontinence symptoms,” says William Snape, M.D., medical director of California Pacific’s Gastrointestinal Motility Service. Both Snape and Colorectal Surgeon Jeffrey Sternberg,

M.D. are co-investigators of the sacral nerve study at California Pacific

In the procedure, an electrode is placed through the sacrum and into the sacral nerve. The electrode is connected to a stimulator outside the body that stimulates the nerves supplying the pelvic floor, detrusor muscle and lower gastrointestinal tract. With the stimulator in place, physicians evaluate anal pressure with anal manometry and measure the integrity of the anal sphincter with anal rectal ultrasound. If these studies show measurable improvement, the stimulator is implanted in the lower abdomen, where it permanently sends signals to the sacral nerves.

To refer patients for the sacral nerve stimulation study, contact California Pacific’s Specialty Referral Service at 1-888-637-2762.



Sacral nerve stimulation is being researched as a new therapy for reducing or eliminating fecal incontinence symptoms.

Hepatitis B and C, continued from page 1

## Hepatitis C

Research into HCV treatments and vaccines seeks to uncover ways in which the body can clear or prevent the virus. While the availability of pegylated interferon has increased response rates among HCV patients, additional therapies are needed.

### Longer-acting interferons introduced

In the past few years, both Schering and Roche have introduced pegylated interferons (PEG-IFN). Combined with ribavirin, their overall sustained response rate is about 55%. Currently, Human Genome Sciences and InterMune have initiated additional interferon research. Human Genome Sciences is investigating an albumin-interferon (Albuferon®) that, according to preclinical studies, is longer acting and remains in the blood substantially longer than recombinant interferon alpha and

PEG-IFN. InterMune produces both interferon gamma (Actimmune®) and consensus interferon (Infergen®).

### Challenges confront HCV vaccine research

“The development of a HCV vaccine remains a challenge for many reasons,” explains Gish. One of the most significant obstacles is the virus’ ability to mutate and avoid detection by the body’s immune system. Still, research is underway to explore an HCV vaccine and Chiron Corporation recently published Phase I trial data demonstrating the safety of a HCV vaccine in high-risk patients. According to Gish, “Recent advances in recombinant protein technology, novel adjuvants and DNA-based vaccines will play a major role in providing new techniques for vaccine development.” He reminds physicians to vaccinate all patients for HBV and HAV if they aren’t

already immune. “With the availability of the new TwinRx® vaccine, only three injections versus five are needed for vaccination,” says Gish.

### Human genome may offer solutions

Over the past nine years, scientists have extensively studied the human genome and identified various HCV protein products involved in viral replication, translation and packaging. They isolated one enzyme, the HCV RNA-dependent RNA polymerase, which is responsible for replication of the entire HCV genome. In the future, it may be possible to develop drugs that target this enzyme and prevent HCV virus replication.

California Pacific’s Hepatology Research Program offers numerous trials for viral hepatitis. For trial information, call (415) 600-1100 or visit [www.cpmc.org/research](http://www.cpmc.org/research).

Gastroenterology Clinical Trials, continued from page 2

### Inclusion Criteria:

- 18 years of age or older
- Patients who have upper abdominal pain and will be undergoing upper endoscopy as part of their work up of UAP

### Exclusion Criteria:

- Patients with UAP having endoscopy primarily:
  - For work up of an abnormal radiologic study
  - To rule out Barrett’s or varices
  - For dysphagia

- For follow-up of gastrointestinal malignancy or restaging
- Upper gastrointestinal bleeding

- Patients who have undergone gastric surgery
- Patients who have had prior imaging studies (CT, MRI, US) within last 12 months

EUS will be provided free of charge to patient.

**Contact:** Please fax referrals for this study to Danielle Hauptman, R.N. at (415) 600-1126 (fax) or call (415) 600-1155 for more information.

## Gastric Varices

Treatment of gastric varices with cyanoacrylate glue (Dermabond): An efficacy, safety and cost utilization study

**Study Purpose:** Evaluate the effectiveness of cyanoacrylate glue for the treatment of gastric varices in the United States. Cyanoacrylate glue is used routinely for treatment of gastric varices in Europe but is only approved for external use in the U.S.

**Contact:** Danielle Hauptman, R.N. (415) 600-1155 or [hauptmd@sutterhealth.org](mailto:hauptmd@sutterhealth.org).

# Non-Invasive Device Enables Physicians to Analyze Stomach Function

Electrogastrography Records Stomach's Electrical Activity

by Laura Miyashita

California Pacific now offers non-invasive assessment of gastric motility with a new procedure named electrogastrography. This technology, which uses four electrodes to monitor the stomach's electrical activity, is performed as a one-hour outpatient procedure. During the procedure, electrodes are placed on the abdominal wall to correspond to the stomach's position in the abdomen. The electrodes record and display gastric electrical activity on-screen to enable recognition of normal and abnormal gastric motility.

As the only site in Northern California currently offering this procedure, California Pacific's Gastrointestinal Motility Service has

seen encouraging results to date. "The electrogastrography application is unique in that it provides a non-invasive way of following the stomach's function," says William Snape, M.D., medical director and chief investigator. "We then correlate these results with gastric emptying and antroduodenal motility findings to determine the best course of treatment."

Candidates for electrogastrography include those with difficulty or delays in gastric emptying, or unexplained nausea, upper abdominal pain and vomiting.

To refer patients for electrogastrography, contact California Pacific's Specialty Referral Service at 1-888-637-2762.



## Liver Disease Management and Transplant Program

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