

# An August 15th 2002 thru September 15th 2002 Review of HCV, HBV and HIV/HCV Coinfection Related News and Highlights

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Editor-in-Chief

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## **1. On August 15<sup>th</sup>, 2002 the press released an article titled “Molecular Evidence Suggests that the Hepatitis C virus Can Replicate in the Oral Mucosa”**

HCV may occasionally replicate in oral lichen tissue, possibly contributing to the pathogenesis of mucosa damage, claims a study in the September issue of the *Journal of Hepatology* (J Hepatol 2002; 37(3) 364-369).

Patients infected with the hepatitis C virus (HCV) often have extrahepatic manifestations, which significantly contribute to HCV-related morbidity, but whose pathogenesis is largely unknown.

A joint team of researchers from Italy and Switzerland has therefore investigated the extent of HCV replication in the oral mucosa of patients with chronic hepatitis C. Oral mucosa specimens were collected from 17 anti-HCV-positive and 4 anti-HCV-negative patients. Of these 21 patients, 15 had oral lichen, 12 of who were in the anti-HCV-positive group. Total mucosa RNA was extracted and analyzed for presence and titer of genomic and negative-strand HCV RNA and findings were then compared with clinical and pathological features.

The researchers identified genomic and negative-strand HCV-RNA in 12 of 17 (71%) and 4 of 17 (24%) of samples, respectively. Only lichen tissues appear to contain replicating HCV. No negative-strand HCV RNA was detected in 5 anti-HCV-positive patients without lichen (including three with normal mucosa).

Presence and titer of the negative-strand HCV RNA were independent of HCV genotype, serum viral load, and histological diagnosis of liver lesions. The phylogenetic analysis of the envelope 2 region cloned from a normal mucosa and the corresponding serum further suggested that only lichen tissues appear to harbor replicating HCV.

The research group therefore concludes that HCV may occasionally replicate in oral lichen tissue, possibly contributing to the pathogenesis of mucosa damage.

## **2. On August 16<sup>th</sup>, 2002 Roche Expresses Optimism over Oncology Franchise and Two New Drugs for Viral Diseases**

After a few sluggish years, Roche AG is counting on its burgeoning oncology franchise and two new drugs for viral diseases, AIDS and hepatitis C, to lift its pharmaceutical division.

The Swiss drug maker, which bases its North American pharmaceutical unit in Nutley, told Wall Street on Thursday it expects a double-digit sales increase for its pharmaceutical products in 2003. The optimism stems in part from its oncology franchise, which showed growth of 31 percent in half-year results reported by the company.

By early next year, Roche also expects approval for its hepatitis C treatment Pegasys and a new HIV drug, Fuzeon. Also helping will be Roche's acquisition of Japanese drug maker Chugai.

"I wouldn't say we are riding the wave yet, but we are building the wave," said William Burns, Roche's global

head of pharmaceuticals. Burns spoke with The Record following the company's morning meeting with analysts and investors.

Roche is a prime New Jersey example of the potential consequences when a company's pharmaceutical core stalls. In May 2001, Roche blamed setbacks with various drugs for a cost-cutting review that led to layoffs of 300 workers at Nutley. After restructuring the company's research operations, Burns now says the company is turning a corner. The success of that turnaround, analysts say, will be predicated in part on the success of Pegasys and Fuzeon.

Although he said too much emphasis is placed on the next new drug to determine fates of companies, Burns did concede that Fuzeon and Pegasys are "certainly two significant upcoming opportunities."

Roche pushed back its timeline for Pegasys last fall so the Food and Drug Administration could review changes to its manufacturing processes. The delay gave its head-to-head competitor, Schering-Plough Corp., at least a year's head start with its new hepatitis C treatment.

Roche received a boost last month when the FDA said it would give Pegasys a priority review. That designation puts the drug on track for approval in October. Burns touted Pegasys as "the better product" Thursday and said he thinks "the stage is set for a very good battle."

Fuzeon, meanwhile, represents the first new attack on HIV since the advent of protease inhibitors, Burns said. The company plans to submit its application to the FDA for the drug by year's end for approval early next year.

Roche will not be able to build a giant reserve of Fuzeon because the drug is complicated to produce, so Burns said the company will work with governments and patient advocacy groups to ensure fair distribution.

A near-term threat to Roche's drug sales is the impending approval of generic versions of the company's acne drug, Accutane. Roche's exclusivity on Accutane expired in February, but no generic versions -- which would quickly erode Roche's sales -- have won approval. Roche voiced concern in February that any generic competitor put in place the same safety controls as Roche has done for Accutane. The side effect profile of the drug has been a subject of controversy since its approval 20 years ago.

The company said Thursday it expects that generics could reach the market at any time.

### **3. On August 18<sup>th</sup>, 2002 the press released an article titled "Hepatitis C Impact Is Still Growing"**

Twenty-six years ago, a blood transfusion saved Cathey Hamlin's life. Three months ago, the Long Beach resident found out that same blood may now be threatening it.

Hamlin is learning firsthand about the much-misunderstood but potentially deadly disease known as hepatitis C.

Although discovered less than 15 years ago, the blood-borne virus is entrenched as the main reason for liver transplants, adding to the chronic demand for too few organs. It is also the leading cause of liver cirrhosis as well as of a cancer known as hepatocellular carcinoma in the United States.

And experts say the worst is yet to come. The rate of new infections peaked in the late 1980s and, because infected individuals may not show any symptoms for two decades or more, the full burden is unlikely to be felt until 2010 or even later. When that happens, hepatitis C-related deaths and the need for liver transplants are expected to triple.

More than 4 million Americans have been infected, but most don't yet know it. Many in the metropolitan region

learned of their infections only after Sept. 11 - when they donated blood.

Injection drug use remains the leading risk factor, and "indiscretions of youth," as one clinician calls them, are often blamed. The virus is not transmitted through casual contact, food, or body fluids other than blood.

Hamlin is one of thousands infected instead through blood transfusions - the vast majority before stringent screening measures took effect in 1992. Infection also has been reported through mother-to-child transmission, accidental needle sticks, or sexual contact, albeit far less commonly. In up to a third of the cases, no identifiable cause has emerged.

"We see people from all walks of life, from homeless people up to judges," said Angela DeLisle, a physician's assistant at Connecticut Gastroenterology Consultants in New Haven. DeLisle's caseload tripled after Sept. 11.

Patient numbers have grown "exponentially" in recent years, said Dr. David Bernstein, director of Hepatology at North Shore University Hospital in Manhasset. "We're just getting inundated."

Once the infection has been identified, individuals can slow the progression to cirrhosis by avoiding alcohol, researchers say.

High mutation rates among the six known genetic versions of the virus have hindered efforts at developing a vaccine. The most successful approaches at treating infection so far involve the antiviral compound ribavirin and a modified version of the body's natural anti-viral interferon molecules (called pegylated interferon). Some doctors are using the word "cure" to describe the absence of detectable virus in a patient six months after such therapy has ended, and overall success rates now exceed 50 percent.

## **HEPATITIS C**

### ***Signs and Symptoms***

*80 percent of infected individuals have no signs or symptoms, which can include jaundice, fatigue, abdominal pain, dark urine, flu-like symptoms.*

### ***Transmission***

*Primarily through the blood of infected individuals; risk from contaminated needles 10-fold greater than that of HIV.*

### ***Effects***

*85 percent of infected individuals acquire chronic form of infection. Of those, 10 to 15 percent develop cirrhosis after 20 years, which can lead to liver failure or hepatocellular carcinoma. Leading cause for liver transplants.*

*At-risk populations: Injecting drug users, recipients of clotting factors before 1987, recipients of blood or organs before 1992, infants born to infected mothers, hemodialysis patients. At relatively lower risk are health-care workers and persons with multiple sexual partners.*

### ***Prevention***

*No vaccine available. Avoid sharing toiletries or needles. Condoms may reduce the transmission of the virus, but efficacy is unknown.*

### ***Treatment***

*Pegylated Interferon with ribavirin effective in about half of patients with the chronic form; avoiding alcohol helps to slow progression of liver disease.*

### ***Trends***

*At least 4 million Americans infected, including at least 2.7 million with the chronic form; rate of new infections dropped in the late 1980s, but hepatitis C-related deaths and demand for liver transplants expected to triple within next 10-15 years.*

#### **4. On August 19<sup>th</sup>, 2002 Hemispherx Biopharma Receives Letter of Intent for Potential Multimillion-Dollar Investment by Royal Family of United Arab Emirates**

Hemispherx Biopharma has received a Letter of Intent for a potential multimillion-dollar investment in the Company by the Royal Family of the United Arab Emirates. Hemispherx President and CEO William A. Carter, M.D. announced the understanding at the Company's annual shareholders' meeting, held last week in Philadelphia.

Dr. Carter announced that the number of patents held by the Company has neared the 400 mark, further expanding the reach of Hemispherx's global technology. Additionally, clinical trials for HIV and Hepatitis C are set to begin in Spain, conducted by the Barcelona-based Laboratorios Del Dr. Esteve S.A.

The biopharmaceutical company focuses on the development of nucleic acids to enhance anti-viral defense systems.

It is the leading company in the experimental-stage development of immune-based therapies primarily addressing the diseases of HIV AIDS and Chronic Fatigue Syndrome. "The multimillion-dollar understanding, presented by a legal and banking representative of the Royal Family of the United Arab Emirates, could represent, through a series of steps called tranches, anticipated during calendar year 2002, the largest single investment to date in Hemispherx," said Dr. Carter. "Additionally, we welcome the collaboration of the UAE with a U.S.-based biotechnology company, in the interest of furthering medicine as well as commerce."

*Hemispherx Biopharma, Inc. is a biopharmaceutical company that focuses on the innovative development of ribonucleic acid (RNA) drug technologies intended to enhance the natural anti-viral defense system of the human body, representing a potential new class of pharmaceutical products. Its primary product, Ampligen, is in two phase IIb clinical trials for HIV/AIDS, one experimental Salvage Therapy and one Strategic Treatment Intervention (STI), and a phase III clinical trial for Chronic Fatigue Syndrome (CFS).*

#### **5. Additionally on August 19<sup>th</sup>, 2002 it was announced that “Virax to Develop Hepatitis B Treatment with New York Blood Center”**

Virax Holdings Limited (ASX: VHL) announced today that it has signed a development agreement with the New York Blood Center to develop a novel treatment for hepatitis B (HBV) infection.

The new treatment is Virax's third product under development and is a significant addition to the company's portfolio of potential drugs in the development pipeline. Dr. David Beames, CEO of Virax Holdings, commented, "The collaboration with Alfred Prince MD of the New York Blood Center will further broaden Virax's infectious disease treatment programs."

"The new development program will be based in part on Virax's Co-X-Gene™ technology," explained Dr Beames. "Virax is continuing its strategy of using the Co-X-Gene™ platform to add new products to its portfolio."

"It is gratifying that the Company's expertise in early development of immune therapies is being recognised around the world and that we have this opportunity to work with a scientist of the eminence of Dr Prince," said Dr Beames.

"Hepatitis B is an extremely serious and widespread problem for which there is currently no cure. Virax is pleased to have established this collaboration in an effort to meet this vital need."

"Preclinical work is expected to commence next year, with late 2003 as the goal for commencement of clinical trials."

Commercial terms of the development agreement have not been disclosed. Both parties will be involved in the development of novel candidate drugs. Virax will contribute its Co-X-Gene(tm) technology and viral vector expertise to commercialise the New York Blood Center hepatitis B research. In exchange, Virax will retain commercial rights to further develop the most promising leads.

### **New York Blood Center**

*New York Blood Center (NYBC) is the USA's largest independent blood distribution and services organisation, supplying blood and blood products to more than 200 hospitals and 20 million people in the greater New York area.*

*The NYBC is also the home of the prestigious Lindsley F Kimball Research Institute which has 18 laboratories dedicated to the study of blood and the prevention, treatment and cure of blood-borne and blood-related diseases. It has an impressive record of taking products from early stage development through to commercial products.*

*Internationally renowned hepatitis expert Alfred M Prince MD, heads the NYBC Virology Laboratory studying DNA-based HBV immunisation and immunotherapies. This laboratory was instrumental in developing a series of tests for the diagnosis of HBV in the 1960s and 1970s. It was also responsible for developing a plasma derived HBV preventative vaccine which is now in widespread use in Asia for mass immunization. "Our collaboration with Virax is an important and promising step towards providing a much needed treatment for a devastating illness," said Dr Prince.*

### **Hepatitis B**

*According to the World Health Organisation (WHO), hepatitis B is one of the most common infectious diseases in the world. The WHO estimates that over 2 billion people have been infected with hepatitis B virus worldwide, and more than 350 million are chronic carriers of the virus. These chronically infected persons are at high risk of death from cirrhosis of the liver and liver cancer, diseases that kill about one million persons each year.*

*While vaccines for preventing hepatitis B have been launched successfully in many instances, safe and effective treatments and cures have proven more difficult to develop. Existing hepatitis medications have shown an alarming tendency to become ineffective as the virus quickly develops resistance to the treatments. Therefore the need for a more effective product to treat hepatitis B has never been greater.*

### **Virax Development Program Update**

*Virax is developing its Co-X-Gene™ platform to deliver a range of new therapies which harness the body's immune system to fight disease. The Company is currently involved in another two significant clinical development programs.*

*In the area of HIV/AIDS, the results of a Phase I/IIa human clinical trial of VIR201, an immune-based drug therapy are due at the end of this year. This is a major milestone for the company as it will provide preliminary safety and some immunogenicity data on the platform technology Co-X-Gene™.*

*Virax has also just filed a patent application for a future prostate cancer treatment. Preclinical testing of this medication is due to commence at the beginning of 2003.*

*Melbourne-based Virax Holdings Limited is a publicly listed (ASX: VHL) development stage biotechnology company engaged in the commercial development of immune-based therapies for HIV/AIDS, cancer, other infectious diseases, and auto-immune diseases.*

*Virax's business strategy is to identify, in-license and take promising early stage biotechnologies through the early stages of clinical development towards the pharmaceutical market.*

## SUMMARY:

- ◆ Virax expands development program into third product area
- ◆ Prestigious US organization seeks Virax collaboration
- ◆ Visit <http://www.virax.com.au> more information

## **6. Additionally on August 20<sup>th</sup>, 2002 Transition Therapeutics Inc. Commences Phase I Clinical Trial with Interferon Enhancing Therapy**

Transition Therapeutics Inc. today announced that it has commenced a Phase I human trial of its interferon enhancing therapy, a therapy that has been demonstrated in pre-clinical studies to be significantly more effective than interferon alone in the treatment of Multiple Sclerosis ("MS").

Patient dosing in this Phase I trial has begun and Transition expects that the trial should be complete by the end of 2002.

Interferon is the current gold standard in the treatment of MS and is also used for the treatment of Hepatitis C, Hepatitis B and Cancer. Worldwide sales of interferon are approximately US \$5.3 billion. Transition previously reported that its interferon enhancing therapy significantly reduced the symptoms and pathologies associated with MS in several different animal models for MS.

Transition has new data showing that this therapy also has more potent anti-viral and anti-proliferative effects than interferon alone and therefore may have applications in Hepatitis C, Hepatitis B and Cancer. Transition plans to perform additional pre-clinical studies in these areas.

### **About Transition Therapeutics**

*Transition Therapeutics Inc. is a publicly listed biopharmaceutical company developing innovative therapeutics focusing on the treatment of multiple sclerosis, diabetes and restenosis. Transition offers a deep product portfolio and a strong management team with expertise in product development. Transition's management intends to continue to build shareholder value by rapidly and cost effectively advancing products from discovery to the clinic and licensing to corporate partners.*

## **7. Additionally on August 20<sup>th</sup>, 2002 the press released the following article titled "Coalition Launches National Campaign to Cut Infection Risk from Improperly Disposed Needles-Policy Void Leaves Workers, General Public at Risk: AMA, ADA, AADE, APHA, ASTHO, NASTAD"**

Improper disposal of used hypodermic needles and other "sharps" outside healthcare facilities poses a potentially serious risk of infection or injury to thousands of Americans, according to the American Medical Association and five other leading public health organizations.

"Used, improperly discarded needles pose a serious risk of injury and even infection to unsuspecting workers, families and pets across the U.S. in their homes, workplaces and public areas," said Anne Burns of the American Pharmaceutical Association, the national professional society of pharmacists. "Current practices, regulations and resources are often incomplete, inconsistent and misleading, resulting in an unintended public safety hazard," she added.

U.S. residents use needles and syringes to inject themselves more than 3 billion times each year. One out of every 12 households includes someone who uses hypodermic needles and syringes. Most used needles end

up in the solid waste system, where they pose a grave health risk to anyone encountering them through the course of their work, spills or other accidents. Used needles can transmit numerous blood-borne pathogens, including HIV, the virus that causes AIDS, as well as hepatitis B and C.

To address this risk, six organizations -- the American Medical Association, American Diabetes Association, American Association of Diabetes Educators, American Pharmaceutical Association, Association of State and Territorial Health Officials and National Alliance of State and Territorial AIDS Directors -- have agreed to serve as an advisory council to the newly-formed Coalition for Safe Community Needle Disposal and have issued a national call to action for their members to initiate new safe needle disposal practices in urban, suburban and rural communities nationwide. Start-up funding was provided by The Waste Management Charitable Foundation, Inc., and BD (Becton, Dickinson and Company).

"The AMA is concerned about any behavior that puts patients and the public at risk," said Patricia L. Turner, M.D., the resident member of the American Medical Association's Council on Scientific Affairs. "We have studied this problem carefully, and feel that we need clear guidelines for the safe disposal of needles outside the healthcare setting. This is why the AMA has agreed to participate in this important process by becoming a member of the Coalition."

"Regulations and procedures exist in medical facilities and other workplaces handling infectious material to protect healthcare professionals and other workers from potentially dangerous needle sticks; it's time to extend a similar level of protection to individuals in their homes, neighborhoods, and public facilities," Dr. Turner added.

The Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA) are two federal entities that currently provide guidelines for used needle disposal. However, the EPA's Web site guidelines fall short of the ideal and OSHA's regulations apply only to workplaces under OSHA's jurisdiction.

"We are pleased that both the EPA and OSHA have indicated a commitment to working with the Coalition to identify better, safer and more practicable ways for the nation to dispose of used needles," said Burns.

The Coalition will work to educate individuals and policy makers about alternatives and options available to communities to assure safe needle disposal. In addition, the Coalition will use advocacy and education to support guidelines that may be used by federal, state and local officials to develop locally tailored programs for safe community disposal of used sharps.

The Coalition supports development of disposal programs that are:

- ◆ Accessible. Safe sharps collection and disposal options should be easily accessible to all members of the community and conveniently available in terms of location, days and hours to ensure maximum utilization.
- ◆ Affordable. Programs should be within reach of people at all income levels, including through reimbursement or subsidy when necessary.
- ◆ Confidential. Individuals should be able to dispose of sharps privately.
- ◆ Distinct. Disposal programs should consider directing sharps into a waste stream separate from the standard public waste stream.
- ◆ Safe. Programs should assure the safe collection and disposal of used sharps and comply fully with any pertinent federal, state or local requirements.
- ◆ Well-publicized. Information on disposal programs should be available to (and through) physicians, diabetes educators, nurses, pharmacists, substance abuse counselors, veterinarians and other health professionals who come into contact with those who use sharps.
- ◆ Inclusive. Solutions should address the needs of all individuals in the community who use sharps.
- ◆ Supported by the community. To be effective, solutions should have broad-based community support.

Several different types of programs currently operating in the U.S. fulfill these principles, including:

- ◆ Community drop-off sites, such as pharmacies, police and fire departments, and public drop boxes.
- ◆ Syringe exchange programs.
- ◆ Municipal waste pick-up programs.
- ◆ Mailback programs. Home users place sharps in a special container and return by U.S. Mail to a collection point where they are incinerated.

According to the Coalition, national statistics indicate that home needle use will continue to increase in coming years as diabetes and other chronic diseases that require self-administration of injectable medicines become more prevalent, as baby boomers age, as health care relies more heavily on out-patient procedures and as more people enter home health care:

- ◆ There are 8 million in-home syringe users, approximately 3 percent of the U.S. population.
- ◆ Of those 8 million, some 3.4 million people with diabetes require an estimated 1-2 billion injections each year. Each year injection drug users (IDUs) will administer approximately 1 billion injections of illicit drugs.
- ◆ An unknown number of injections will be given for infertility, allergies, multiple sclerosis and other home health treatments, as well as to pets.
- ◆ Needle stick injuries cost approximately \$3,000 per injury for follow-up tests and care if no infection is incurred. Costs soar if there is a serious infection.

The Coalition for Safe Community Needle Disposal is a 501(c)3 organization available to provide technical and other assistance. For more information, please call 713/980-3120 (toll free 800/643-1643) or visit our Web site at [www.safeneedledisposal.org](http://www.safeneedledisposal.org)

## **8. On August 21<sup>st</sup> the medical editors from Cancer Weekly released an article titled “Sector of Hepatitis C Virus May Interrupt Work of Cancer Prevention Gene”**

The findings of a new study are pointing to the NS5A protein of hepatitis C virus (HCV) as an inhibitor of p53-mediated apoptosis. Normally the p53 protein could suppress tumor formation by inducing programmed cell death, or apoptosis. However, scientists have now found evidence that NS5A may interact with p53 to block that effect, igniting cancer growth. "HCV NS5A binds directly to p53 and colocalizes p53 in the perinuclear region," said K-H. Lan and colleagues of the protein interaction. Lan, of the Taipei Veterans General Hospital and National Yang-Ming University School of Medicine in Taiwan, was one of several collaborators on a multicenter research team to examine NS5A protein and p53 relationships.

According to investigators, p53 would usually activate p21/waf1, an interrupter of cell cycle progression, but p21/waf1 was downregulated in liver cancer cell lines where NS5A was also present. NS5A had the effect of overriding p53-induced apoptosis in Hep3B liver cancer cells treated with exogenous p53, said Lan and coauthors. "The p53-induced apoptosis was abrogated by NS5A and the inhibition effect correlates well with the binding ability of NS5A to p53," researchers stated.

NS5A also controlled the effects of a sector of the transcription factor TFIIID, an important p53 protein activator. The data is being published in *Oncogene*, 2002;21(31):4801-4811).

Based on the data, Lan and colleagues concluded HCV NS5A seizes control of p53 and other apoptosis activators, leaving liver cells vulnerable to cancer formation.

Key points reported in this study include:

- ◆ The NS5A protein of hepatitis C virus (HCV) interacts with p53 tumor suppressor protein in liver cells

- ◆ NS5A inactivates p53-induced apoptosis in liver cancer cells
- ◆ NS5A capture of p53 may contribute to the formation of liver cancer in patients infected with HCV

## **9. Additionally on August 21<sup>st</sup> the medical editors of Hepatitis Weekly released an article titled “SkyePharma and GeneMedix Sign Interferon alpha-2b Development Agreement”**

SkyePharma, plc, (SKYE) and GeneMedix, plc, announced the signature of a joint agreement to develop an extended release formulation of interferon alpha-2b using SkyePharma's proven DepoFoam injectable drug delivery technology.

Interferon alpha-2b is already accepted as a part of the standard therapy in the treatment of hepatitis C and hepatitis B infection, and as an adjunct to chemotherapy in certain forms of cancer.

Paul Edwards, GeneMedix's CEO, commented: "This agreement is an important milestone in the development of GeneMedix. Our stated objective is to develop innovative formulations of our recombinant proteins, enabling us to compete more successfully, especially in Europe and the U.S.A. This deal with SkyePharma gives us access to an advanced project using proven drug delivery technology."

SkyePharma has already formulated interferon alpha-2b with its DepoFoam technology. Reflecting this, and the value of the DepoFoam licensing rights, SkyePharma received from GeneMedix an initial payment of \$5 million.

The payment was satisfied through the issue of an unsecured note, carrying a 5% coupon, which is convertible at any time into between approximately 8.3 million and 11.2 million fully paid, ordinary GeneMedix shares. GeneMedix has the option to redeem the note for cash in certain circumstances.

In addition, SkyePharma will receive undisclosed milestones payable against progress through clinical development. The two companies will assume equal shares of further development and manufacturing costs and will also share potential milestones received and royalties from a third party on the eventual out-licensing and sales of the product. This article was prepared by Hepatitis Weekly editors from staff and other reports.

## **10. Additionally on August 21<sup>st</sup>, 2002 the medical editors of Hepatitis Weekly issued an article titled “Slim Window Separates Benefits from Disadvantages in Liver Disease Patients”**

High doses of dietary retinoids may exacerbate liver disease in patients who already have liver fibrosis, a new study suggests.

Vitamin A, a retinoid, is deemed essential for maintaining vision and for cellular growth and differentiation. Hoping to clear up conflicting information about the benefits or disadvantages of retinoids in individuals with liver fibrosis, who are highly susceptible to hepatotoxicity, Brigitte Vollmar and colleagues at the University of Saarlands' Institute for Clinical and Experimental Surgery in Germany have completed a series of animal model experiments indicating that too much of a good thing can be extremely harmful, particularly for that patient population.

During the study, researchers fed the rodents meals containing high, low, or normal doses of vitamin A and treated the rats with carbon tetrachloride CCl(4), a liver toxin that induces fibrosis. "In animals with high dietary hepatic retinoid levels, liver fibrosis was more pronounced and was associated with an increased CCl(4)-toxicity resulting in high mortality (73%)," described Vollmar and coauthors.

Several studies have determined retinoids may regulate the manufacture of collagen. The researchers found almost twice as much collagen deposition, a fibrosis marker, in the livers of rodents fed the high vitamin A diets than in rodents fed standard diets. This data is published in the *Journal of Gastroenterology and Hepatology*, 2002;17(7):791-799).

Those same animals also demonstrated more damage to their liver cells, fewer sinusoids, and greater interruption of flow in the bile ducts. "CCI(4) reduced hepatic retinoid levels in high vitamin A diet-fed animals, but restored hepatic retinoid levels in animals fed with a vitamin A-deficient diet, implying major interference of vitamin A metabolism with hepatotoxic agents such as CCl4," investigators argued.

The effects of low vitamin A diets were negligible, with liver fibrosis remaining unchanged and rodents exhibiting no increased mortality. "While dietary vitamin A shortage does not promote liver fibrogenesis, high levels of vitamin A have the potential to increase systemic and hepatic toxicity of CCl4," Vollmar and coauthors said, adding "The narrow therapeutic window for nutritional vitamin A substitution must take into account that liver fibrotic patients may display enhanced susceptibility to the adverse effects of vitamin A."

Key points reported in this study include:

- ◆ High doses of vitamin A increased liver injury in rodents given the liver toxin carbon tetrachloride to induce liver fibrosis
- ◆ Low doses of vitamin A did not increase liver damage in rats given the fibrosis inducer
- ◆ Individuals with liver fibrosis should remain cognizant that vitamin A substitution is beneficial, but may also be harmful at select doses

## **11. Additionally on August 21<sup>st</sup>, 2002 the medical editors from Blood Weekly wrote an article titled "Age a Factor in Transfusion-Related Chronic Hepatitis C and Liver Disease"**

Older individuals who become infected with hepatitis C virus (HCV) upon receiving blood transfusions shoulder a higher risk for developing liver cirrhosis than their younger counterparts do.

It was only during the early 1990s that screening tests became available for hepatitis C virus (HCV) infection. "Before the introduction of HCV screening for blood donors, the risk of acquiring HCV infection as a result of a transfusion was about 10%," noted researchers working in Bergamo and Milan, Italy.

Data exploring the relationship between transfusion-associated chronic hepatitis C and cirrhosis progression suggests older age at the time of infection may be a significant factor in disease outcomes, according to Dario Conte and coauthors, IRCCS, Greater Hospital, Milan.

After evaluating more than 2700 patients with liver disease, the researchers identified 392 HCV-positive individuals who, after other risk factors were ruled out, probably became infected after receiving a transfusion. Researchers performed liver biopsies on 268 of those patients.

"After a mean interval of 18.4 years, 54 patients (20.1%) had cirrhosis, which multivariate analysis showed to be independently associated with the duration of follow-up, age at infection and at the time of liver biopsy, and serum alanine aminotransferase levels at biopsy," Conte and coauthors said, adding, "The time necessary to have a 50% probability of developing cirrhosis in patients ages 21-30, 31-40, and more than 40 years was 33, 23, and 16 years, respectively."

The risk ratio for progression to cirrhosis within the next 30 years among people between the ages of 21 and 30 was nearly triple that of people younger than 20. This data is published in *Blood*, 2002;99(12):4588-4591).

"Our findings suggest that an aggressive therapeutic approach should be adopted in patients infected by HCV at an older age to prevent the progression to end-stage liver disease," Conte and colleagues stated.

Key points reported in this study include:

- ◆ Individuals who became infected with HCV by transfusion and who were younger than 20 had a significantly lower risk for eventually developing cirrhosis than did those infected at an older age
- ◆ Age at infection and disease activity were the most important factors for predicting cirrhosis in patients with transfusion-associated HCV
- ◆ Patients infected by transfusion-associated HCV should receive more aggressive therapies in order to reduce their risks for developing chronic or acute liver disease

## **12. Additionally on August 21<sup>st</sup>, 2002 medical editors from Hepatitis Weekly released an article titled "Donor Age a Factor for Lower Survival in Hepatitis C Virus Transplantees"**

Scientists believe the rising age of donors may be a cause for decreasing survival rates in liver transplant recipients who are hepatitis C virus (HCV) positive.

Researchers in Spain have come to this conclusion after investigating survival rates in a population of more than 500 people with cirrhosis who received liver transplantations during the 1990s. Of the 522 transplant recipients, 283 were HCV positive. "With similar follow-up, the percentage of deaths in the HCV-positive group was significantly higher than in the HCV-negative group (37% vs. 22%,  $p < 0.001$ ), and patient survival was lower (77%, 61%, 55% vs. 87%, 76%, 70% at 1, 5, and 7 years, respectively;  $p = 0.0001$ )," said Marina Berenguer and coinvestigators in the Hepato-Gastroenterology Service at La Fe University Hospital in Valencia, Spain.

Decompensated graft cirrhosis was a major cause of death in people with HCV, whereas in those without HCV, death was primarily caused by infection. Berenguer and colleagues said that increased donor age and immunosuppression were two of the major reasons for poorer outcomes in transplant recipients with chronic hepatitis C. The data is published in *Hepatology*, July 2002;36(1):202-210).

"Patient survival is lower among HCV-positive recipients than among HCV-negative ones and has been decreasing in recent years," researchers said. "The aging of donors is a major contributor to this worse outcome," they declared.

Key points reported in this study include:

- ◆ Survival among hepatitis C virus (HCV)-positive, cirrhotic liver transplant recipients has decreased but among HCV-negative transplantees has increased
- ◆ Decompensated liver cirrhosis accounted for a large number of the deaths of HCV-positive liver transplant recipients
- ◆ Advancing age among liver donors is one, major reason for decreasing survival among HCV-positive liver transplant recipients

## **13. Additionally on August 21<sup>st</sup>, 2002 the medical editors of Hepatitis Weekly published an article titled "Feeling Excessively Tired Is a Major Complaint in Chronic Hepatitis C"**

A new study has found that fatigue is major symptom in individuals diagnosed with hepatitis C virus (HCV). "Fatigue is the most frequent extrahepatic manifestation in patients infected with HCV," Thierry Poynard and

coauthors announced in the July issue of Journal of Viral Hepatitis (J Viral Hepat, 2002;9(4):295-303). Poynard's research team works at the Groupe Hopital La Pitie-Salpetriere in Paris, France.

In one of the first prospective studies to look at fatigue as a complication of HCV, Poynard evaluated more than 1600 patients initially receiving diagnoses of HCV. They also examined associations between fatigue and other manifestations of HCV infection.

"Fatigue was present in 53% of patients (95% CI, 51-56)," said Poynard and coauthors. "In 17% of patients (95% CI, 15-19) fatigue was severe, impairing activity." Other major symptoms arising apart from the liver included arthralgia, paresthesia, myalgia, pruritus, and sicca syndrome, researchers said. Statistical analysis independently linked being female, being older than 50, and having cirrhosis, depression and purpura with having fatigue symptoms. Fibromyalgia, marked by fatigue and muscle or joint pain, was prevalent in nearly 20% of the patient population.

Based on the data, doctors might expect a large number of their HCV-positive patients to experience symptoms of fatigue.

Key points reported in this study include:

- ◆ More than 50% of patients diagnosed with hepatitis C virus (HCV) infections experienced fatigue
- ◆ Independent risk factors for fatigue in HCV-infected patients included being female, older than age 50, and having depression, purpura, and cirrhosis
- ◆ Fatigue is the most common extrahepatic manifestation of HCV infection

#### **14. Additionally on August 21st, 2002 the press announces the following: "U.S. Approves Testing of Drug for West Nile Virus"**

The U.S. Food and Drug Administration has given the go-ahead for a trial of a drug for use against the West Nile virus, while the government pledged more money on Wednesday to track and control the disease.

The mosquito-borne West Nile virus has killed 13 people in the United States so far this year. The virus, which first appeared in the United States in 1999, is spreading more quickly than scientists had predicted, and the season has not hit its peak yet.

There is no cure for West Nile virus, but Schering-Plough Corp. said the FDA had approved trials of its drug Intron A, also known as interferon, now used to treat hepatitis C virus, for use against West Nile.

Schering spokesman Bob Consalvo said the work was being done by an independent researcher in New York, Dr. James Rahal of New York Hospital Queens. He said Rahal also had done some work with Intron A against a related virus that has been in the United States for years and also is carried by mosquitoes, called St. Louis encephalitis.

"We are supplying the drug," Consalvo said.

Rahal said in a statement that the trial will involve 40 patients infected with West Nile virus, and that he expected it to begin immediately in Louisiana, Mississippi and the New York City area.

New York Hospital Queens said the trial seeks to determine if Intron A can decrease the duration of the illness, make neurological symptoms less severe and prevent death. The hospital said Intron A has been shown to be effective in the laboratory against West Nile virus.

West Nile virus does not cause any symptoms in eight out of 10 people it infects, but in some it can cause encephalitis, an inflammation of the brain and death.

Rahal said patients age 50 and older are eligible to be enrolled in the study, with younger patients eligible

only if they are diagnosed with encephalitis.

#### *MORE FEDERAL FUNDING*

*The federal government said it was providing an extra \$4 million to states to spend on tracking and controlling West Nile virus.*

*The U.S. Centers for Disease Control and Prevention said it had confirmed 269 cases and 13 deaths from the virus, eight in Louisiana, two in Mississippi and one each in Kentucky, Illinois and Texas.*

*"This latest funding will help states with West Nile virus activity to rapidly identify new cases of the virus, expand laboratory capacity for this testing, and continue to track the spread of the virus through the monitoring of infection in birds, horses and mosquitoes," CDC Director Dr. Julie Gerberding said in a statement. "We are committed to doing all we can to help states monitor the spread of West Nile virus, detect new cases and protect their citizens from this epidemic," Health and Human Services Secretary Tommy Thompson said.*

*The money also is earmarked to use for public awareness campaigns. While some states are spraying pesticides and others are using bacteria that kill mosquito larvae, the CDC is stressing personal responsibility for avoiding the virus by telling people to cover up with long sleeves, to use repellents and to clear any standing water.*

*West Nile virus has now been found in mosquitoes, birds, horses and people in all 37 states east of the Rocky Mountains, and it is expected to spread further as it is carried by migrating birds. The CDC has said that as many as 1,000 people could become infected this year.*

*The extra \$4 million brings total CDC funding to states for West Nile virus so far this year to more than \$31 million. CDC has given \$54 million to states, cities and territories since West Nile virus was first detected in 1999.*

## **15. Additionally on August 21<sup>st</sup>, 2002 medical editors from Blood Weekly published an article titled "Pre-market Approval Application Filed with FDA for Hepatitis C Viral Load Assay"**

Bayer Corporation, Business Group Diagnostics, announced that it has filed a premarket approval application (PMA) to the U.S. Food and Drug Administration (FDA) for its viral load test for hepatitis C virus, (HCV) - VERSANT HCV RNA 3.0 Assay (bDNA).

The HCV bDNA test is a quantitative assay designed to measure HCV RNA levels (viral load) in serum or plasma, using Bayer's proprietary branched DNA (bDNA) signal amplification technology. It is the first quantitative test for HCV RNA submitted to the FDA for review.

This submission compliments that of the company's development partner, Gen-Probe, Inc., which in March filed a PMA to the FDA for the VERSANT HCV RNA Qualitative Assay Transcription Mediated Amplification (TMA).

The VERSANT HCV TMA assay, which utilizes Gen-Probe's proprietary TMA technology, is designed for the ultra sensitive detection of hepatitis C RNA. Bayer has the exclusive worldwide diagnostics rights to market and sell the HCV TMA assay. "The submissions by Bayer and our partner Gen-Probe are critical steps in the global commercialization of these two very important diagnostic tests," stated Peter Knueppel, senior vice president, nucleic acid diagnostics business segment. "Hepatitis C can be a devastating disease. With approval, these assays should provide clinicians with valuable tools to aid in the diagnosis and management of HCV infection," added Knueppel. "Along with the VERSANT HCV Genotype Assay (LiPA), these assays comprise our worldwide market leading HCV product line and are an important part of Bayer's strategy to solidify our position as a leader in infectious disease nucleic acid diagnostic testing," he said.

## **16. Additionally on August 21<sup>st</sup>, 2002 the medical editors of Hepatitis Weekly released an article titled “Lamivudine Beats Famciclovir for Suppressing Hepatitis B Virus in Asian Study” based upon results published in this month’s issue of the Journal of Medical Virology**

A comparative study has shown lamivudine is more effective than famciclovir for suppressing viral replication in patients with chronic hepatitis B virus (HBV) infections.

Lamivudine and famciclovir are both antiviral agents. While lamivudine has been added to a standard arsenal of therapies used for treating HBV, famciclovir is best known for the control of herpes virus infections. Comparisons of both therapies in Chinese patients infected with HBV shows lamivudine beats down HBV infections better than famciclovir does.

One hundred patients participated in the prospective randomized trial. Investigators at the University of Hong Kong prescribed lamivudine or famciclovir to equal numbers of patients for the first 12 weeks of the trial, and then had all of them to begin receiving lamivudine for the remaining trial period.

"Significantly more patients treated by lamivudine than by famciclovir had undetectable HBV DNA levels after 12 weeks of therapy," reported C.L. Lai and coauthors.

Researchers noted that at as early as the second week of the study, median HBV DNA levels were substantially lower in patients who received lamivudine. The results are published in the *Journal of Medical Virology*, 2002;67(3):334-338).

"At week 16, 4 weeks after the famciclovir-treated patients were put on lamivudine, there was no longer any difference in HBV DNA levels between the two groups of patients," they said. With both of the therapies being well-tolerated, neither caused any serious side effects in the patient groups.

Lai and colleagues concluded that lamivudine induced viral suppression earlier than famciclovir did and was overall more effective for treating chronic hepatitis B than famciclovir was.

Key points reported in this study include:

- ◆ Viral suppression occurred earlier in patients given lamivudine than in those given famciclovir among Asian patients with chronic hepatitis B
- ◆ Lamivudine and famciclovir were both well tolerated and both induced very few side effects
- ◆ Lamivudine was a stronger agent for suppressing hepatitis B virus infection in Asian patients than famciclovir was

## **17. On August 22<sup>nd</sup>, 2002 the medical editors from Hepatitis Weekly published an article titled “New Testing Methods May Improve Detection and Treatment”**

Hepatitis C virus (HCV) is the most common chronic infectious disease in the United States, affecting an estimated 2.7 million people, or nearly 2% of the population.

While HCV causes mild, asymptomatic disease in many people, chronic HCV infection can cause cirrhosis, liver failure, and hepatocellular carcinoma.

Recently, combination treatment for HCV has been able to eradicate the virus in approximately half of all cases, greatly expanding the need for laboratory tests for HCV infection. Because different tests are needed for different purposes, new tests have become available to assist clinicians in diagnosing the infection, and to monitor treatment efficacy.

D. Robert Dufour, MD, chief of pathology and laboratory medicine at the Veterans Affairs Medical Center in Washington, DC, and professor of pathology at the George Washington University Medical Center, also in Washington, recently provided an update on the status of HCV testing during the 54th Annual Meeting of the American Association of Clinical Chemistry, held in Orlando, Florida, July 28-August 1, 2002.

The hepatitis C virus is a single-stranded RNA virus. To date, it has not been possible to grow the virus in a culture. It is the most common chronic infectious disease in Europe and North America and affects an estimated 170 million people worldwide. There are six genotypes of the virus, although only three of these are commonly seen in the U.S.

The most widely used test is designed to detect antibodies to one or more HCV proteins. Most laboratories report results as either positive or negative; positive results indicate that the person has been exposed to HCV. The U.S. Centers for Disease Control and Prevention recently developed new guidelines for laboratories that will require them to separate "low positive" from "strong positive" tests and do follow up testing before reporting results to a physician. The guidelines are expected to be released this fall.

However, in most instances of patient testing, the clinical question is not whether the person has been exposed to HCV, but whether the individual is currently infected, which requires testing of another sort: HCV RNA. There are two major types of HCV RNA testing, one qualitative (which simply tells whether the virus is present) and one quantitative (which tells how much of the virus is present).

Most qualitative HCV RNA tests are used for initial analysis to identify positive individuals. Recently, a test to detect a protein produced by HCV (core antigen) has become available, and seems to provide similar information to HCV RNA tests, but at a lower cost.

But because antibody and HCV RNA tests do not indicate which strain of HCV has infected an individual, tests to determine the genotype have been developed. Most rely on detecting sequences in the RNA that correspond to those of the six known strains of HCV. The simplest technique, termed the Line Probe assay (LiPA), involves immobilized HCV RNA sequences that are allowed to hybridize to RNA in the sample, with visual detection of hybrids by an enzyme reaction.

The pattern of bands allows determination of genotype in most cases. By contrast, direct sequencing of a segment of the HCV genome, and comparison to libraries of known HCV genotypes, allows detection of infection by more than one strain of the virus.

There are three potential treatments for individuals positive for HCV RNA: interferon monotherapy, standard interferon plus ribavirin, and pegylated interferon plus ribavirin. Combination treatments are more effective than interferon monotherapy, but some patients cannot take ribavirin. With combination therapy, it has been shown that individuals who are genotype 2 or 3 will respond just as well to 24 weeks of treatment as to 48 weeks of treatment.

Treatment for HCV with interferon is both expensive and has many side effects. Therefore, it is important to determine whether the treatment is effective in eliminating HCV RNA from the blood. Treatment is usually monitored by using very sensitive assays for HCV RNA and the criteria for determining treatment "response" can vary, based on the type of treatment used.

The goal of treatment is to eradicate HCV RNA from the body, which correlates with the absence of HCV RNA in the blood after treatment has been stopped for 6 months. Proposed consensus guidelines from the National Institutes of Health (NIH) are considering whether to recommend testing at 12 weeks of treatment to see if the patient is responding, rather than waiting 24 weeks.

The testing being considered would check viral load before treatment begins, and whether it has fallen a certain amount after 3 months of treatment [www.guidelines@nih.gov](http://www.guidelines@nih.gov)

Dufour said that the following are the most common risk factors for HCV infection:

- ◆ Illegal drug use, especially injectable drugs.
- ◆ Blood transfusion(s) before 1992.
- ◆ Ten or more sex partners.
- ◆ Dialysis.

**18. Additionally on August 22<sup>nd</sup>, 2002 the medical editors from Hepatitis Weekly published the following article titled “Patients Undergoing Fertility Treatments Should Be Tested for Hepatitis C Virus” after data was published in this month’s issue of Human Reproduction**

Since there is a risk that patients who undergo assisted reproduction procedures may be infected with hepatitis C virus (HCV), doctors have recommended that all infertile patients be screened for infection. Doing so may reduce the risk for occupational exposure or vertical transmission, or even the contamination of other embryos, according to E. Pandolfi Passos and colleagues, investigators in the Departments of Obstetrics and Gynecology and Pediatrics at the Hospital de Clinicas de Porto Alegre in Brazil.

"In assisted reproduction, HCV transmission may pose a risk for the baby, technicians, and gametes or embryos from noncontaminated parents," explained Passos and coauthors in the August 2002 issue of *Human Reproduction* (Human Reprod, August 2002;17(8):2085-2088).

From 1997 until 1998, the investigators screened for HCV and hepatitis B virus (HBV) in 409 patients undergoing treatment for infertility in a Brazilian hospital. "The overall prevalence of anti-HCV was 3.2% (8/248) among women and 3.7% (6/161) among men," they reported. None of the individuals were positive for either HBV or human immunodeficiency virus (HIV). Two of the HCV-positive patients were eventually lost from the data set, leaving 12 people for additional testing. Of those 12 patients, 5 of them, including 1 woman and 4 men, were positive for HCV-RNA, signaling active infection.

Among the females who were HCV-positive based on antibody screening, having a male partner who was HCV-positive was the main risk factor for infection, whereas among men who were HCV-positive, using intravenous drugs was the main risk factor for infection.

"Since the risk for vertical and laboratory HCV infection is not well determined, and HCV prevalence is not negligible in this group, we recommend that infertile patients be screened before assisted reproductive techniques," Passos and colleagues urged.

Key points reported in this study include:

- ◆ Approximately 3% of patients who underwent assisted reproduction techniques at a Brazilian hospital were carrying antibodies to HCV
- ◆ Several more of those patients carried HCV RNA, signaling the presence of replicating virus
- ◆ Patients who undergo assisted reproduction techniques should be screened beforehand for HCV infection
- ◆

**19. Additionally on August 22<sup>nd</sup>, 2002 the medical editors of Hepatitis Weekly published an article titled “Images Depict Link Between Chronic Hepatitis C Activity and Node Appearance” after data was published in this month’s issue of the American Journal of Roentgenology**

Physicians have been able to distinguish chronic hepatitis C activity by the way patients' lymph nodes appear

on magnetic resonance (MR) imaging. A team at Thomas Jefferson University in Philadelphia, Pennsylvania, has used MR images of local lymph nodes to differentiate mild, moderate, and severe hepatitis activity in patients with chronic hepatitis C, according to a report in the *American Journal of Roentgenology* (August 2002;179(2):417-422).

"Fifty patients with chronic active hepatitis C, who had MR imaging examinations and a related histology report from a liver biopsy obtained within 1 month of the MR imaging were chosen from our radiology database and studied retrospectively," described Xio-Ming Zhang, an investigator in the Department of Radiology. For 4 years, doctors monitored the chronic hepatitis C patients for the evolution of cirrhosis or hepatocellular carcinoma, a type of primary liver cancer. Radiologists, blinded to the patients' medical histories, evaluated and graded the patients' MR images for nodal characteristics, including size, number, and location, and research team members subsequently compared those findings to the patients' histological activity levels. "Forty-four (88%) of 50 patients had perihepatic lymph nodes larger than 5 mm on MR images, including 64.2% (9/14) of the patients with mild activity, 96.3% (26/27) of the patients with moderate activity, and 100% (9/9) of the patients with severe activity ( $p=0.0034$ )," reported Zhang's team. Patients with severe activity had, on average, more than three times as many perihepatic lymph nodes as did those with minimal activity, and the average size of their lymph nodes was over three times larger. T-2-weighted MR images indicated that chronic hepatitis C patients with severe activity had significantly more hyperintense nodes.

Among the 50 patients enrolled in the study, there was no correlation between histologic activity and liver function test results, researchers said. The investigators concluded MR imaging could be used to correlate lymph node characteristics with hepatic activity in patients with chronic hepatitis C.

Key points reported in this study include:

- ◆ Chronic hepatitis C patients with more severe activity had larger and greater numbers of perihepatic lymph nodes upon MR imaging
- ◆ Those patients also had more hyperintense nodes
- ◆ Lymphadenopathy correlates with hepatic activity in patients with chronic hepatitis C

## **20. Additionally on August 22nd, 2002 the press announced that “Roche Molecular Systems Initiates U.S. Clinical Trials Of COBAS AmpliScreen(TM) HBV Test”**

Roche Molecular Systems, Inc. today announced the start of comprehensive clinical trials of its COBAS AmpliScreen(TM) HBV Test. The trials mark an important milestone because, for the first time in the U.S., Roche's PCR nucleic acid amplification technology (NAT) test will be evaluated for its safety and effectiveness in screening blood donations for the Hepatitis B virus (HBV). In the process, researchers expect to gain a clearer understanding of the prevalence of HBV.

"The clinical trials of the AmpliScreen test will help us learn more about HBV by identifying cases earlier in the course of infection," said Paul V. Holland, MD, chief executive officer and medical director of BloodSource, and a principal investigator in the study. "We may also identify chronic, low-level HBV carriers who have not made a serologic response yet, but who nonetheless present a transmission risk, which would help us further optimize blood safety."

Serological tests currently approved to screen blood donations usually just detect a person's antibodies to a viral infection, but these antibodies take time to develop -- a period known as a "serologically silent window" or preseroconversion window period. In 1996, the National Heart, Lung, and Blood Institute's Retrovirus Epidemiology Donor Study (REDS) estimated that one in 63,000 donations in the United States were made during the preseroconversion window period, thus posing a risk for transmission of HBV infection.

The AmpliScreen Test is able to amplify a single molecule of viral DNA or RNA billions of times, and is therefore capable of directly revealing the presence of viral genetic material in blood, which may contribute to narrowing the window period.

"It is important that we conduct a trial to determine the efficacy of this approach for hepatitis B, particularly in the context of pool testing, and finding additional sensitivity to achieve a reduction in HBV window cases over and above current licensed and unlicensed assays," noted D. Michael Strong, PhD, executive vice president of operations for Puget Sound Blood Center, and also involved in the trial. "The Roche test has demonstrated the most sensitive potential in this regard."

The Japanese Red Cross is already using Roche's AmpliNAT(TM) system to screen for HBV in their blood donations. This system was developed to meet the needs of the 5 million donations screened by the Japanese Red Cross each year since February 2000. AmpliNAT is a triplex assay capable of simultaneously screening HBV, HCV and HIV viral material.

"The experience in Japan showed the presence of more than 260 'window' cases of HBV using the more advanced NAT screening technology. It is reasonable to expect that we will identify similar results through this clinical trial," added Dr. Holland.

Roche is able to move forward with the clinical trials of its COBAS AmpliScreen HBV Test, based on receiving Investigational New Drug Application (IND) permission to proceed to clinicals from the U.S. Food and Drug Administration in July. The trials will be conducted at five of America's Blood Centers locations throughout the United States: BloodSource in Sacramento, California; Puget Sound Blood Center in Seattle, Washington; Community Blood Center of Kansas City, Missouri; Memorial Blood Center in Minneapolis, Minnesota; and Gulf Coast Regional Blood Center in Houston, Texas.

"The start of clinical trials for the COBAS AmpliScreen HBV test is an important milestone, as it will allow for the collection of data that ultimately will enhance blood screening efforts in the United States," said Heiner Dreismann, PhD, head of Roche Molecular Diagnostics. "The trials also underscore Roche's long-term commitment to blood screening, and the application of PCR technology to the public health arena."

### **About HBV**

*Although HBV can be prevented with a vaccine, in the United States approximately 5,000 people die from HBV each year. HBV is the most common serious liver infection in the world, and the leading cause of liver cancer. It is highly infectious (100 times more infectious than HIV), and more than 200,000 people contract HBV annually in the U.S. Approximately 90 percent of those infected will completely recover as their immune systems eradicate the disease; however, up to 10 percent remain carriers of HBV. In approximately 50 percent of adult cases, no symptoms are observed; however carriers are able to transmit the virus throughout their lives. There are more than one million chronic HBV carriers in the U.S., one-third of whom do not know how they were infected.*

### **About AmpliScreen**

*The COBAS AmpliScreen products, used for screening blood donations, are based on Roche's polymerase chain reaction (PCR) technology, which is now the leading nucleic acid amplification technology (NAT) in the world. Roche's PCR blood screening tests for HCV and HIV-1 are already approved for commercial use in Italy, France, Germany, Australia, and Switzerland. Poland has approved the COBAS AmpliScreen HCV Test, v2.0 for commercial use, and Spain has approved the COBAS AmpliScreen HIV-1 Test, v1.5 for these purposes. The products are also used in other countries where registration is not required.*

### **About Roche and the Roche Diagnostics Division**

*Headquartered in Basel, Switzerland, Roche is one of the world's leading research-oriented healthcare groups in the fields of pharmaceuticals, diagnostics and vitamins. Roche's products and services address prevention, diagnosis and treatment of diseases, thus enhancing well-being and quality of life. Roche's Diagnostics Division, the world leader in in vitro diagnostics with a uniquely broad product portfolio, supplies a wide array of innovative testing products and services to researchers, physicians,*

patients hospitals, and laboratories world-wide. Roche Molecular Diagnostics, a business area of Roche Diagnostics, has made polymerase chain reaction (PCR) the leading nucleic acid amplification technology (NAT) in the world. Roche's website is located at [www.roche-diagnostics.com](http://www.roche-diagnostics.com).

Statistics on HBV from: "Facts About Hepatitis B For Adults," National Coalition for Adult Immunization, August 2001, [www.nfid.org](http://www.nfid.org); "WHO Fact Sheet/204," World Health Organization, October 2000, [www.who.int](http://www.who.int); and The Centers for Disease Control and Prevention, "Viral Hepatitis B Fact Sheet," December 2001, [www.cdc.gov](http://www.cdc.gov).

The COBAS AmpliScreen products are available for research only use in the U.S.

## **21. Additionally on August 22<sup>nd</sup>, 2002 the medical editors from Hepatitis Weekly published an article titled "Entecavir May Alter Outlook for Hepatitis B Patients Resistant to Lamivudine" as a result of data published in the August issue of Antimicrobial Agents and Chemotherapy**

Individuals who become resistant to lamivudine during treatment for hepatitis B virus (HBV) infection may benefit from receiving entecavir.

Patients on lamivudine often sustain the risk of developing HBV mutants that become resistant to therapy. Entecavir, another antiviral, is presently undergoing evaluation in clinical trials. Researchers at Bristol-Myers Squibb Pharmaceutical Research Institute in Wallingford, Connecticut, have completed a series of laboratory experiments suggesting entecavir may be as much as 300 times more potent for stamping out HBV infection than lamivudine is.

In the laboratory experiments, researchers tested entecavir on common wild-type virus and lamivudine-resistant virus. "These enzyme inhibition studies demonstrated that entecavir triphosphate is a highly potent inhibitor of wild-type HBV DNA polymerase and is 100- to 300-fold more potent than lamivudine against lamivudine-resistant HBV DNA polymerase," reported S. Levine and colleagues. Mutations at selective regions of HBV DNA are what make the virus resistant to lamivudine.

According to the results of cross-resistance assays, as much as 30 times more entecavir was needed to stop viral replication in lamivudine resistant viruses. Investigators noted that when they treated liver cancer cells to pharmacological doses of entecavir, the cells could accumulate enough of the drug to be effective against both wild-type and mutant virus. The data is published in this month's issue of *Antimicrobial Agents and Chemotherapy* (August 2002;46(8):2525-2532).

"These findings are predictive of potent antiviral activity of entecavir against both wild-type and lamivudine-resistant HBV," Levine and coauthors stated.

Key points reported in this study include:

- ◆ Entecavir was extremely potent against lamivudine-resistant HBV DNA polymerase
- ◆ Liver cancer cells could accumulate concentrations of entecavir that were effective against lamivudine-resistant HBV
- ◆ Entecavir may be a highly valuable therapy for treating both wild-type and lamivudine-resistant HBV

## **22. On August 24<sup>th</sup>, 2002 the press announced that "Japan Researchers Find New Transplant Drug"**

Japanese researchers have discovered a new drug, which does not appear to cause any side effects, to prevent organ rejection in transplant patients, a Japanese newspaper reported.

According to the Yomiuri Shimbun newspaper, a team of researchers from Tsukuba University, just north of Tokyo, and a pharmaceutical research institute at Ajinomoto Co Inc, a food ingredients company known for monosodium glutamate, jointly came up with the drug, which is called APC0576.

Their findings are set to be announced at a meeting of the International Transplantation Society currently taking place in the United States, the paper said. Company and university officials could not immediately be reached for comment.

Immunosuppressant transplant drugs are used to prevent the body from rejecting a transplanted organ, but currently available drugs tend to cause harmful side effects to organs such as the kidneys and liver. According to the Yomiuri, the researchers gave the drug twice a day for a month to two monkeys which had undergone kidney transplants. Their kidneys functioned normally and they did not suffer side effects.

Shinichi Oshima, a director of the Japan Transplantation Society and professor at Nagoya University in central Japan, was quoted by the paper as saying further study was still necessary. "However, it is a positive sign that researchers were able to suppress rejection symptoms without any side effects. I expect future developments," he was quoted as saying.

### **23. On August 26<sup>th</sup>, 2002 the press announced that “Ribapharm Files Patent Infringement Lawsuit Against Hoffmann-La Roche, Inc. in the United States”**

Ribapharm Inc. today announced that it has filed an action in the United States District Court in Los Angeles against Hoffmann-La Roche, Inc., to enforce its patents on the use of ribavirin. Earlier this month, the company initiated patent infringement actions against Roche in the Netherlands and Germany, and will be filing a counter-action for patent infringement against Roche in Switzerland where Roche is seeking a declaratory judgment that their marketing of ribavirin does not infringe Ribapharm's patents.

"Roche has communicated to the financial community their intention to market a ribavirin product, an action that would be in violation of the patents in place for ribavirin and in disregard of our intellectual property rights," said Johnson Y.N. Lau, M.D., President and CEO of Ribapharm. "These legal actions against Roche, taken together, make clear Ribapharm's resolve to vigorously enforce and defend our patents."

Ribavirin, a nucleoside analogue, is licensed to Schering-Plough and marketed in combination with Schering-Plough's interferon alfa-2b product (Rebeton(TM)) and with pegylated interferon alfa-2b (PEG-Intron(R)/Rebetol(R)) for the treatment of chronic hepatitis C.

In June 2002, the National Institutes of Health (NIH) convened a Consensus Conference Panel to examine current management and treatment practices for hepatitis C. The panel noted that the hepatitis C virus is the leading cause of chronic liver diseases in the United States, including liver cirrhosis and hepatocellular carcinoma. In a draft consensus statement, the NIH panel concluded that the most effective treatment of chronic hepatitis C is with a combination therapy of pegylated interferon and ribavirin.

Hepatitis C is a viral infection of the liver, caused by the hepatitis C virus, or HCV. Globally, an estimated 170 million people are chronically infected with HCV. Hepatitis C currently accounts for an estimated 10,000 deaths in the U.S. annually.

Ribapharm is a biopharmaceutical company that seeks to discover, develop, acquire and commercialize innovative products for the treatment of significant unmet medical needs, principally in the antiviral and anticancer areas.

### **24. On August 26<sup>th</sup>, 2002 the medical editors published an article titled**

## “Magnetic Resonance Images Depict Link Between Chronic Hepatitis C Activity and Node Appearance”

Physicians have been able to distinguish chronic hepatitis C activity by the way patients' lymph nodes appear on magnetic resonance (MR) imaging.

A team at Thomas Jefferson University in Philadelphia, Pennsylvania, has used MR images of local lymph nodes to differentiate mild, moderate, and severe hepatitis activity in patients with chronic hepatitis C, according to a report in the *American Journal of Roentgenology*.

"Fifty patients with chronic active hepatitis C, who had MR imaging examinations and a related histology report from a liver biopsy obtained within 1 month of the MR imaging were chosen from our radiology database and studied retrospectively," described Xio-Ming Zhang, an investigator in the Department of Radiology.

For 4 years, doctors monitored the chronic hepatitis C patients for the evolution of cirrhosis or hepatocellular carcinoma, a type of primary liver cancer. Radiologists, blinded to the patients' medical histories, evaluated and graded the patients' MR images for nodal characteristics, including size, number, and location, and research team members subsequently compared those findings to the patients' histological activity levels.

"Forty-four (88%) of 50 patients had perihepatic lymph nodes larger than 5 mm on MR images, including 64.2% (9/14) of the patients with mild activity, 96.3% (26/27) of the patients with moderate activity, and 100% (9/9) of the patients with severe activity ( $p=0.0034$ )," reported Zhang's team.

Patients with severe activity had, on average, more than three times as many perihepatic lymph nodes as did those with minimal activity, and the average size of their lymph nodes was over three times larger.

T-2-weighted MR images indicated that chronic hepatitis C patients with severe activity had significantly more hyperintense nodes. This data is published in the August issues of the *American Journal of Roentgenology* (August 2002;179(2):417-422).

Among the 50 patients enrolled in the study, there was no correlation between histologic activity and liver function test results, researchers said.

The investigators concluded MR imaging could be used to correlate lymph node characteristics with hepatic activity in patients with chronic hepatitis C.

Key points reported in this study include:

- ◆ Chronic hepatitis C patients with more severe activity had larger and greater numbers of perihepatic lymph nodes upon MR imaging
- ◆ Those patients also had more hyperintense nodes
- ◆ Lymphadenopathy correlates with hepatic activity in patients with chronic hepatitis C

## 25. On August 27<sup>th</sup>, 2002 the press released an article titled “Long-term Impact of Chronic Hepatitis B Treatment Remains Uncertain” after data was published in the August issue of the *Journal of Infectious Diseases*

Treating children with chronic HBV infection accelerates time to seroconversion, although the long-term benefits of early therapy need to be established, finds a team from Montreal, Canada.

The researchers investigated chronic hepatitis B virus (HBV) infection in children of different ethnic origins,

and published the results in the *Journal of Infectious Diseases* (J Infect Dis 2002; 186; 295-301).

Seroconversion rates were studied in 174 hepatitis B e antigen (HBeAg)-positive children, who were of different ethnic origins and living in Canada. Overall, 40% became anti-HBeAg positive, and 9% were hepatitis B surface-antigen positive during a mean follow-up of 4.5 years.

Treatment accelerated seroconversion by 3 years. The spontaneous seroconversion rates were lower in Asian-born, mainly vertically infected, children, versus those born either in Canada or where horizontal transmission predominates (24% vs. 44%). At 13 years after diagnosis, HBeAg had persisted in 25% of Asian-born children and 6% of all others. The team found that treatment of 27 children accelerated seroconversion by 3 years, without influencing the proportion seroconverting over time.

Thus, although Asian-born children seroconvert more slowly, a large proportion will seroconvert before adulthood.

The team, led by George Marx, concluded that, as treatment appears to accelerate anti-HBe seroconversion, longitudinal studies are required in order to assess the long-term benefits of early treatment.

## **26. Additionally on August 27<sup>th</sup>, 2002 the press released an article titled “New Techniques May Boost Tolerance of Donor Organs”**

Suppressing the immune systems of organ recipients before transplant and then reducing or even eliminating immunosuppressant drugs after transplant seems to promote acceptance of the new organ, at least for a short period of time, according to new research to be presented this week.

The researchers also found that giving recipients infusions of stem cells and other types of tissue from living donors before transplant appeared to block rejection.

The studies are being presented in Miami, Florida, at the XIX International Congress of the Transplantation Society.

Tolerance means that the recipient's immune system accepts a transplanted organ as the body's own. This is an elusive goal; the immune system will generally reject the new organ if immunosuppressant drugs are not given.

High-dose immunosuppression has been successful, but can make a person more susceptible to infection. The drugs can also have extreme side effects. Even with immunosuppression, half of kidneys from living or cadaveric donors will be rejected within 10 to 12 years, said Samuel Strober, a Stanford University professor and transplant pioneer.

Strober and colleagues were able to wean two of four kidney transplant recipients off immunosuppressives within a year of undergoing their experimental protocol. The recipients were given both stem cells and a kidney from the same donor. All four donors did not match the tissue type of the recipients.

Weeks before the transplant, the four donors were given drugs to boost stem cell production. The kidney was transplanted, and then, beginning the day after surgery, recipients had 10 radiation treatments, targeted at the lymph nodes, spleen and thymus, to weaken immune system function. They were also given thymoglobulin to deplete immune system T cells. Then, the stem cells were transfused into the recipients.

For 2 to 3 months, three patients showed signs of donor and host cell mixing, or chimerism. Two showed no immune system reaction to the donor cells, and those two had been completely weaned off immunosuppressive drugs by one year post-transplant.

But after 5 months of being drug-free, the patients showed signs of rejection. They were treated and returned

to low-dose immunosuppression. The third patient is about to be weaned completely, and the fourth was never weaned because of rejection.

In another study, Indian researchers transplanted kidneys into 43 patients after infusion of stem cells from the same donor into their blood, marrow, liver and thymus gland. Thirty-two were weaned off drugs within a year. They are rejection-free, said H. L. Trivedi of the Institute of Transplantation Sciences in Gujarat, India.

In another study by the same group, 26 patients were drug-free 3 months after surgery. They had received stem cell infusions into their blood and marrow before transplantation, and were also given infusions of crushed donor kidney tissue directly into the thymus 19 days before surgery--if from a living donor--and during transplant if from a cadaveric donor.

Scientists from the Thomas E. Starzl Institute at the University of Pittsburgh presented results of several tolerance trials. Kareem Abu-Elmagd and colleagues gave 22 candidates for small intestine transplants a one-time dose of thymoglobulin before surgery. Seventeen were receiving grafts that had been irradiated before transplant. Fifteen of the 22 met criteria for weaning, which began 90 days post-transplant. They were started with a single dose of tacrolimus daily for a few weeks; patients were monitored for rejection clinically and through endoscopic biopsies. With no rejection, they were moved to an every-other-day dosing, and then to once a week. Four of the 15 had weaning delayed, and another three developed rejection. One is on once-weekly dosing, and five are on an every-other-day dose, Abu-Elmagd said.

On Wednesday, Starzl will report similar success rates in weaning kidney and liver transplant recipients with the same protocol, and suggested that the current practice of high-dose immunosuppression should stop.

"What we're looking at here is drastic reduction of immunosuppression, and that, of course, is a necessary step...if you're going to get real tolerance," Starzl said at a press briefing.

Several transplant experts disagreed, saying that tolerance was not that simple. Megan Sykes, of the Massachusetts General Hospital, said that despite promising studies, "our understanding of human (tolerance) right now is very limited."

Alan Kirk, from the National Institutes of Health, said no patient should reduce their immunosuppressive regimen just because of the upbeat results. "None of these protocols are ready for prime-time as it were," said Kirk, adding that, "the important thing is that they go forward so we can learn how to make them generally applicable."

## **27. On August 28<sup>th</sup>, 2002 the press released an article titled “Researchers Develop Model to Predict Post-Transplant Survival in Liver Transplant Patients” based upon data published in the September issue of the *Annals of Surgery***

Survival following liver transplantation can be accurately predicted based on a model using 8 straightforward factors, finds a study reported in the September issue of the *Annals of Surgery* (Ann Surg 2002; 236 (3): 315-23,)

Researchers from California and Pennsylvania, USA, developed a prognostic model that determines patient survival outcomes after orthotopic liver transplantation (OLT), using readily available pretransplant variables. Variables that may affect patient survival following OLT were analyzed in hepatitis C (HCV) recipients at the authors' center. This was because HCV is the most common indication for OLT.

The resulting patient survival model was examined and refined in both HCV and non-HCV patients in the United Network for Organ Sharing (UNOS) database.

Among HCV recipients, mortality was predicted using recipient age, recipient creatinine levels, donor female

gender, and urgent UNOS classification. The above variables, in addition to donor age, total bilirubin, prothrombin time (PT), retransplantation, and warm and cold ischemia times, were then applied to the UNOS database.

Of the 46,942 patients transplanted over the last 10 years, 25,772 patients had complete data sets.

An 8-factor model that accurately predicted survival was derived.

A post-transplantation mortality index was calculated using a combination of these variables, and was applicable to first or second liver transplants. Patient survival rates, based on model-predicted risk scores for death and observed post transplant survival rates, were similar. Additionally, the model accurately predicted survival outcomes for HCV and non-HCV patients.

Dr Rafik M. Ghobrial, of the David Geffen School of Medicine at UCLA, Los Angeles, California, said on behalf of fellow authors, "Post-transplant patient survival can be accurately predicted based on 8 straightforward factors."

"The balanced application of a model for liver transplant survival estimate, in addition to disease severity, would markedly improve survival outcomes and maximize patients' benefits following OLT," it was concluded.

## **28. Additionally on August 28th, 2002 the Immunotherapy Weekly medical editors released an article titled "Fibromyalgia: Exercise Therapy May Help"**

Prescribed graded aerobic exercise is a simple, cheap, and effective treatment for people with fibromyalgia (medically unexplained chronic muscular pain and joint tenderness), finds a study in the *British Medical Journal* (Br Med J, 2002;325:185-187).

Researchers identified 132 patients with fibromyalgia who were attending a hospital rheumatology clinic between January 1997 and June 1998. Patients were then randomly assigned to either aerobic exercise classes or relaxation classes, twice weekly for 12 weeks. The classes were carried out by personal trainers with no special experience in providing exercise for people with ill health.

Compared with relaxation, exercise led to significantly more participants rating themselves as much or very much better at 3 months. Benefits were also maintained or improved 1 year later.

These results show that a 3-month program of prescribed graded aerobic exercise is an effective treatment that leads to improvements in self-reported health status, said the authors. Furthermore, prescribed exercise can be undertaken effectively in the community by personal trainers previously inexperienced in managing people with ill health.

However, compliance with exercise treatment is a considerable problem, giving high dropout rates, said the authors. Future strategies to increase the efficacy of exercise as an intervention should confront this issue, they said.

## **29. Additionally on August 28<sup>th</sup>, 2002 the press released an article titled "Researchers Evaluate Two Options for Treating Recurrent Variceal Hemorrhage" based upon data published in the August issue of *Endoscopy***

A team from Heidelberg, Germany has identified both benefits and disadvantages of endoscopic ligation plus propranolol and TIPS for the prevention of recurrent variceal bleeding. The investigators compared endoscopic variceal ligation (EVL) plus propranolol with transjugular intrahepatic portosystemic stent shunt (TIPS) for the prevention of variceal rebleeding. They reported their findings in the September issue of

*Endoscopy* (Endoscopy 2002; 34 (9): 690-7).

A total of 85 patients were randomly allocated to receive TIPS (n = 43) or EVL (n = 42). The groups were comparable regarding age, sex, etiology of liver cirrhosis, and liver function. The mean observation times were 4.1 years in the TIPS group and 3.6 years

in the EVL group. Although the probability of rebleeding was higher in the EVL group (30%) than in the TIPS group (19%), the difference was not found to be statistically significant. TIPS dysfunction requiring shunt revision occurred in 89% of cases.

The authors found that 3 of 5 patients of the EVL group successfully underwent TIPS placement after treatment failure. The probability of TIPS dysfunction requiring shunt revision was 89%. Hepatic encephalopathy was observed more often in the TIPS group (41%) than in the EVL group (21%). However, the probability of survival was similar in both groups (TIPS group 76%, EVL group 82%).

Author P. Sauer, of the University of Heidelberg concluded on behalf of the group, "In view of its good efficacy and the lower cost of treatment, endoscopic ligation plus propranolol may be recommended as initial procedure for prevention of recurrent variceal hemorrhage. "On the other hand, TIPS seems to be the preferable procedure in patients with recurrent bleeding after adequate endoscopic and pharmacological treatment."

### **30. On August 30th, 2002 the press released an article titled "Transplants Help HIV Patients"**

Larry Kramer was given six months to live. His liver was failing, but because he was HIV positive, he was told he wouldn't qualify for a liver transplant. Then the longtime AIDS activist found one of the few hospitals willing to transplant people with HIV. After surgery in December at the University of Pittsburgh, he says his health took a nearly miraculous turn for the better.

"I haven't felt like this since I was a kid," said Kramer, 67, who hopes more centers will open to people with HIV. "It's very hard to convince the old guard that the next guard has come. I'm glad to be a poster boy."

There's now data to back up his case. Researchers Thursday reported that patients with HIV are successfully receiving liver and kidney transplants, challenging widespread reluctance by transplant centers to give scarce organs to people with the incurable disease.

The research, presented at a transplant conference in Miami, offers the latest medical ripple traced to the powerful drugs that revolutionized AIDS care in the mid-1990s. Because thousands of HIV patients are living longer with the drugs, some develop organ failure for other reasons, making them candidates for transplants. The competition for organs is fierce. More than 80,000 people are now waiting for transplants, and more than 6,000 die each year waiting. While livers and kidneys are typically given to the sickest patients waiting, doctors will not give organs to anyone who is too sick to benefit. In many places, that means anyone with HIV.

Just four or five hospitals offer organs to HIV-positive patients, with most others arguing that limited organs should be saved for patients who do not have another disease complicating their chances for survival. There have also been concerns that drugs taken after transplant surgery may exacerbate patients' HIV, the virus that causes AIDS.

Still, an editorial last month in the *New England Journal of Medicine* argued that these patients should be considered eligible for transplants just like other patients who have chronic diseases such as hepatitis C and diabetes or older patients, all of whom face lower long-term survival chances. HIV, they said, is just another medical factor to consider.

"On ethical grounds alone, there is no justification for providing organs to these groups of patients but not to patients infected with HIV," a trio of researchers argued. Others say there isn't enough data on the long-term

survival of patients with HIV to justify taking an organ that would have gone to an otherwise healthy patient.

"It's true agony for patients on waiting lists, who wonder if they'll live to get transplanted," said Dr. Marlon Levy, surgical director for liver and kidney transplantation at Baylor All Saints Medical Center in Ft. Worth, Texas, one of the nation's busiest transplant centers. "It just becomes an almost overwhelming burden to consider transplantation for someone who has another illness when there are so many people who don't have those barriers."

So far, the HIV transplants have proved successful, according to data presented Thursday at the International Congress of the Transplantation Society, taken from several U.S. centers and one in France that offer kidneys and livers to HIV-positive patients. A year or so after their transplants, these patients are just as likely to survive as other transplant recipients, they said.

### **Specifically:**

In San Francisco, 13 of 14 liver and kidney recipients are alive, reported doctors from the University of California, San Francisco. And there is no evidence that the HIV has advanced in any of these patients.

In Philadelphia, 17 of 20 kidney recipients are alive a year after their transplants. None of the three deaths was related to HIV.

In Pittsburgh, two of seven liver recipients died and all four kidney recipients are alive, several months to five years after the transplants.

In Miami, all six liver recipients are alive, one to three years after transplants.

Pittsburgh researchers also reported the drug issues are tricky but can be overcome. They warned that these patients require special attention after transplant because drugs given to prevent the body from rejecting the new organ can worsen their HIV. They said it's important to achieve the right balance between HIV and anti-rejection medicines.

Some of the HIV-positive patients were given lower-quality organs or organs from donors at risk of HIV, which is one way to bypass others on the waiting list who may be pickier. Other patients received kidneys or partial livers from living family or friends. Still others came to the top of the waiting list and got organs from people who had died the same way other transplant patients do.

## **31. On August 31<sup>st</sup>, 2002 the press announced that “State Fines Mount Sinai \$66,000 and Bans Live Liver Transplants Indefinitely”**

Citing serious problems with patient care that may have contributed to several deaths, the state has fined Mount Sinai Medical Center \$66,000 and extended its suspension of the hospital's live liver donor program indefinitely.

The state health commissioner, Dr. Antonia C. Novello, announced the results of what she called the state's largest-ever investigation into a health institution at a news conference in Manhattan yesterday. She said the state had found 33 serious violations, mostly in the liver transplant unit. The fines levied, \$2,000 per violation, are the highest allowed by law.

"Due to the severity and widespread impact of these violations," Dr. Novello said, "I cannot allow Mount Sinai Medical Center to reopen its living donor adult liver transplant program."

The program will not start again until the hospital comes up with a comprehensive plan to address the department's findings and undergoes a complete inspection and survey, Dr. Novello said.

Gary Rosenberg, an executive vice president at Mount Sinai, said the report had no surprises. "We have been working very closely with the Health Department on each of these issues," Dr. Rosenberg said. "Most of them we have already corrected. A few of them we are still working on."

In addition to meeting staffing and follow-up care requirements, the hospital will have to have an independent panel - including a surgeon other than the operating surgeon, a nurse, a medical ethicist and an infectious disease specialist - sign off on every liver transplant before it is performed. The hospital must also submit reports to an external review panel that will examine transplant cases and report on them to the State Health Department. The hospital has until Sept. 13 to submit a plan.

The investigation, which was prompted by the death of a healthy 57-year-old man who donated part of his liver to his brother, is the latest in a series of problems for the hospital, one of the nation's largest. It has an operating deficit of more than \$100 million, and has struggled with complaints of poor patient care.

The death of the liver donor, Mike Hurewitz, a reporter for The Times Union in Albany, tarnished what had been a marquee program at the hospital.

He died on Jan. 13, three days after donating part of his liver to his brother, Adam Hurewitz.

Mike Hurewitz choked on his own blood in a ward filled with 34 postoperative patients being cared for by a single first-year resident. His brother, a physician on Long Island, survived the transplant operation and is recovering.

Dr. Novello said she had met with the new managers at Mount Sinai before the report was released and believed that Dr. Larry Hollier, who was named president earlier this month, was committed to fixing the problems. But she said systemic changes in Mount Sinai's culture were needed.

"The biggest problem we found was that Mount Sinai failed to police itself," Dr. Novello said. Because the hospital did so many living donor transplants, more than 100 since the program began in 1998, the staff might have gotten sloppy, Dr. Novello said. "I tend to believe that because they did so many they were a little too confident," she said.

The fines are in addition to a \$48,000 fine levied in March after an investigation into Mr. Hurewitz's death found he had received "woefully inadequate postsurgical care." The investigation was quickly expanded as complaints about patient care at Mount Sinai Medical Center flooded in. So far the State Health Department has received 158 complaints and investigated 92 of them. Violations were found in 53 of those cases. Of those, 41 were in the transplant unit.

The problems cited included the failure of a surgeon to check up on a patient after an operation, and failing to prevent patients from falling. One patient died of severe head trauma after a fall, the report said.

In 10 transplant cases, the surgeon named on the consent form was not the surgeon who performed the operation, a change that was made without the patient's consent. The hospital also failed to have adequate nursing staff, giving each nurse five to seven patients, rather than four, which is the norm, Dr. Novello said.

The investigation also found problems with Mount Sinai's liver transplants from cadavers. In three cases transplants were performed despite serious problems that would normally halt an operation, like the recipient's having cancer or sepsis. In all three cases the patients died.

Victoria Hurewitz, Mr. Hurewitz's widow, who has become a vocal critic of live liver transplants as they are currently performed, said the report confirmed what she saw with her own eyes when her husband was in the transplant unit. "This shows me that Mike's death was preventable," Mrs. Hurewitz said. "It just shoved it right in my face. Hopefully this will force them to clean up their act."

### **32. On September 2<sup>nd</sup>, 2002 the press released an “Update of the International Tumor Registry on Liver Transplantation in Association with HCC”**

A team from Dallas, Texas, USA, has investigated liver transplantation in association with hepatocellular carcinoma (HCC), and has updated the International Tumor Registry.

HCC is an epithelial tumor derived from hepatocytes that accounts for more than 80% of all primary hepatic tumors. The severity of the underlying disease is almost always the key factor in deciding whether to consider liver resection or transplantation as its treatment.

The registry comprises almost 800 patients from transplant centers throughout the world.

Factors affecting patient survival after transplantation:

1. Histologic grade
2. Tumor size > 5 cm
3. Presence of positive nodes

Reporting in September's *Liver Transplantation* (Liver Transpl 2002; 8: 736-48), the authors found that histologic grade, tumor size > 5 cm, and the presence of positive nodes significantly affected patient survival after liver transplantation. Recurrence-free survival showed a correlation with tumor size > 5 cm, positive nodes, bilobar spread, and vascular invasion.

At the time of the study, 59% of patients in the authors' registry were alive, 84% of whom were free of tumor. Of those who died, half did so without evidence of tumor.

### **33. Additionally on September 2<sup>nd</sup>, 2002 the medical editors from Hepatitis Weekly released an article titled “SEN Virus: Novel Virus Plays No Role in Non-A to -E Hepatitis”**

The newly detected SEN virus (SEN V) does not play a role in liver disease, according to a research team in Tokyo, Japan.

"SEN V was discovered recently as a potential causative agent of non-A, non-B, non-C, and non-E (non-A to -E) hepatitis," researchers at Nihon University School of Medicine described in the *Journal of Medical Virology* (J Med Virol, August 2002;67(4):624-629).

Though originally implicated as a source of hepatitis in some individuals, medical researchers are now rethinking that theory. The study conducted by Nihon University School of Medicine investigators lends credence to a growing belief that SEN V is a common virus that does not contribute to the pathogenesis of liver disease.

For the study, Morio Mikuni and colleagues tested 49 blood donors and 67 patients admitted to the hospital for non-A to E liver disease for SEN V DNA. The patients had been diagnosed with a variety of liver disorders, including liver cancer, cirrhosis, and acute and chronic hepatitis.

"The prevalence of SEN V DNA was similar among patients with various liver diseases, including hepatocellular carcinoma (42.1%), cirrhosis (57.1%), chronic hepatitis (55.6%) and acute hepatitis (47.8%), and among blood donors (28.6%)," Mikuni and coauthors reported.

The clinical profiles of individuals within the different disease groups was similar, regardless of SEN V status, researchers said "SEN V infection is present among many blood donors and is common in patients with non-A to -E liver disease," and concluded that at this point, there is no evidence to link SEN V infection with non-A

through E hepatitis.

Key points reported in this study include:

- ◆ At one point, SEN virus (SEN V) was thought to be the cause of non-A to -E hepatitis
- ◆ Both blood donors and patients with a variety of liver diseases are likely to be infected with SEN V
- ◆ There is no current evidence that non-A to -E hepatitis is caused by SEN V

### **34. Additionally on September 2<sup>nd</sup>, 2002 the medical editors from Hepatitis Weekly released an article titled “Race Makes Difference for Value of Alpha-Fetoprotein as Cancer Marker”**

Researchers at Stanford University School of Medicine say alpha-fetoprotein is not as useful a marker for primary liver cancer in African-Americans with chronic hepatitis C-related liver cirrhosis as it is in other ethnic groups.

Blood levels of the protein marker alpha-fetoprotein (AFP) are used as a marker for fetal neural tube defects during pregnancy, and in patients with cancers of the liver, testis, and ovaries. Data from one of the first studies of its kind has discounted the use AFP for predicting hepatocellular carcinoma HCC, a primary form of liver cancer, in African-Americans with cirrhosis arising as a result of hepatitis C virus infection.

"Limited data concerning the diagnostic value of AFP for hepatitis C virus (HCV)-related HCC have to date come only from Asian and European studies, and results are conflicting," commented Mindie H. Nguyen and colleagues, investigators in the Division of Gastroenterology and Hepatology at Stanford University School of Medicine.

The group's study now provides answers to questions about ethnicity with respect to AFP and HCC. The multicenter, retrospective case-control study evaluated AFP levels in HCC patients who were HCV-positive and in HCV-positive controls with cirrhosis.

Study data indicated that the greater the level of AFP, the more likelihood of developing HCC, with the highest odds for HCC being predicted for those with AFP levels between 101 and 200 ng/mL. "No controls had AFP greater than 200 ng/mL," remarked Nguyen and coauthors.

"The sensitivity of AFP for the diagnosis of HCC in African-Americans with HCV infection was lower than that of patients of all other ethnic groups combined (57.1% vs. 81.6% for AFP >10 ng/mL, and 42.9% vs. 66.0% for AFP >20 ng/ml)," the researchers stated. The data is published in *Hepatology*, (August 2002;36(2):410-417).

Thus, while AFP levels, especially those higher than 200 ng/mL, can predict the occurrence of HCC in patients with HCV-associated cirrhosis, the protein cannot do the same for African-Americans, Nguyen and colleagues concluded.

Key points reported in this study include:

- ◆ Few studies have looked at alpha-fetoprotein (AFP) as a marker for HCV-related cirrhosis and liver cancer in ethnicities other than those of European or Asian origin
- ◆ AFP sensitivity for predicting HCV-related cirrhosis and primary liver cancer in African-Americans was lower than in a combination of all of the other investigated ethnic groups
- ◆ AFP is not a valuable prognostic indicator for the formation of primary liver cancer in African-Americans with HCV-related cirrhosis

### **35. Additionally on September 2<sup>nd</sup>, 2002 the medical editors from Hepatitis Weekly released an article titled “Hepatitis C Increases Risk for Death Following Pancreatic Transplantation”**

Being hepatitis C virus (HCV)-positive can increase the risk for graft dysfunction and death in patients who undergo pancreas transplantations, according to a new report.

A study comparing outcomes in HCV-positive and matched HCV-negative patients has established that being infected with HCV exacerbates not only graft function, but also patient survival. The study was reported in the August 2002 issue of *Clinical Transplantation* (Clin Transplant, 2002;16(4):243-251).

"There was a trend toward a higher incidence of all cause mortality in HCV-positive recipients compared with HCV-negative recipients, 30% vs. 10%, respectively," reported Marsha R. Honaker and coauthors, University of Tennessee - Memphis.

The 10 HCV-positive patients received pancreas transplantations either alone or in combination with or following renal transplantations, and the 20 matched controls received similar combinations of transplants. Renal graft survival in HCV-positive and HCV-negative patients were 50% and 94%, respectively.

Sepsis accounted for approximately a fourth of the deaths in HCV-positive organ recipients but only 1 out of the 20 HCV-negative cases.

Despite increased mortality among HCV-positive transplantees, pancreatic graft survival was similar, according to Honaker and colleagues.

Being HCV-positive may have affected renal function, because over two times as many HCV-infected individuals who received renal and pancreas transplants had elevated protein levels in their urine as did noninfected transplant recipients.

Finally, HCV infection tended to affect pancreatic graft function. "In order to maintain comparable glycemic control between the groups, there was a significant increase in oral hypoglycemic requirement in HCV-positive recipients compared with HCV-negative recipients, 33% vs. 0%, respectively," Honaker and coauthors said.

More long-term studies that include a larger patient population are needed in order to better understand the effect of HCV status on organ function and survival after pancreatic transplantation, Honaker and coauthors recommended.

Key points reported in this study include:

- ◆ Patients infected with hepatitis C virus sustain higher death rates after pancreas transplantation
- ◆ Sepsis was a significant cause of death among patients who received pancreas transplantations
- ◆ Being HCV-positive affected graft functioning in patients who received only a new pancreas or both a new pancreas and kidneys

### **36. On September 3<sup>rd</sup>, 2002 the press released an article titled “Value of Imaging Examinations for Detection of Malignancies in Cirrhotic Patients”**

Currently, imaging techniques cannot accurately determine the exact tumor burden in cirrhotic patients before transplantation, claims a team from Leuven, Belgium. The researchers investigated the use of pretransplantation imaging techniques to detect focal lesions in cirrhotic patients. Focal lesions detected by

imaging examinations during pretransplantation evaluation were correlated with focal lesions detected during detailed pathological examination of 49 cirrhotic explant livers.

The findings of the study were published in the September issue of *Liver Transplantation* (Liver Transpl 2002; 8: 749-61).

Within 6 months before transplantation, 3 types of imaging examinations were conducted. These were color Doppler ultrasonography (US), contrast-enhanced computed tomography (CT), and magnetic resonance (MR) imaging, and were performed in 94%, 33%, and 55% of patients, respectively.

In 2% to 8% of patients, different types of benign focal lesions were present. A considerable proportion was interpreted as premalignant or malignant on imaging examination. Contrast-enhanced MR examination is best for detecting malignancies early in Liver Transplantation. US detected only the largest hepatocellular carcinomas (patient sensitivity, 40%; specificity, 100%) and no dysplastic nodules.

On a per-patient basis, contrast-enhanced CT and MR imaging had poor sensitivity (20% and 27%, respectively) and good specificity (100% and 94%, respectively) for dysplastic nodules.

Patient sensitivity and specificity of both techniques for hepatocellular carcinoma were reasonable (50% for CT, 70% for MR imaging) and good (79% for CT, 82% for MR imaging), respectively. However, the authors found that neither technique was able to detect smaller premalignant or malignant lesions. As a consequence, 10% of patients underwent transplantation, although they exceeded the tumor number limit.

Louis Libbrecht, of the University of Leuven, said on behalf of his group, "Currently-used imaging techniques cannot correctly determine the exact tumor burden in some cirrhotic patients." "Regular contrast-enhanced MR examination of cirrhotic patients waiting for liver transplantation is the best tool for the early detection of premalignant or malignant lesions," he concluded.

### **37. On September 4<sup>th</sup>, 2002 it was announced that Enanta Pharmaceuticals Signs Collaboration Agreement with Chiron Corporation for Hepatitis C Therapeutics**

Enanta Pharmaceuticals, Inc, a chemistry-driven biopharmaceutical company developing macrolide antibiotics and immunosuppressants, announced today that it has signed an exclusive, joint collaboration with Chiron Corporation for the discovery and development of small molecule therapeutics for the Hepatitis C (HCV) virus. Within the parameters of this collaboration, Enanta will apply its novel macrocyclic chemistry and medicinal chemistry expertise to the design and synthesis of compounds targeting key enzymes involved in the replication of the virus. The financial terms of the agreement were not disclosed.

"Working with Chiron in a disease area that they are strongly committed to and affects so many people worldwide, affords Enanta an excellent opportunity to apply our drug discovery capabilities to develop effective therapies to treat HCV," said Spiros Jamas, President and CEO of Enanta. "This collaboration aligns itself strongly with our business goal of combining our chemistry expertise with a corporate partner's know-how on novel targets. We feel that Chiron's selection of Enanta as an exclusive partner for their internal HCV program is an endorsement of the research strategy and chemistry capability of our company."

The joint research program will involve the synthesis of compounds, structure-based drug design and testing in enzyme assays, whole cell assays and animal models. Chiron will grant Enanta a non-exclusive license to certain of its HCV patents and Enanta will grant Chiron an exclusive worldwide license to compounds that are developed for treatment of HCV. Enanta will also receive research funding, milestone payments and royalties on worldwide product sales from Chiron, while Chiron will be responsible for preclinical and clinical development, manufacturing and sales and marketing. A Collaboration Management Team comprised of representatives from each company will manage this program.

According to the World Health Organization, Hepatitis C has become a global epidemic, affecting approximately 170 million people worldwide - 3 percent of the world's population. The majority of those infected with the HCV virus have it for life and can develop cirrhosis, which can lead to cancer or liver failure.

### **About Enanta**

*Headquartered in Watertown, Mass., Enanta Pharmaceuticals is using its breakthrough chemistry technology -- Drug Morphing(TM) and Peptide Morphing(R) -- to create new intellectual properties by 'morphing' existing drugs, natural products, and biologically active peptides into novel, small-molecule drugs. The Company is initially focusing on new chemical entities derived from existing drugs that address significant unmet medical needs: (a) new-generation macrolide antibiotics to overcome bacterial resistance; and (b) anti-inflammatory drugs for a variety of indications, including asthma, psoriasis and inflammatory bowel diseases.*

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*SOURCE: Enanta Pharmaceuticals*

## **38. Additionally on September 4<sup>th</sup>, 2002 it was announced that SciClone Pharmaceutical is Going to Test Combination Of Unapproved Drugs**

SciClone Pharmaceuticals Inc. (SCLN) said it will save about \$20 million through a deal struck with Swiss drug giant Roche AG (RHHBY), which will provide its Pegasys interferon free of charge for clinical trials with SciClone's Zadaxin immune system enhancer to treat the hepatitis C virus.

But SciClone now finds itself in an odd spot because it enrolled patients for a trial to test its Zadaxin as a combination therapy with Pegasys pegylated interferon, although neither has been approved by the Food and Drug Administration.

SciClone has warned in filings with the Securities and Exchange Commission that if Pegasys isn't approved by the FDA, the company would need to repeat the Zadaxin HCV trial with an approved interferon, causing delays and increased expenses. The company is conducting a phase 3 trial in the U.S. of Zadaxin to boost the effects of interferon in patients with the hepatitis C virus, or HCV, who previously didn't respond to interferon therapy.

HCV is a chronic infection that attacks the liver. The pegylated form of interferon remains in the body longer, cutting down the number of doses.

A Roche spokeswoman said the company would provide Pegasys for the trial at no charge to SciClone if SciClone shares its trial data with Roche.

SciClone Chief Financial Officer Rick Waldron told Dow Jones Newswires the company will test Zadaxin in 1,000 patients it plans to enroll in a multi-center, placebo-controlled trial for HCV.

"Using two unapproved drugs is rare but the FDA cleared (the trial)," Waldron said.

An FDA spokeswoman said it isn't unheard of for the agency to allow trials of a combination of two unapproved products as long as the company has sufficient data from preclinical tests showing the drugs are safe.

Under FDA rules, even if two drugs weren't approved on an individual basis, they could be packaged

together and sold as one therapy if the agency found the drugs were safe and effective and approved them in combination.

### **Minor Risks Exist**

*In July, the FDA gave priority review designation to Pegasys in combination with ribavirin for the treatment of HCV and Roche has said it expects U.S. approval by the end of the year for the drug. But recently no marketing application has been a sure bet with the FDA.*

*Waldron said he expects approval of Pegasys by the end of the year, and though there is a small risk that Pegasys wouldn't be approved, it still is a risk, so SciClone had to include it in its filings with the SEC.*

*Pegasys was approved in June by the European Union. Waldron said Zadaxin is already approved in 28 countries, mostly developing countries, and generated about \$14 million in sales during 2001, mainly for the treatment of hepatitis B.*

*H.C. Wainwright analyst Ron Opel said it is difficult to gauge the risk from the Roche deal because he doesn't follow Roche and has no insight on the odds for approval of Pegasys, but he said he has heard from Pegasys users who found the product superior to Schering-Plough Corp.'s (SGP) PEG-Intron, a pegylated interferon that already has FDA approval.*

*It is important for SciClone to break into the U.S. market with Zadaxin, Opel said, because the level of third-party reimbursement in the U.S. offers a much greater market opportunity than SciClone has found so far in places like China.*

*The analyst rated the company a speculative buy, stating that buy is the firm's second-highest rating, but SciClone is considered speculative because of its small market capitalization. Opel's firm did investment banking for SciClone more than two years ago.*

### **Multiple Drugs A More Common Approach**

*Using multiple drugs to treat disease has become more common in recent years, particularly since the success of using drug cocktails to treat HIV/AIDS. Currently, HCV patients usually get a combination of interferon and ribavirin.*

*Schering-Plough currently sells PEG-Intron in combination with Rebetol, a ribavirin licensed from Ribapharm Inc. (RNA), for HCV treatment.*

*Aside from its collaboration with SciClone, Roche is seeking approval of Pegasys for the treatment of HCV in combination with its own version of ribavirin, though Ribapharm recently sued Roche in the U.S. and Europe alleging infringement of its ribavirin patent.*

*Schering-Plough's sales of Intron/Ribavirin products, which are mainly used for HCV, totaled \$659 million for the quarter ended June 30, according to a company filing with the SEC.*

*Waldron said SciClone originally planned to test Zadaxin with alpha interferon but waited until the company could get access to longer lasting pegylated interferon. The company was concerned pegylated products would take over the HCV market and feared it would get approval for Zadaxin in combination with something patients no longer used.*

*Though SciClone spoke to Schering-Plough as well as Roche, Roche's offer was difficult to refuse from a business standpoint, Waldron said. Due in part to the deal, as well as the revenue from foreign sales, SciClone didn't need to partner with a larger company to fund the trials and so expects to keep a larger percentage of any Zadaxin revenue.*

*Ironically, Zadaxin was originally developed at Roche. However, Roche was also developing interferon at the time and put off Zadaxin, Waldron said. SciClone eventually acquired all the rights to the drug for about \$3.2 million in 1998, according to SEC filings.*

*Waldron said Zadaxin works in several ways to boost the immune system against HCV. The injectable product, a manufactured version of a naturally occurring substance, helps stem cells differentiate into*

*virus-fighting immune system cells. The drug also helps ease potential side effects by working to prevent the immune system from fighting the effects of interferon therapy.*

*SciClone's trial, which started patient enrollment in April, is planned for 500 patients with HCV but no liver cirrhosis and 500 HCV patients with some cirrhosis. It will take about two years to complete the trial and organize the data for regulatory filings with the FDA.*

*A Roche spokeswoman said the company could benefit from a Zadaxin approval but doesn't get any rights to Zadaxin through its deal with SciClone.*

*Waldron said other HCV treatments are needed on the market as interferon and ribavirin combinations only work for about 30% of HCV patients with the highest viral loads - those with the highest number of virus copies in their blood. SciClone is focusing its Zadaxin testing on this group.*

*SciClone has yet to partner with a big drug maker, but it will need to establish some kind of partnership because of the size of the HCV market, Waldron said. SciClone plans to see what results the clinical trials yield before it gets into any partnering discussions.*

### **39. Additionally on September 4<sup>th</sup>, 2002 the press released an article titled “Living Donor Liver Transplantation is Feasible and Safe”**

Living donor liver transplantation is a practicable and safe procedure, although there is considerable risk of postoperative complications among the donors, claim researchers from Berlin, Germany.

The authors evaluated the outcomes of donors in adult-to-adult living donor liver transplantation (LD-LTx), and reported their results in the September issue of *Liver Transplantation* (Liver Transpl 2002; 8: 829-37). Potential donors underwent a comprehensive multistep evaluation protocol to exclude any conditions that could lead to an increased operative risk. Follow-up investigations were performed after 6 and 12 months. Liver regeneration was assessed by computed tomography scan and magnetic resonance imaging scan. Quality of life (QOL) was investigated according to the Anamnestic Comparative Self-Assessment Scale (ACSA) before donation, and 6 and 12 months after donation.

As of December 2001, 43 right lobe living donations were performed. None of the donors died or has suffered life-threatening or persisting complications. All patients recovered completely. The researchers found that complications occurred in 18% of the donors. The incidence of perioperative surgical complications was 9%, comprising temporary biliary leakages (6.8%), as well as postoperative bleeding (2.2%). Liver volume regeneration approximated 72% of predonation volume by 6 months and 85% by 12 months. There was no evidence of significant psychological impairment after donation. It was discovered that QOL increased after donation, compared with the preoperative state.

Dr Andreas Pascher said on behalf of fellow authors, "In our experience, LD-LTx has proven to be a practicable and safe procedure." "However, there is a considerable risk of postoperative complications. The donor selection process plays a pivotal role in preventing such complications," Dr Pascher added. "The discussion of potential risks, especially potential life-threatening risks, must be an integral part of informed consent," it was concluded.

### **40. Additionally on September 4<sup>th</sup>, 2002 the press released an article titled “Steatosis in Chronic Hepatitis C Associated with NASH Risk Factors”**

Steatosis in HCV infection is associated with risk factors for NASH, particularly obesity, rather than alcohol consumption, finds research published in the September issue of *Hepatology* (Hepatology 2002; 36: 729-36).

Researchers from San Francisco, California, USA, assessed the relative contribution of obesity, diabetes

mellitus, and alcohol to steatosis in chronic hepatitis C. They studied 297 consecutive patients with hepatitis C virus (HCV) who met inclusion criteria. Alcohol consumption, demographics, and serologic tests were correlated with degrees of steatosis and fibrosis on liver biopsy. BMI and genotype 3a HCV infection are independent predictors of steatosis. Liver biopsy specimens were also examined for evidence of significant alcohol or nonalcoholic steatohepatitis (NASH) injury.

In univariate analysis, steatosis was found to correlate with type 2 diabetes mellitus and body mass index (BMI), but not with the intensity of alcohol intake. In multivariate analysis, BMI and genotype 3a HCV infection were independent predictors of steatosis.

However, when patients with risk factors for NASH were excluded, genotype 3a infection was the only independent predictor of steatosis.

Steatosis and inflammation scores on liver biopsy were the only independent predictors of fibrosis. Furthermore, significant alcohol or NASH injury was found in only 6% of biopsy specimens.

Alexander Monto, of the Veterans Affairs Medical Center, San Francisco, concluded on behalf of his group, "Steatosis in HCV infection is associated with risk factors for NASH, particularly obesity, rather than alcohol consumption."

#### **41. Additionally on September 4<sup>th</sup>, 2002 the press released an article titled "Opportunities for Prevention: Hepatitis C Prevalence and Incidence in a Cohort of Young Injection Drug Users"**

This study suggests prevention interventions: street outreach with education to IVDUs to teach them about the risks for contracting HIV & HCV; the health risks facing them; present opportunities for rehabilitation to these individuals; provide an appropriate clean needle exchange program; educate about safe sex; provide condoms; this study suggests if you teach person how to inject by themselves perhaps they will not need to share needles with another.

The objective of this study was to compare sociodemographic, drug, and sexual risk characteristics between hepatitis C virus (HCV) baseline positive and negative young (13-24 years) injection drug users (IDUs) and to determine prospective risk factors for HCV seroconversion among the youth. Data were collected through the Vancouver Injection Drug Users Study (VIDUS).

To date, more than 1,400 Vancouver-area IDUs have been enrolled and followed up; 234 were aged 24 years and younger. Semiannually, participants have completed an interviewer-administered questionnaire and have undergone serologic testing for human immunodeficiency virus (HIV) and HCV. Univariate and multivariate logistic regression analyses were undertaken to investigate predictors of baseline HCV positivity. In the multivariate analyses, Cox regression models with time-dependent covariates were used to identify predictors of HCV seroconversion. Of the 232 young injectors, 107 (46%) were HCV positive at baseline and a further 37 HCV seroconverted during the study period for an incidence rate of 37.3 per 100 person-years. Baseline positivity was associated with Aboriginal ancestry, older age, greater number of years injecting drugs, recent incarceration, sex trade work, more than 100 lifetime sexual partners, a previous sexually transmitted disease, living in the IDU epicenter, and injection more than once per day of heroin, cocaine, and speedball. Factors independently associated with HCV seroconversion were having a partner who uses injection drugs, requiring help to inject, and injection of cocaine more than once daily.

In conclusion, unlike older IDUs, more than one half of young injectors were HCV negative at recruitment. Thus, there is a window of opportunity for prevention. However, the incidence rate of HCV among these young IDUs is alarming, suggesting that the opportunity to intervene is exceedingly small. This data is published in the September issue of *Hepatology* (Hepatology Sept 2002, Vol 36, Number 3)

## 42. On September 5<sup>th</sup>, 2002 GenOdyssee Announces Positive Results of Proprietary Interferon-alpha Variants for the Treatment of Hepatitis C and Cancer

GenOdyssee S.A., a biotherapeutics company specializing in discovering and developing drugs from functional genomics, today announced preclinical results for its proprietary interferon (IFN) alpha variants for the treatment of hepatitis C (HCV) and cancer. In the studies conducted by independent French laboratories, GenOdyssee's variants demonstrated up to one hundred times greater efficacy compared to IFN alpha molecules currently on the market.

Professor Michael TOVEY, Director of the Viral Oncology Laboratory at CNRS Research Institute (French National Center for Scientific Research) commented, "GenOdyssee's interferons display excellent toxicity profiles and are much more specific and active than interferons 2a and 2b that are currently on the market for HCV and cancer. Such a significant improvement could herald a major advancement in patient treatment for both conditions. Undoubtedly, GenOdyssee's unique approach has significantly contributed to our understanding of the underlying mechanisms behind interferon activity, which are currently not well documented."

The studies compared GenOdyssee's nine IFN alpha variants to the currently marketed IFN alpha 2a and 2b variants in viral infectious disease models for HCV and immunotherapy models for cancer. Certain IFN alpha variants demonstrated up to one hundred times greater antiviral, immunomodulatory and antiproliferative activities than IFN alpha 2a and 2b. Other variants exhibited differential activities, for example, having greater antiproliferative but reduced antiviral and immunomodulatory properties. Initial in vivo toxicology studies reveal few side effects and suggest the company's IFN alpha variants are better tolerated than those currently on the market. Hence, these variants could provide a more specific and efficient therapeutic, with reduced adverse side effects, significantly increasing treatment efficacy. The company believes that the most potent IFN immunostimulating and antiproliferative variants will enable the development of novel immunotherapy treatments for common forms of cancer, including

"Genodyssee's variants could act as a stand-alone cancer therapy or act as an adjunct to therapeutic vaccines, providing greater efficacy than currently available treatments; they make promising candidates for the treatment of cancer and HCV," commented Professor Herve FRIDMAN, from the Paris Pierre & Marie Curie Medical School and Director of INSERM (French institute for Health and Medical research) unit 255. Professor Patrick MAUREL, director of INSERM unit 128, who coordinated the in vitro preclinical studies on hepatocyte culture, confirmed that "GenOdyssee's variants, showing unprecedented activity on human hepatocyte HCV infection, make very promising candidates to significantly improve HCV treatment."

"With these promising results in hand, GenOdyssee now has a proof of concept for our innovative approach to drug discovery and development. By combining our expertise in genetic variability with our understanding of proteins, we hope to be able to select naturally occurring variants of existing therapeutic proteins which demonstrate a higher therapeutic index and fewer side effects," said Dr. Jean-Louis Escary, GenOdyssee's Founder, President & Chief Executive Officer. "The exciting results from the studies of our IFN alpha variants should enable GenOdyssee to start clinical development of the most promising variants in both hepatitis C and cancer in 2003. The HCV market is currently valued at more than \$2 billion, with ten percent annual growth, and the cancer therapeutic vaccines and direct immunotherapy markets are estimated at several hundred million US dollars. Hence, given the poor efficacy and high toxicity of current treatments, our proprietary IFN alpha variants represent exceptional commercial

### **About GenOdyssee S.A.**

*GenOdyssee S.A. is a French biotherapeutics company founded in October 1999. The company pursues a dual business model: it offers genetic analysis services through its division GenOdyssee Genetics and aims to develop its own therapeutics through its division GenOdyssee Pharmaceuticals. GenOdyssee Genetics has developed a fully integrated high throughput (HT) screening platform that provides a unique set of post-genomic services including genetic polymorphism HT detection and identification, HT genotyping, bioinformatics and functional proteomics. Through its division*

*GenOdyssee Pharmaceuticals, the company has developed a unique approach to human genetic variability and applied it to more than 100 genes coding for therapeutic proteins, to their receptors and to the tyrosine kinases involved in the corresponding biological pathways.*

*This program has reaped successful results. As a result of its original product R&D approach, the company started its second year of existence with a portfolio of 84 lead candidates. The company has an ongoing functional proteomics program to study the biological effects of these molecules, and 32 of them have already shown therapeutic potential. In 2001, GenOdyssee filed 30 patent applications and launched preclinical studies with its first ten lead candidates.*

### **43. On September 9<sup>th</sup>, 2002 the medical editors from Hepatitis Weekly released an article titled “Hepatitis B Therapy: New Compound Could Beat Wild-Type and Lamivudine-Resistant Hepatitis B”**

A novel nucleoside analogue could be the answer to overcoming resistance to standard therapy in patients infected with hepatitis B virus (HBV).

The agent is a derivative of phosphonmethoxyethyl purine and is known as MCC-478 (LY582563). The members of a research team in Japan at the University of Tokyo think MCC-478 could be a treatment alternative for those individuals who develop resistance to lamivudine, a drug commonly used for treating HBV.

Researchers have tested MCC-478 in HBV-infected human hepatoma cells, analyzing its effectiveness against wild-type virus and lamivudine-resistant mutants.

"The replicative intermediates of wild-type and lamivudine-resistant mutants were progressively diminished by treatment with increasing doses of MCC-478," Suzane Kioko Ono-Nita and colleagues acknowledged.

The 50% effective concentration (EC(50)) of MCC-478 for treating wild-type virus was 0.027 micromolar and was considered 20 times more potent than lamivudine. Though MCC-478 was also effective against lamivudine mutants, considerably more of it was required for achieving an EC(50). This data is published in the August issue of *Antimicrobial Agents and Chemotherapy* (Antimicrobial Agents and Chemotherapy, August 2002;46(8):2602-2605).

Given the number of new patients who develop lamivudine resistant HBV infections after being on long-term therapy, the analog could eventually be considered a viable treatment alternative for them.

"MCC-478 appears to be a candidate for the treatment of HBV infection and exhibits potent activity against lamivudine-resistant HBV," Ono-Nita and colleagues concluded.

Key points reported in this study include:

- ◆ The novel nucleoside analogue MCC-478 was more efficient against wild-type hepatitis B virus (HBV) than lamivudine
- ◆ MCC-478 was effective for knocking down lamivudine-resistant HBV mutant infections, though higher doses of the agent were required
- ◆ MCC-478 is a potential treatment for wild-type and lamivudine resistant HBV infections

### **44. Additionally on September 9<sup>th</sup>, 2002 the medical editors from Hepatitis Weekly released an article titled “Woodchucks Allow Doctors to Study Hepatitis B Reinfection After Transplantation”**

Doctors can get a better idea of how hepatitis B virus reinfection progresses thanks to a woodchuck transplantation model developed by researchers in Germany.

Woodchuck hepatitis virus (WHV), which infects animals, is very similar to hepatitis B virus, which infects humans. Researchers have commonly used WHV to model HBV pathogenesis, immunogenicity, and vaccine development in animals. Now, they have devised a way to do successful woodchuck liver transplantations, providing a new means of modeling post-transplantation HBV reinfections that often arise in humans.

"For the reinfection study, woodchuck hepatitis virus (WHV)-negative animals were selected as donors, whereas chronic carriers served as recipients (n=3)," described Uta Dahmen and coauthors, University Hospital Essen, Essen, Germany.

Humans typically receive immunosuppressive therapies such as cyclosporine after receiving organ transplants in order to stem graft rejection. The transplanted woodchucks also received daily doses of cyclosporine.

Dahmen and colleagues collected the animals' blood samples to check for viral recurrence and antibody levels at periodic intervals following liver transplantation. They also sampled and tested the animals' new livers for the presence of viral proteins. Shortly after liver implantation, woodchuck hepatitis surface antigen (WHsAg) could be detected in liver biopsy samples at membranous but not intracytoplasmic locations, though woodchuck hepatitis core antigen (WHcAg) and WHV-DNA and WHV-RNA could not be detected. This data is published in the August issue of *Transplantation* (Transplantation, August 2002;74(3):373-380).

"Nearly all hepatocytes in the liver grafts of animals killed at 3 weeks and 10 weeks post-transplant showed strong membranous (WHsAg) and intracytoplasmic (WHsAg and WHcAg (woodchuck hepatitis core antigen)) staining, which was higher in frequency and intensity than in carriers before transplantation," Dahmen and coauthors commented.

Researchers explained there were fewer WHV replication intermediates and lower viral RNA levels in reinfected tissues as compared with pretransplanted tissues, possibly resulting from the substitution of portal infiltrates for liver cells.

"The woodchuck proved to be a suitable model to study WHV reinfection after liver transplantation, because the operative procedure was well tolerated," Dahmen's group stated.

Key points reported in this study include:

- ◆ Researchers identified woodchuck hepatitis virus (WHV) reinfection in once-negative livers donated to WHV carriers
- ◆ WHV surface antigen could be detected primarily in the sinusoids of transplanted livers, and low levels of WHV RNA could also be detected in transplanted livers after some time
- ◆ The woodchuck liver transplantation model could be a useful, analogous model for studying HBV reinfection in human liver recipients

## **45. On September 10<sup>th</sup>, 2002 the press released that Maxim Advances Ceplene Phase 2 Trial**

Data Safety Monitoring Board Reports Interim Safety Review and Recommends that Maxim Complete Phase 2 Clinical Trial of Ceplene(TM) Triple-Drug Combination Therapy

Maxim Pharmaceuticals (Nasdaq:MAXM) (SSE:MAXM) today announced that the Data Safety Monitoring Board (DSMB) responsible for reviewing its Phase 2 trial of Ceplene (histamine dihydrochloride) for the treatment of hepatitis C nonresponder patients has concluded that there have been no safety concerns

associated with the triple-drug combination of Ceplene, Peg-Intron(R) (peginterferon alfa-2b) and Rebetol(R) (ribavirin, USP).

The randomized, controlled Phase 2 study is designed to compare the treatment of nonresponder hepatitis C patients with a triple-drug combination of Ceplene, Peg-Intron and Rebetol versus treatment with Peg-Intron and Rebetol combination therapy alone. The study will include up to 282 patients who failed to respond to prior therapy with the combination of interferon-alpha and ribavirin.

The DSMB reported to Maxim that it has reviewed the safety data through 12 weeks of treatment for the first 41 patients enrolled in the trial, and has concluded that there have been no safety concerns and that the trial should proceed under its approved protocol.

"This report from the DSMB is an important step in the development of Ceplene as this study represents the first time that Ceplene has been administered in humans in combination with Peg-Intron and Rebetol for the treatment of hepatitis C," said Philippe Prokocimer, M.D., Maxim's Vice President of Drug Development. "As with any new drug combination, patient safety is a primary concern. We are pleased that initial results from this large Phase 2 study support the feasibility of adding Ceplene to the current standard of care in an attempt to improve the treatment of hepatitis C patients who have failed prior treatments."

The DSMB includes world-leading clinicians experienced in the treatment of hepatitis C who review the safety data from this Phase 2 clinical trial on an ongoing basis. Maxim is conducting the Phase 2 trial under an agreement whereby Schering Corp., a division of Schering-Plough Corp., is contributing two of its products, Peg-Intron and Rebetol, and performing the viral testing for the study.

The Maxim Phase 2 trial is designed to evaluate the Ceplene triple-drug combination therapy for the treatment of nonresponder patients infected with hepatitis C who failed to respond to prior therapy. Patients will be treated for up to 48 weeks and followed for an additional 24 weeks after completion of treatment. The primary measures of efficacy in the study are sustained complete viral response and sustained biochemical response (normalization of the liver enzyme ALT, a standard measure of liver function) at 72 weeks. The trial is being conducted in Western Europe and Israel.

### **Hepatitis C**

*Hepatitis C is the leading blood-borne infection in the United States. The U.S. Center for Disease Control and Prevention estimates that over 4.5 million Americans are infected with the hepatitis C virus. The World Health Organization and other sources estimate that at least 200 million people are infected worldwide. Hepatitis C is a viral infection in which oxidative stress causes inflammation and tissue damage in the liver and, in many cases, permanent cirrhosis (scarring). The cycle of disease from infection to significant liver damage can take 20 years or more. Some experts estimate that without substantial improvements in treatment, deaths from hepatitis C will surpass those from HIV. Hepatitis C is the leading cause of liver cancer and the primary reason for liver transplantation in many countries.*

*The standard treatment for hepatitis C is interferon-alpha, an immunotherapeutic agent given in combination with the anti-viral drug ribavirin. The most recent advance in hepatitis C therapy approved for sale is a pegylated, or sustained release, formulation of interferon-alpha given in combination with ribavirin. Even with recent advances, approximately half of patients still do not attain a sustained response with current therapies.*

*"While we need to continue to improve the treatment available to all hepatitis C patients, the largest unmet need today is patients who have failed prior therapy," stated Larry G. Stambaugh, Maxim's Chairman and Chief Executive Officer. "The steady accumulation of patients over the past several years who have failed existing therapies has resulted in a large population of patients in need of the next generation of treatment, and this group is the focus of our current Phase 2 trial."*

### **Overview of Ceplene and Maxim Pharmaceuticals**

*Research has shown that oxygen free radicals released by certain immune cells can suppress the immune system and damage normal tissue, a process commonly referred to as oxidative stress. Oxidative stress, implicated in numerous diseases, is most pronounced in the liver and can damage or*

*destroy liver tissue in patients with hepatitis and other chronic liver diseases.*

*Ceplene, based on the naturally occurring molecule histamine, has been shown in preclinical work to prevent the production and release of oxygen free radicals, thereby reducing oxidative stress. Accordingly, treatment with Ceplene has the potential to prevent or reverse damage induced by oxidative stress, thereby protecting critical cells and tissues, including the liver.*

*In addition to hepatitis C, Ceplene is currently being tested in Phase 3 clinical trials for advanced metastatic melanoma and acute myelogenous leukemia, and Phase 2 trials of Ceplene have been completed in advanced renal cell carcinoma (kidney cancer). Clinical trials are also planned in chronic liver diseases such as nonalcoholic steatohepatitis (NASH) and alcoholic liver disease (ALD). More than 1,400 patients have participated in the company's completed and ongoing clinical trials. Ceplene is an investigational drug and has not been approved by the U.S. Food and Drug Administration or any international regulatory agency.*

*Maxim Pharmaceuticals is a global biopharmaceutical company with a diverse pipeline of therapeutic candidates for life-threatening cancers, hepatitis C and other chronic liver diseases. Maxim's research and development programs are designed to provide hope to patients most in need by developing safe and effective product candidates that extend survival while maintaining quality of life. Maxim has attracted an experienced international management group and a team of employees dedicated to commercializing life-enhancing product candidates. Joining this motivated team in its mission are world-leading scientific and clinical investigators and major pharmaceutical development partners.*

*In addition to Ceplene, Maxim is also developing small-molecule inhibitors and activators of programmed cell death, also known as apoptosis, that may serve as drug candidates for cancer, cardiovascular disease and other degenerative diseases.*

*Furthermore, the company's MaxDerm(TM) technology is designed for the treatment of medical conditions for which topical therapy is appropriate such as oral mucositis, herpes, decubitus ulcers, shingles, burns and related conditions.*

## **46. Additionally on September 10<sup>th</sup>, 2002 the press released an article titled “High Proportion of Patients at an Emergency Department Infected with HCV”**

Researchers from the USA have discovered that 17% of patients who presented to an emergency department in Albuquerque, New Mexico, were infected with hepatitis C virus. The findings of the study were published in the September issue of the *American Journal of Emergency Medicine* (Am J Emerg Med 2002; 20: 476-80).

The team measured the prevalence of and identified risk factors associated with hepatitis C virus (HCV) in emergency department (ED) patients. Adults presenting to an urban university teaching hospital, in Albuquerque, New Mexico, were included in the study.

The patients were having blood drawn as part of their routine evaluation, and had an extra tube drawn and tested for HCV. English-speaking adults, consenting to participate in the survey portion of the study, were administered an in-depth risk factor questionnaire.

A case-control analysis was used to identify risk factors in HCV-positive compared with HCV-negative individuals. History of injection drug use dramatically increased risk of HCV infection. The researchers found that, of 223 blood samples, 17% were positive for antibodies for HCV. Some 121 patients agreed to the risk factor survey, 18 (15%) of whom were HCV-positive. Of the 18 HCV-positive survey participants, 12 new diagnoses of HCV were made.

It was discovered that a history of injection drug use was the most significant risk factor associated with HCV (OR 859). Dr Judith C. Brillman, of the Department of Emergency Medicine, University of New Mexico School of Medicine, Albuquerque, said on behalf of her colleagues, "A high prevalence of HCV is found in selected urban ED patients." "Most of these patients have a constellation of risk factors including a history of injection

drug use," she added. "Efforts to identify at risk patients for serologic testing and follow-up should be initiated. "Identifying undiagnosed HCV can lead to interventions to decrease transmission, as well as reduce the morbidity and mortality of disease," she concluded.

## **47. On September 13<sup>th</sup>, 2002 Nautilus Biotech Announces Advancement of Improved Interferon Alpha for Hepatitis C virus infection**

Nautilus Biotech today announced that it has developed a set of improved IFN-alpha molecules, engineered to have a substantially increased half-life in order to minimize side effects and maximize therapeutic efficacy and patient compliance.

The novel molecules, developed using Nautilus' proprietary 2D-scanning technology for protein rational evolution, show a significantly higher level of stability (half-life > 50x) in vitro compared to wild type interferon alpha.

As the level of activity of natural IFN-alpha already meets market expectations and patient needs, and given the strong possibility that multiple secondary effects are tightly linked to the activity of interferon, Nautilus Biotech set out to develop products with improved stability.

"Improved stability is a key objective for the improvement of interferon alpha, as it will increase the half-life of the molecule in the body and decrease the frequency of repeat treatments. This is one of the most important clinical criteria for any next generation product. Our results have been achieved without the use of PEGylation technology, and thus offer a manufacturing advantage, less variation in product and hopefully a lower regulatory burden " said Manuel Vega, Nautilus CEO.

At the same time Nautilus has filed a key patent application in the US covering its 2D-scanning technology, used to create the optimised IFN-alpha. "Nautilus' unique scanning approach is the first and only rational, function & structure-based protein optimization method," said Dr Lila Drittanti Nautilus' VP of R&D. "It blends a number of computational methods into a rational predictive tool together with experimental high-throughput mutagenesis, protein expression and cell-based assays and is a powerful process for the creation of new intellectual property." This new patent application further strengthens Nautilus' proprietary technology platform in the field of rational evolution.

Nautilus has created a portfolio of novel interferon alpha molecules with improved profiles. It is aggressively establishing a strong intellectual property position covering enhanced versions of this billion dollar molecule and is rapidly moving these products towards clinical trials.

"The program on interferon alpha is a demonstration of the power of Nautilus' rational evolution technology to rapidly generate therapeutic product candidates," said Keith Powell Nautilus' Executive VP for Corporate Business Development. "We believe we have unlocked information in the sequences of a large number of therapeutic proteins. The rapid development of IFN-alpha is the first step in the development of a pipeline of improved therapeutic proteins".

### **About Nautilus Biotech**

*Using its proprietary rational evolution technologies, Nautilus offers its partners a high quality services for protein and cell line improvement. Nautilus' target markets include protein pharmaceuticals, vaccines, chemicals and agricultural products. In addition, through its in-house programs, Nautilus is strongly focused on applying its proprietary rational evolution technologies to improving human protein pharmaceuticals and next generation products. Corporate headquarters and R&D facilities are in Evry (France), while corporate business development is driven from its subsidiary in California.*

## **48. Additionally on September 13<sup>th</sup>, 2002 the medical press released an article**

## **titled “Predictors of Pain Medication Use After Liver Biopsy are Identified”**

Previous intravenous drug abuse and anxiety are predictive of pain medication use after percutaneous liver biopsy, finds a study published in the October issue of *Digestive Diseases & Sciences* (Dig Dis Sci 2002; 47 (10): 2151-3).

A researcher from the Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA, identified risk factors for analgesic use following liver biopsy. Thomas R. Riley prospectively examined 121 consecutive biopsies.

A total of 5 variables were selected that might predict analgesia use. These were anxiety, request for sedation, chronic use of addictive medications, previous intravenous drug use, and analgesia requirement with previous biopsies.

Analgesia and narcotic requirement after liver biopsy were 35% and 15%, respectively. Previous IV drug use increased pain medication use after biopsy by almost 10-fold. There was a lower average age (43 vs 47) and a higher Knodell score (7.2 vs 5.8) in those that required analgesics. It was found that the diagnosis of HCV, previous intravenous drug abuse, request for medications before biopsy, anxiety expressed, and chronic use of addictive medications all predicted analgesia use. Furthermore, previous intravenous drug abuse (OR 9.3) and anxiety (OR 3.9) were predictive of pain medication use.

Dr Riley commented, "Patient characteristics play an important role in pain medication requirement after liver biopsy. "If pain after liver biopsy is to be reduced, one has to understand the predisposing factors." "Further studies utilizing behavior modification are warranted," he concluded.

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