

# HCV ADVOCATE WEEKLY NEWS REVIEW

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*Review of HCV, HBV and HIV/HCV Coinfection Related News and Highlights*

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## ***Predicting which HIV/HCV-coinfected patients will respond to HCV treatment: some expected and some surprising answers***

[www.aidsmap.com](http://www.aidsmap.com)

Michael Carter, Saturday

Patients who have an undetectable hepatitis C viral load within four weeks of the initiation of hepatitis C therapy are likely to be successfully treated for hepatitis C infection, according to a German study presented to the Fourth International Workshop on HIV and Hepatitis Coinfection in Madrid on June 20th. The investigators also found that stable HIV infection without a need for anti-HIV therapy predicted an undetectable hepatitis C viral load twelve weeks after starting anti-hepatitis C treatment.

Investigators in the western German cities of Bonn and Cologne wanted to determine the factors associated with successful hepatitis C therapy in HIV/hepatitis C-coinfected patients.

They therefore designed a retrospective study involving 227 individuals who received anti-hepatitis C therapy that included pegylated interferon and ribavirin.

Most of the patients were male (73%), the mean age was 41 years, and 59% of individuals were taking anti-HIV treatment. Average CD4 cell count at the initiation of anti-hepatitis C treatment was 531 cells/mm<sup>3</sup>, with average HIV viral load being a little over 11,000 copies/ml, reflecting the fact that over 40% of patients were not on antiretroviral therapy.

The most common hepatitis C genotype was the hard to treat genotype 1 (56%), with a further 7% of patients having infection with genotype 4, which is also associated with a poor response to anti-hepatitis C treatment.

Overall, 41% of patients achieved a sustained virological response. The investigators then looked at which factors predicted this outcome.

The first of the factors they identified was, as expected, infection with the easier to treat hepatitis C genotypes 2 and 3 ( $p < 0.001$ ). They also found that a “rapid virological response” to anti-hepatitis C therapy – an undetectable hepatitis C viral load within four weeks of its initiation – was also associated with successful anti-hepatitis C therapy ( $p < 0.001$ ), as was an “early virological response” – an undetectable hepatitis C viral load after twelve weeks of anti-hepatitis C treatment ( $p < 0.001$ ).

When the investigators looked at factors associated with an early virological response, they found that these once again included infection with genotypes 2 and 3 ( $p < 0.001$ ), a rapid virological response ( $p < 0.001$ ), but also a lack of antiretroviral therapy ( $p = 0.043$ ).

The investigators were surprised by this final finding. But they said that patients with high CD4 cell counts, and therefore no need to take anti-HIV treatment, were therefore able to avoid the possible liver-toxic interactions between antiretroviral and anti-hepatitis C drugs, increasing the chances of their livers clearing hepatitis C infection.

## Reference

Janke M. et al. Which factors predict early and sustained virological response under combination hepatitis C therapy in HIV/HCV co-infected patients? Fourth International Workshop on HIV and Hepatitis Coinfection, Madrid, abstract 14, 2008.

## ***Prognosis of HIV/HCV-coinfected patients may be better than previously thought***

[www.aidsmap.com](http://www.aidsmap.com)

Michael Carter

The long-term outlook for HIV-positive individuals with hepatitis C coinfection may be much better than previously thought, according to information from a cohort of patients in Milan which was presented to the Fourth International Workshop on HIV and Hepatitis Coinfection in Madrid. The investigators found that over 20 years after infection with HIV, the vast majority of patients with hepatitis C-coinfection were still alive and that the probability of progressing to end-stage liver disease was 9%.

Doctors are now optimistic that successful treatment with potent anti-HIV treatment will mean that HIV-positive patients will be able to live a normal lifespan. But liver disease, often associated with hepatitis B or hepatitis C infection, is now a major cause of illness and death in HIV-positive patients, and in a recent prognostic model, individuals coinfecting with HIV and hepatitis C had a significantly poorer prognosis than patients who were only infected with HIV.

Although it is accepted that infection with HIV speeds up the course of hepatitis C disease there is little information available on the long-term risk of progression to cirrhosis, liver failure and liver cancer (end-stage liver disease) in patients with HIV and hepatitis C coinfection who have not received treatment for their hepatitis C infection.

Investigators in Milan therefore looked at the medical records of patients in the city who were diagnosed with HIV before 1988 with confirmed infection with hepatitis C infection, but who had not received any anti-hepatitis C treatment. They defined end-stage liver disease as a diagnosis of oesophageal varices or decompensated cirrhosis.

The investigators identified 1223 patients who were diagnosed with HIV 20 or more years ago. Of these, 628 had confirmed infection with hepatitis C infection, and 528 had not received anti-hepatitis C treatment. The investigators did not provide any information on the duration of hepatitis C coinfection. However, 86% of patients had injecting drug use documented as their risk factor and given the high prevalence of hepatitis C infection amongst injecting drug users it is likely that both HIV and hepatitis C infection were acquired at approximately the same time.

Analysis of the medical records showed that end-stage liver disease had developed in 49 individuals (9%). Of these patients 22 (38%) had died, 15 (14%) were lost to follow-up, and twelve (3%) were still alive.

A diagnosis of type-2 diabetes was significantly associated with the development of end-stage liver disease ( $p = 0.008$ ), further confirmation of the connection between insulin resistance and poorer outcome in HIV/hepatitis C coinfecting patients. The investigators also found that patients

with end-stage liver disease were significantly more likely to have been diagnosed with AIDS ( $p = 0.047$ ).

No cases of end-stage liver disease developed within the first ten years of diagnosis with HIV. After 15 years of HIV infection, the probability of developing end-stage liver disease was 2%, increasing to 9% after 20 years and 18% after 25 years.

The investigators then looked more closely at the details of the patients who had died with a diagnosis of end-stage liver disease. They found that 25% of these patients had developed end-stage liver disease within 17 years of their diagnosis with HIV, 50% within 20 years and 75% within 25 years.

Cause of death was available for 48 patients (72%). In 14 (29%) of these individuals, death was attributed to cirrhosis.

The investigators found that the patients who progressed to end-stage liver disease received less treatment with potent combination antiretroviral therapy (median 5.5 years vs. 8.4 years,  $p = 0.0005$ ) and had lower CD4 cell counts (median 173 cells/mm<sup>3</sup> vs. 373 cells/mm<sup>3</sup>,  $p < 0.001$ ). But in subsequent “multivariate” analysis, only shorter duration of potent antiretroviral therapy remained a significant predictor of progression to end-stage liver disease ( $p = 0.0001$ ).

“In HIV/hepatitis C-positive patients infected before 1988, the overall probability of developing end-stage liver disease is 9%”, conclude the investigators, “suggesting that the natural history of hepatitis C virus disease in this population may be more benign than previously thought.”

### **Reference**

De Bona A. et al. Probability to develop HCV-related ESDL in patients with long-term exposure to HIV infection. Fourth International Workshop on HIV and Hepatitis Coinfection, Madrid, abstract 29, 2008.

## ***Champion for Ailing Vets Needs Help of His Own***

<http://www.theledger.com>

By Rick Rousos

*The Ledger*

*Longtime volunteer now ill, needs money for a liver transplant.*

Charlie Summerall, whose longtime habit is collecting and delivering supplies to ailing military veterans, has hepatitis C and needs a liver transplant.

Summerall's friends from the Sons of AMVETS will hold a fundraiser for him Sunday at AMVETS Post 32., 1339 E. Gary Road in Lakeland.

Summerall is a retired Lakeland Electric lineman who worked for the utility for 31 years. He got involved with Sons of AMVETS because his late father was a World War II veteran.

The Lakeland man is best-known for an underwear drive in 2004 in which he collected hundreds of packages of new underwear. Summerall delivered the briefs to James A. Haley Veterans Hospital in Tampa, where they were badly needed.

The underwear drive has become part of the Sons of AMVETS annual national budget and has caught on across the country.

Summerall used to be a physically powerful man, but now he's very weak. He's lost 45 pounds. His face looks gaunt, and he looks considerably older than 53 years. He moves and sounds like he's pushing 80.

"He lays down all the time," said Summerall's wife, Patti. "It hurts him just to walk from the couch to the bathroom."

Pete Capua is the Sons of AMVETS state commander and is based at AMVETS Post 32 in Lakeland, also Summerall's home base.

"Charlie has been non-stop, very dedicated," Capua said. "You name it, he does it. He's unselfish. With Charlie, it's not about getting credit, it's about the veterans getting the benefit."

Before feeling weak toward the end of 2007, Summerall had been serving as a church escort, driving veterans hospitalized in Tampa to church. He also had continued to drive loads of toiletries, socks, underwear and bras to Haley Hospital.

Doctors have told Summerall that he got hepatitis C not from drinking, which he did in moderation, but from blood-to-blood contact.

Summerall suspects that it could have happened during one of his hurricane duty trips, when Lakeland Electric crews were sent elsewhere to help.

Linemen work long hours at a fast pace to restore power "and sometimes there are cuts, especially to the hands. Then you're meeting new people and shaking hands.

"I'm not saying that's how it happened," Summerall said. "But I think there's a good chance." He has urged his former cohorts at Lakeland Electric to be tested.

Summerall is at the top of a list for a liver transplant. His health insurance will cover the most of the cost of that operation. But he's going to wind up paying thousands of out-of-pocket dollars for anti-rejection drugs and other medications he'll take for the rest of his life. That's the reason for the fundraiser Sunday.

AMVETS Post 32 is already reeling from the recent death of its commander, John Lane. "He would have run the show Sunday," Summerall said. "I miss him bad."

The "show" Sunday will open at noon and stay open into the night. At 2 p.m. they'll begin serving \$12 T-bone steak dinners. A handful of bands have donated their services and will play non-stop, more or less. The post will also hold auctions and raffles for Summerall.

Chapter 5, a military veterans motorcycle club next to the AMVETS post on Gary Road, will also be open for the fundraiser's overflow.

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**June 23, 2008**

## ***Genelabs Provides Update on Hepatitis C Drug Development With Collaboration Partners***

<http://www.businesswire.com>

REDWOOD CITY, Calif.--(BUSINESS WIRE)--Genelabs Technologies, Inc. (Nasdaq:GNLB) announced today that based on progress to date, its hepatitis C drug development and commercialization collaboration with Novartis is continuing to the next phase.

In September 2006, Genelabs and Novartis entered into a two-year collaboration to discover and develop certain non-nucleoside inhibitors (NNI) of the NS5b polymerase in HCV. Genelabs was responsible for drug discovery research and Novartis is responsible for development and commercialization. The research phase of the collaboration was completed on June 2, 2008. Genelabs and Novartis will continue to hold joint research committee meetings to monitor the progress of compounds discovered during this phase as they advance.

Genelabs also announced that Gilead has exercised its right to terminate a similar research collaboration agreement for nucleoside-based inhibitors for the NS5b HCV polymerase, and will return to Genelabs all rights to the compounds developed in the program.

“We are very pleased that Novartis is continuing to advance compounds identified in the research phase of our collaboration,” said Ronald C. Griffith, Genelabs’ Chief Scientific Officer. “We look forward to the potential of future milestone achievements with this program. At the same time, we are continuing to independently discover and develop nucleoside-based inhibitors for this important NS5b HCV target and are discussing further collaboration in this area with various third parties.”

### **About the Novartis HCV Collaboration**

Under the terms of the agreement, Genelabs received \$19.1 million, including a \$12.5 million initial up-front payment over a two-year research period. Additional payments to Genelabs could exceed \$175 million if all potential clinical, regulatory and sales milestones are met. Genelabs is also entitled to a royalty on net sales of products arising from the collaboration.

## ***Doc Sued Over Sloppy Handwriting***

<http://www.therapeuticsdaily.com>

A New York doctor's sloppy penmanship put a patient's health at risk when he was given the incorrect medication for several months, a lawsuit contends.

Jeffrey Deutchman, 55, of New York, allegedly received lithium carbonate, a medication typically used to treat manic depression, when he was supposed to get lanthanum carbonate for his kidney failure, court documents indicate.

Dr. Heino Anto of Peninsula Hospital Center is accused of illegibly writing Deutchman's prescription in March 2005, the New York Post reported Sunday.

The suit, lodged this month in Queens Supreme Court, says workers at Deutchman's pharmacy were unable to read Anto's handwriting.

"They realized the prescription was illegible. The doctor rewrote it, and the issue is whether he rewrote it illegibly or they took it down wrong," Deutchman's attorney Rose Day said.

Deutchman allegedly took the wrong drug for as long as nine months, the Post said.

**June 25, 2008**

### ***Cuba Set to Eradicate Hepatitis B***

<http://www.radionuevitas.co.cu>

Havana, Jun 23 (RHC-ACN) - With 7 cases reported in 2007 and only four so far this year, Cuba is ready to eradicate Hepatitis B transmission with a highly effective vaccine produced in the country, reports Prensa Latina news agency.

A government-sponsored immunization program for newborns began in 1992. A recent Granma article recalls that over 2,100 cases were reported that year.

Today, all Cubans under 26 and large parts of the rest of the population have been immunized and the infection rate has been cut by 99.2 percent in 15 years.

The newspaper states that worldwide, one in every 12 people is infected with Hepatitis B or C, while 1.5 million die of these liver infections every year.

The illness is caused by a virus transmitted via blood and other body fluids such as saliva and semen. It can also be passed from mother to child at birth or during breastfeeding.

The highest risk of contracting the disease in Cuba nowadays is through unprotected sex with an infected partner, explains the article.

Cuba's vaccination scheme covers all newborns and students, as well as groups with an increased risk of infection like health-care workers and dialysis patients.

The Recombinant HB vaccine is under large scale production at the Genetic Engineering and Biotechnology Centre in Havana (CIGB). The product is marketed in over 40 countries and since 1992 the CIGB has produced almost 157 million doses for export and over 14 million for the Public Health Ministry's National Vaccination Program.

According to the publication, the result lays the foundations of HB dependent Hepatic cancer and cirrhosis eradication in the next three or four decades.

## ***NICE Issues Final Appraisal Determination (FAD) Which Recommends Baraclude(R) (Entecavir) as a Treatment Option for Eligible Chronic Hepatitis B Patients***

<http://biz.yahoo.com>

UXBRIDGE, England, June 25 /PRNewswire/ -- NICE (National Institute for Health and Clinical Excellence) has announced today, in its Final Appraisal Determination (FAD), that Baraclude® (entecavir) is recommended as an option for treatment of eligible patients with chronic hepatitis B (CHB). Entecavir is a potent anti-viral treatment for chronic Hepatitis B that has been shown to be more effective at suppressing the virus than the most widely used anti-viral treatment (lamivudine)(1) and is less prone to the development of treatment resistance.(2) The recommendation in this FAD is due to be published as final NICE guidance in August of this year.

Richard Marsh, Director of External Affairs and Market Access, Bristol-Myers Squibb said, "Bristol-Myers Squibb welcomes the news that NICE has issued a positive FAD recommending Baraclude as a treatment option for all chronic Hepatitis B patients, in line with its licence.

"Chronic Hepatitis B is a leading cause of liver cirrhosis and liver cancer. It is highly infectious, growing in prevalence in the UK and an increasing cost to NHS resources. Baraclude is a clinically effective and cost effective treatment for all eligible patients with chronic Hepatitis B. Its favourable resistance profile, in particular, makes it a very valuable treatment option for patients and for the NHS."

"If the FAD remains unchanged, it will be published as final guidance in August this year. PCTs will then be required to make funding available for Baraclude for patients prescribed it by their specialist. Bristol-Myers Squibb will continue to work proactively with clinicians and PCTs to enable access to Baraclude for those patients who will benefit from it."

## ***Vertex Investors Balk at New Study Plans***

<http://www.thestreet.com/>

Adam Feuerstein

A speedier-than-expected regulatory filing for Vertex Pharmaceuticals' VRTX hepatitis C drug appears less likely after the company disclosed plans Monday for a new phase III study of the drug.

Investors have been hoping that Vertex and partner Johnson & Johnson JNJ could seek regulatory approval for telaprevir in 2009 based on data from existing clinical trials in treatment-resistant patients.

However, the companies posted details of a new phase III study of telaprevir in treatment-resistant hepatitis C patients on the ClinicalTrials.gov Web site Monday. The disclosure dampened investor outlook for a quick telaprevir filing.

If Vertex cannot file telaprevir with the U.S. Food and Drug Administration in 2009, the filing will likely come in the second half of 2010 after studies of the drug in treatment-naïve hepatitis C patients are completed.

Vertex shares fell 5% to \$31.66 Monday as a result.

"We have learned that telaprevir's phase III study in treatment experienced hepatitis C patients is different from PROVE 3 and study 107, which in our view decreases the chances of an early filing," wrote Citibank analyst Yaron Werber in a note to clients Monday evening. PROVE 3 and study 107 refer to the existing telaprevir studies in treatment-resistant patients.

Werber has a hold rating on Vertex, and perhaps echoing the sentiment of his momentum and catalyst-driven hedge fund clients, he added that, "We are no longer warming up to the stock and believe the momentum has cooled off as we believe that the chances for an early approval on PROVE 3 and 107 are low."

### **The New Phase III Study**

Vertex spokesman Michael Partridge says Monday's disclosure of a new phase III telaprevir study is in line with the company's previous guidance and "not closely connected to a possible [FDA] filing based on PROVE 3 results."

Partridge added that Vertex and the FDA are still discussing the previously disclosed PROVE 3 data, but that "initiation of a new phase III study is a natural extension of the PROVE 3 results which we would have started no matter the path to a filing."

The new phase III study disclosed Monday will test two different regimens of telaprevir in patients who previously did not respond to conventional hepatitis C treatment with pegylated interferon and ribavirin.

The study differs from previous studies in that patients will be treated with two regimens of telaprevir for a full 48 weeks instead of the accelerated 24-week treatment cycle used for treatment-naïve patients.

In addition, one of the arms of the new study will see whether a "lead-in" treatment with interferon and ribavirin alone before dosing of telaprevir may improve overall cure rates.

The design of the new study is sufficiently different from the previous PROVE 3 and study 107 trials to suggest that regulators want more and different data on telaprevir's effect on treatment-resistant patients before considering the drug for approval.

Cowen & Co. analyst Rachel McMinn views Monday's selloff as an overreaction to expected news. She reiterated her outperform rating on Vertex.

"We believe that yesterday's [Vertex] sell off was driven by an over-reaction to two-week old information. Timelines for commercial launch of ... telaprevir (late 2010/early 2010) are unchanged, and we see 50% upside relative to the market on the basis of this timeframe. While probability of an early 2009 FDA approval is low, we see 100% upside relative to the market under this scenario over the next 6-12 months."

Schering-Plough SGP recently announced the start of phase III studies for its competing hepatitis C drug.

### ***PU student prepares cancer, hepatitis C medicine***

<http://www.dailytimes.com.pk/>

LAHORE: A PhD scholar at the Punjab University (PU) has made history by successfully preparing Interferon Alpha 2B – a medicine used in the treatment of cancer and hepatitis C patients. Pakistan spends large amounts to import the drug from Belgium, China and several other European countries every year. The drug controls the hepatitis C virus and growth-affected cells. According to a press release issued by the PU on Tuesday, Nasir Mehmood, a PhD scholar at the university's School of Biological Sciences (SBS) prepared the medicine under the supervision of SBS Director General Prof Muhammad Akhtar. The medicine was then sent to the British National Institute of Biological Standards and Control (NIBSC) for testing. The NIBSC has certified its effectiveness. "This antiviral recombinant protein drug is active biologically," states the NIBSC report. Nasir Mehmood told Daily Times that according to an estimate, one out of every 10 Pakistanis was infected with hepatitis, which is alarming. He said that he had prepared the drug in a laboratory at the university and if sufficient funds were provided to the PU, it could produce the medicine at an industrial level in the next three to four years. "It took me about five years to prepare the medicine. It was difficult, but interesting." A single dose of Interferon Alpha 2B costs at least Rs 750 and the complete treatment of a patient requires the drug in large quantities, which costs millions of rupees. SBS Director Prof Javed Iqbal said PhD scholars at his school were working on the production of medicine to combat various diseases. He said many of the drugs they were working on were of 'immense importance'. staff report

**June 25, 2008**

### ***Sorafenib Effective in Asian-Pacific Liver Cancer Patients***

[www.medscape.com](http://www.medscape.com)

Zosia Chustecka

June 16, 2008 (Chicago, Illinois) — The recent approval of sorafenib (Nexavar, Onyx/Bayer) for use in liver cancer was based on a large placebo-controlled trial conducted in Spain. Although these results were described as "dramatic," there remained concerns about whether the drug would be as effective in an Asian population with a high incidence of hepatitis infection, poorer health status, and more advanced stages of liver cancer.

"These lingering doubts have now been laid to rest," said Margaret Tempero, MD, from the University of California, San Francisco, speaking here recently at the American Society of Clinical Oncology 44th Annual Meeting. The results from the latest trial show that sorafenib is

just as effective in this patient population, "so we can stop worrying about this problem," she said during a discussion of the abstract at a "highlights of the day" session.

The latest results come from a phase 3 trial conducted in 226 Asian patients with advanced hepatocellular carcinoma, and were presented at the meeting by Ann-Lii Cheng, MD, PhD, from the National Taiwan University Hospital, in Taipei. Sorafenib demonstrated a "clear survival benefit in Asia-Pacific patients and had comparable results to last year's SHARP [Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol] trial, despite these patients in the Asia-Pacific trial having poorer health status and more metastases," she said in a statement.

Liver cancer, resulting primarily from chronic hepatitis infections, is a particular concern in the Asia-Pacific region, where more than 8% of the general population is infected with hepatitis B and 2% to 4% is infected with hepatitis C. More than half of all the cases of liver cancer diagnosed worldwide (>600,000 per year) are found in this region, with China, South Korea, Japan, and Taiwan accounting for more than 400,000 of cases per year.

### **Latest Results Echo Previous Results**

The SHARP trial, conducted in 602 patients, was presented at last year's ASCO meeting. It showed a 44% improvement in overall survival, with a median overall survival of 10.7 months for sorafenib and 7.9 months for placebo. It also showed a 73% prolongation of time to progression, with a median time to progression of 24 weeks for sorafenib and 12 weeks for placebo. The trial was stopped early because the results were so positive.

These results were greeted enthusiastically by experts at the 2007 meeting, who pointed out that there was no widely accepted standard of care for advanced liver cancer. Sorafenib has since been approved for this indication in more than 40 countries.

The latest results in Asian patients echo the results from the SHARP trial. Both trials were sponsored by the manufacturer. Again, there was a significant improvement in overall survival, 47.3% in this case, with a median overall survival of 6.2 months for sorafenib and 4.1 months for placebo. There was also a significant 74% improvement in time to progression, with a median time to progression of 2.8 months for sorafenib and 1.4 months for placebo. In addition, the disease control rate (comprised of complete and partial responses and stable disease  $\geq 12$  weeks) was 35% for sorafenib and 16% for placebo.

The survival benefit was seen across multiple patient subgroups, including age, extrahepatic spread, and/or macroscopic vascular invasion. Adverse reactions were low to moderate in severity, the researchers said, and the most common serious adverse effects were hand-and-foot reaction, diarrhea, alopecia, fatigue, and rash/desquamation.

"These data provide further evidence that sorafenib is efficacious in liver cancer across multiple geographic regions and independent of disease characteristics and etiologies of underlying disease," said Susan Kelly, MD, vice-president, Therapeutic Area Oncology at Bayer HealthCare Pharmaceuticals. "Sorafenib has quickly become the systemic standard of care for liver cancer."

*American Society of Clinical Oncology (ASCO) 44th Annual Meeting. Abstract 4509. Presented June 2, 2008.*

## **MELD Allocation System Boosts Liver Transplants in HCC Patients**

[www.medscape.com](http://www.medscape.com)

NEW YORK (Reuters Health) Jun 18 - Introduction in early 2002 of the Model for End-Stage Liver Disease (MELD), a new liver donor organ allocation system allowing priority status to patients with limited-stage hepatocellular carcinoma (HCC), has resulted in a six-fold increase in the proportion of liver transplant recipients with HCC, research shows.

According to data from the United Network for Organ Sharing, during the 5 years immediately before adoption of the MELD system (1997-2002), 4.6% of liver transplant recipients had HCC, compared with 26% in the 5 years immediately after adoption of the MELD system (2002-2007).

In the June issue of *Gastroenterology*, Dr. George N. Ioannou from the Veterans Affairs Puget Sound Health Care System, Seattle and colleagues also note that the vast majority of HCC patients who received donor livers in 2002-2007 received "HCC-MELD-exceptions" providing expedited transplantation.

Moreover, the data suggest that introduction of the MELD system with HCC-MELD-exceptions was "successful" in achieving high posttransplantation survival in patients with HCC, the researchers report. "This success is likely related to both the selection of patients with limited stage HCC and the ability to promptly transplant these patients because of the arbitrarily high priority score assigned to them," Dr. Ioannou and colleagues say.

In post-MELD 2002-2007, patients with an HCC-MELD-exception had similar survival to patients without HCC. However, this does not appear to be true for a subset of HCC patients with tumors measuring 3 to 5 centimeters.

Other predictors of "particularly poor posttransplantation survival" were MELD scores greater than or equal to 20 and serum alpha-fetoprotein levels greater than or equal to 455 ng/mL, the investigators report.

"We hope that these results are useful in continuing to optimize the policies that guide liver transplantation for HCC in the United States," they conclude.

This study, comment Drs. Michael Volk and Jorge A. Marrero of University of Michigan, Ann Arbor in a related editorial, "provides important information about the survival of patients with HCC after transplantation. The question still remains, however, if these patients receive enough benefit to justify the harm caused to other patients by the use of scarce organs."

*Gastroenterology* 2008;134:1342-1351;1612-1614.

## **Studies Show Quality of Life Linked to Cancer Survival**

[www.medscape.com](http://www.medscape.com)

Allison Gandey

June 19, 2008 (Chicago, Illinois) — Patients reporting a good quality of life have statistically significant better overall survival, suggest 2 large meta-analyses. The studies, presented here at

the American Society of Clinical Oncology (ASCO) 44th Annual Meeting, show that patient self-reporting can be an important prognostic indicator and might offer insight in predicting survival.

"Quality of life appears to affect the survival of cancer patients," lead investigator Angelina Tan, MD, from the Mayo Clinic, in Rochester, Minnesota, told Medscape Oncology. "If physicians can identify patients who are not doing well, they will be able to intervene and, we hope, improve not only their patients' sense of well-being, but also the length of their life." Dr. Tan presented the first of the meta-analyses.

During a "highlights of the day" session, Joanna Brell, MD, from the Ireland Cancer Center, in Cleveland, Ohio, drew attention to the studies. Dr. Brell said she was pleased with the large sample sizes and suggested that the results provide an important premise that should be followed up.

Dr. Brell said it would be great to have a simple instrument that could measure baseline quality of life and in some way quantify what patients are trying to tell their doctors when they explain how they are feeling.

Session discussant Jamie Von Roenn, MD, from Northwestern University, in Chicago, Illinois, echoed these sentiments and applauded ASCO for including more papers on patient care than ever before. "We are moving in the right direction," she said.

### **Study of More Than 3700 Patients**

Dr. Tan's group conducted a meta-analysis of more than 3700 patients. Participants were from 24 oncology clinical trials and provided data at baseline on overall quality of life rated on a 100-point scale.

The researchers used Cox proportional hazards models and adjusted for the effects of performance score, race, site, age, and sex. They found that baseline quality of life is a strong and independent prognostic factor for overall survival.

### **Role of Baseline Quality of Life in Overall Survival**

| <b>Quality of Life</b>                          | <b>Months</b> | <b>P Value</b> |
|-------------------------------------------------|---------------|----------------|
| Low vs high                                     | 12.3 vs 18.4  | <.0001         |
| Clinically deficient vs nonclinically deficient | 9.3 vs 16.8   | .0001          |

Investigators found that the effect sizes were consistent across different disease sites, including gastrointestinal, genitourinary, lung, breast, and brain.

"Patient well being is an important consideration that is related to patient survival," Dr. Tan said. "If patients reported a clinically meaningful deficit in quality of life, as indicated by a score of 5 or less on a 10-point scale (or 50 or less on a 100-point scale), median survival was significantly shorter than if they did not report a quality-of-life deficit at baseline."

Dr. Tan pointed out that having a high quality of life at baseline did not guarantee longevity, but having a poor quality of life at the outset roughly doubled the baseline likelihood of death at 1, 2, and 3 years.

### **Second Study of More Than 10,000 Patients**

Chantal Quinten, from the quality-of-life department at the European Organization for Research and Treatment of Cancer (EORTC), in Brussels, Belgium, presented results from the second meta-analysis.

Her group studied 30 randomized controlled trials with more than 10,000 patients. Participants had completed a baseline quality-of-life assessment using an EORTC measure and survival data. Researchers evaluated health-related quality of life on a set of 15 standard scales. Clinical data included age, sex, distant metastasis, World Health Organization performance status, and disease site.

Investigators assessed prognostic significance using Cox proportional hazards models. They applied bootstrap resampling to check the stability of the models.

#### **Clinical Variables Found to be Prognostic**

| <b>Variable</b>              | <b>Hazard Ratio</b> | <b>P Value</b> |
|------------------------------|---------------------|----------------|
| <b>Physical functioning</b>  | 0.994               | <.0001         |
| <b>Cognitive functioning</b> | 1.003               | .0105          |
| <b>Global health status</b>  | 0.996               | .0006          |
| <b>Fatigue</b>               | 0.997               | .0160          |
| <b>Nausea and vomiting</b>   | 1.005               | .0004          |
| <b>Pain</b>                  | 1.003               | .0003          |
| <b>Dyspnea</b>               | 1.006               | <.0001         |
| <b>Appetite loss</b>         | 1.005               | <.0001         |

The researchers conclude that quality-of-life parameters provide prognostic information; the effect held across the 11 cancer sites.

The investigators call for more study to confirm these findings within cancer sites. If validated, they suggest that future clinical trials consider quality of life as a stratification factor.

Dr. Tan agreed that quality-of-life factors should be considered for routine inclusion in future randomized oncology treatment trials, and that additional study is needed.

She acknowledged to Medscape Oncology that many challenges remain, but said she looks forward to working toward identifying "both how and when clinicians can best support their patients' feelings of well being."

The researchers have disclosed no relevant financial relationships.

*American Society of Clinical Oncology (ASCO) 44th Annual Meeting. Abstract 9515 and 9516. Presented June 2, 2008*

## **Transplant patients should know risks: doctors**

[www.reuters.com](http://www.reuters.com)

By Julie Steenhuisen

CHICAGO (Reuters) - New guidelines are needed to inform people about the risks of organ transplants after four organ recipients in Chicago got HIV and hepatitis C from a single donor last year, U.S. doctors said on Wednesday.

While tests initially showed the organs to be free from infection, the donor was known to have had a high risk of infection with the human immunodeficiency virus, which causes AIDS.

The cases were the first incidence of HIV infection from organ donation in 15 years and have stirred debate about how to best inform people of the risks of transplants.

"This is an issue that goes far beyond those people's unfortunate circumstances," said Dr. Scott Halpern of the University of Pennsylvania School of Medicine, who makes the case for new guidelines in the *New England Journal of Medicine*.

"It is applicable to all patients seeking organ transplants regarding what they have a right to know and when they have a right to know it," Halpern said in a telephone interview.

Halpern said current guidelines do not adequately protect patients' rights to make fully informed decisions.

He and colleagues propose the United Network for Organ Sharing or UNOS, which sets U.S. policy for organ donation, create guidelines to disclose "all foreseeable risks" of transplant surgery when a person is placed on the organ transplant list.

This would give patients the right to opt out of receiving higher-risk organs, including organs from people who are at risk for infectious diseases.

Halpern said currently, if an organ becomes available and a surgeon is aware that it came from a high-risk donor, he or she would disclose that at the time of the transplant.

"That creates a whole host of problems, including inequity and the potential for discrimination," he said. And it wastes precious time, reducing the chances that someone else might be able to use that organ, he said.

## CHOOSING UP FRONT

Instead, Halpern thinks people should be told of the risks up front and indicate whether they would accept a riskier organ or only one that is from a lower-risk donor.

Halpern and colleagues said this would reduce the opportunity for people to "cherry pick" the best organs, or to only decline an organ from someone who was at high risk for HIV -- a group that includes homosexual men, people who have been in prison and injectable drug abusers.

Halpern said telling patients about HIV risk, without disclosing risks about other diseases like high blood pressure, might feed into social biases.

"Because organs are so scarce and there is such a demand and the people who are getting them are in such need, the emphasis has been on increasing the number of donors and improving access to the organs and making sure there is fair distribution," Dr. Matthew Kuehnert, who oversees organ safety at the U.S. Centers for Disease Control and Prevention, said in a telephone interview.

"What hasn't been emphasized is the patient safety part of it about what are the risks of transmitting disease. It's events like (the Chicago cases) that force us to take a look at it," Kuehnert said.

Joel Newman, a spokesman for UNOS, said the cases in Chicago were a "galvanizing moment" for the transplant community.

He said UNOS is working with the CDC to improve the way it talks to potential transplant recipients about all of the risks associated with organ donation.

(Editing by Maggie Fox)

### ***Liver transplant denial questioned; marijuana use examined***

<http://thedaily.washington.edu>

By Joy Yagi

During early May, The Daily printed a story about the death of Seattle resident Timothy Garon. He was denied a liver transplant at two local hospitals and later died. Some believe this was due to his previous marijuana use, and the case was picked up by national media. The UW Medical Center and Garon's lawyer and doctor go on the record about his death.

Timothy Garon appeared frail and gaunt. His abdomen was bloated from liver failure, making him look pregnant, said Sunil Aggarwal, a third-year medical student and doctoral candidate at the UW who visited Garon in his UWMC hospital room.

"But he had such a strength of conviction that said, 'I'm going to get through this, and I really want to live,'" Aggarwal said of Garon.

On May 2, a little more than two weeks later, Seattle musician Timothy Garon, 56, died.

After being denied a spot on the liver transplant lists at Harborview Medical Center and the UW Medical Center (UWMC), Garon's case attracted attention throughout the nation.

The reasons for the denial of Garon's liver transplant are hazy due to patient privacy laws.

Garon's liver problems can be traced to his teenage years. He thought he contracted hepatitis C from sharing needles with "speed freaks," Garon said in an interview with The Associated Press a week before his death.

To relieve the pain and nausea associated with hepatitis C, Garon used medically authorized marijuana.

"I'm not a proponent of medical marijuana," said Dr. Brad Roter, Garon's physician and a member of the UW's medical faculty. "However, in very rare cases, it can be useful. Tim was one of those cases."

Garon had hepatitis C and was smoking marijuana even before Roter authorized his use of medical marijuana.

"Whether he used it for medical reasons only or for recreational reasons or other reasons, I really don't know," Roter said.

Because Garon was already using the substance and the benefits of relieving hepatitis C symptoms outweighed the risks, Roter decided to authorize medical marijuana for Garon.

Roter did not know how long Garon had been using marijuana before he met him.

In December 2007, Garon was arrested in his Mountlake Terrace apartment for growing marijuana, said Douglas Hiatt, his attorney.

While authorized marijuana is legal under Washington state law, it is illegal under federal law. Garon spent several days in prison, where his health noticeably worsened, Aggarwal said.

After his girlfriend posted bail for him, Garon was told he had to move out of his apartment, Aggarwal said.

Garon was denied a place on the transplant list at Harborview Medical Center. After that, Garon and Hiatt went to the UWMC, where he was again denied.

The UWMC said it would reconsider its decision if Garon went through 60 days of drug treatment, Hiatt said. The day before, Garon had been told he had about two weeks to live.

"You tell a dying guy that's got less than two weeks to live that he's got to go through 60 days of drug treatment before you reconsider him again?" Hiatt said.

The UWMC cannot speak specifically about Garon's case due to patient privacy laws, said Tina Mankowski, director of the news and community relations for UW Medicine and Health Sciences.

“I am not sure we can ever predict with accuracy how long a person with a life-threatening disease will live,” she said.

The UWMC reviewed Garon’s case, and it was denied again.

Hiatt said Garon was denied because he used medically authorized marijuana.

However, a statement released by the UWMC claimed medical marijuana “is never the sole determinant in arriving at medical decisions about candidates for organ transplants.”

Because of the scarcity of organs, the transplant committee performs a “very comprehensive ... evaluation for every patient,” Mankowski said.

About 98,000 patients are waiting for organs in the United States, and there are only about 6,000 donors, Mankowski said.

The liver transplant committee considers a patient from a medical and psychosocial standpoint and looks at patient history of substance abuse and dependency.

If a history exists, the committee considers the period of abstinence to date, the effort to abstain and substance abuse potential, Mankowski said.

Garon had been abstinent from marijuana for six months. Realizing marijuana could influence his chances of receiving a transplant, Garon stopped smoking it in October 2007, Hiatt said.

“He thought it’d be better to deal with the symptoms of pain and nausea rather than not getting a transplant and dying — which he did anyway,” Aggarwal said.

Garon had also been sober for the past eight years, Roter said.

Six months of marijuana abstinence and eight years of alcohol sobriety should be adequate, Roter said in regards to the UWMC wanting 60 days of drug treatment.

Potential problems could have arisen due to Garon’s arrest and eviction from his apartment in December 2007, Aggarwal said.

Hiatt, who frequently serves as an attorney for medical marijuana patients, said he believes marijuana was the problem in Garon’s trouble getting on the liver transplant list.

In general, marijuana “perhaps would be one of the considerations,” Mankowski said. “However, I think it’s important to note the use of medical marijuana in and of itself would not prevent somebody from being listed.”

[Reach reporter Joy Yagi at [news@thedaily.washington.edu](mailto:news@thedaily.washington.edu) .]

## ***Insured losing access to healthcare: U.S. study***

[www.reuters.com](http://www.reuters.com)

WASHINGTON (Reuters) - About 20 percent of the U.S. population delayed or were unable to get access to medical care when they needed it in 2007, up from 14 percent four years earlier, a study released on Thursday found.

About 9.5 million more people went without medical care in 2007, compared with 2003, the nationally representative survey released by the Center for Studying Health System Change, a nonpartisan policy group, found.

In a striking finding, the survey said although those without insurance were more likely to report going without care, those with insurance had a greater percentage increase in unmet medical needs.

"It's not a pretty picture, especially for insured people, who are increasingly finding that the access to care once guaranteed by insurance is declining," said Peter Cunningham, co-author of the study, which was funded in part by the Robert Wood Johnson Foundation, which provides grants for projects aimed at improving U.S. health care.

The telephone survey of 18,000 people was based on a random national sample with 43 percent of those polled responding.

Cost was the biggest obstacle to care for both the insured and the uninsured, the study said. For the insured, individuals said they were unable to get their health insurer to pay for treatment, or that a doctor or hospital would not accept their insurance.

About 47 million people in the United States do not have health insurance, a number that has been climbing since 2000.

At the same time, medical costs - driven by drugs, hospital and doctor fees -- have risen at least twice the rate of inflation for several years, making it more expensive for those with insurance to afford care.

UnitedHealth Group, WellPoint Inc. and Aetna Inc. are the three biggest U.S. health insurers.

(Reporting by Kim Dixon, editing by Vicki Allen)

## ***Study finds safer, more efficient medication for hepatitis B treatment***

<http://www.physorg.com>

Patients with hepatitis B who did not respond to lamivudine therapy had a better virological response after switching to entecavir for a year. Continuing the drug for an additional year led to even more clinical improvement without significant side effects, according to a new study in the July issue of *Hepatology*.

Chronic hepatitis B is the tenth leading cause of death worldwide. Infected patients are at high risk of developing serious liver diseases such as cirrhosis and liver cancer, especially if they have high levels of HBV DNA in their blood. Lamivudine is one treatment for HBV, however the virus commonly becomes resistant to it and leads to disease progression. Adefovir dipivoxil is another treatment option, however virologic suppression is not optimal. A third drug, Entecavir, has been shown to be a safe and effective treatment for patients who don't respond to lamivudine.

Researchers led by Morris Sherman of Toronto General Hospital, studied 286 patients taking part in a double-blind, double-dummy, randomized, controlled trial comparing the safety and efficacy of entecavir (1 mg/day) to lamivudine (100 mg/day). The results of the first year of this trial were previously reported. 57 percent of patients taking entecavir, compared to five percent of those taking lamivudine were classified as virologic responders, and were offered continued therapy for an additional year. The researchers then assessed the efficacy, safety and resistance profile of entecavir through 96 weeks of treatment.

"The year-two results demonstrated that patients continue to experience clinical benefit with entecavir therapy beyond one year, while the safety profile remained stable," the authors report. The additional year of treatment increased the proportion of patients with HBV DNA <300 copies/mL from 21 percent to 40 percent.

Analysis showed that seven patients in the total entecavir-treated cohort had baseline resistance to the drug. Another 10 became resistant in year one, and seven more in year two. Virologic breakthrough lagged behind the development of resistance.

"In summary, a second year of entecavir treatment in lamivudine-refractory patients with HbeAg-positive chronic hepatitis B resulted in continued virologic, serologic and biochemical improvement and a safety profile that was comparable with the first year of therapy," they conclude. "A longer duration of treatment and continued treatment of patients with HbeAg loss may lead to higher rates of virologic response and seroconversion in lamivudine-refractory chronic hepatitis B patients."

*Source: Wiley-Blackwell*

## ***European Approval for Roche's Pegasys Personalises Treatment for a Subgroup of Hepatitis C Patients: Chance for Cure With Only Four Months of Treatment***

<http://biz.yahoo.com>

*- Roche Also Announces Start of NCORe Study to Determine Best Length of Treatment in Patients who do not Experience a Rapid Response*

BASEL, Switzerland, June 26 /PRNewswire/ -- Roche announced today that the European Commission has approved a shortened, 16-week course of treatment with Pegasys (peginterferon alfa-2a (40 KD)) plus Copegus (ribavirin) for certain hepatitis C patients.

The four-month treatment course will be for patients with particular strains of chronic hepatitis C (genotype 2 or 3) who have low virus levels before starting treatment, and who show a rapid virological response by clearing the virus from the blood within the first 4 weeks of treatment. This shorter treatment duration with Pegasys/Copegus will provide patients with the full benefits of therapy while reducing unnecessary drug exposure.

This is good news for eligible patients as previously, all patients with genotype 2 or 3 hepatitis C (HCV) received 24 weeks of Pegasys/Copegus therapy, regardless of their baseline virus levels and response while on treatment.

The approval marks an important milestone in a new treatment concept in hepatitis C, which is called "response-guided therapy" and seeks to customise regimens for patients based on how well they respond to treatment. Response-guided therapy is enabled by the use of Roche's highly sensitive, real-time PCR diagnostic tests, which accurately measure the levels of virus in the patient's blood. The automated COBAS AmpliPrep/COBAS TaqMan HCV Test is the newest and most advanced Roche product for measuring hepatitis C virus levels. The test is widely used in many global markets, and is pending FDA approval in the United States.

"Response-guided therapy in hepatitis C is an excellent example of how Roche is uniquely positioned to individualise healthcare and deliver real benefit to patients, physicians and healthcare payers by combining the power of innovative pharmaceuticals and diagnostics," said William M. Burns, CEO, Roche Pharmaceuticals Division. "This approval for 16 weeks of treatment in genotype 2 and 3 patients with a rapid response demonstrates the value of using diagnostic tools to determine an individual treatment regimen and hopefully will encourage more eligible patients to come forward for treatment. Together with the start of yet another large clinical study with Pegasys, NCORE, these initiatives underscore Roche's commitment to advancing the treatment of hepatitis and making personalised medicine a reality."

### **Shortening the Treatment Duration for Many**

This approval is based on data from several studies that show shorter treatment duration in patients who have a rapid response to Pegasys/Copegus results in high cure rates, similar to those achieved with the currently-approved 24 weeks of therapy. (1-4) An analysis of a major study (ACCELERATE) which evaluated the efficacy and safety of 16 weeks vs. 24 weeks of treatment with Pegasys/Copegus in patients with genotype 2 or 3 HCV -- showed that a similar number of patients achieved a cure (82% versus 90% respectively). In patients with low virus levels before treatment and a rapid virological response (undetectable virus 4 weeks after starting treatment), the cure rates for 16 and 24 weeks of treatment were essentially identical (89% vs. 94%).(5)

"This EU approval is important, as it means that we can tailor a patient's treatment with Pegasys based on an early marker of response without a loss in the regimen's effectiveness," said Prof Stefan Zeuzem, Chief of the Department of Medicine I at the Johann-Wolfgang Goethe University Hospital in Frankfurt, Germany. "This is good news for doctors, who now have the reassurance of offering a shorter treatment regimen, and for patients themselves, who will have the possibility to be cured with only 16 weeks of treatment."

### **NCORE Study Commenced to Determine If Genotype 2/3 Patients Without a Rapid Virological Response Need Longer Treatment**

Roche also announced the launch of the NCORe study (ENhancement of Cure Through Treatment Extension Guided by On-Treatment ResponSE in Patients Infected with G2/3 Hepatitis C; Roche study protocol number MV21371). The study aims to further improve treatment outcomes by examining whether genotype 2 and 3 patients who do not have a rapid virological response at 4 weeks should have treatment with Pegasys and Copegus extended to 48 weeks.(6) This global study will enrol approximately 400 patients at 90 centres in seven countries.

### Further information

For broadcast-standard video supporting this press release, please visit <http://www.thenewsmarket.com/roche> . If you are a first-time user, please take a moment to register. Questions may be directed to: [journalisthelp@thenewsmarket.com](mailto:journalisthelp@thenewsmarket.com) .

- Health-Kiosk: <http://www.health-kiosk.ch/index>

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*Source: Roche*

## **SciClone and Sigma-Tau Provide Update on Phase 3 Hepatitis C Study**

<http://biz.yahoo.com>

FOSTER CITY, CA--(MARKET WIRE)--Jun 26, 2008 -- SciClone Pharmaceuticals, Inc. (NasdaqGM:SCLN - News) and Sigma-Tau S.p.A. today announced that all 553 enrolled patients successfully completed a Phase 3 trial. After 48 weeks of therapy, all patients responding to treatment have now completed their 24-week follow-up. The unblinded data from the trial are expected to be available in the fourth quarter of 2008. The Phase 3 trial is evaluating ZADAXIN® (thymalfasin) in combination with pegylated interferon alpha and ribavirin as a treatment for patients with hepatitis C virus (HCV) who have not responded to prior therapy with pegylated interferon alpha and ribavirin. In February 2008, SciClone and Sigma-Tau S.p.A. announced promising blinded interim data from this trial.

"The completion of the study is an important step toward unblinding the data. Previously reported data from this Phase 3 hepatitis C trial have been promising," said Mario Rizzetto, M.D., Professor of Gastroenterology, San Giovanni Battista Hospital, University of Torino, Italy, and lead investigator of the trial. "The standard data review and analysis is underway with an unblinding of the data expected in late 2008."

"We continue to believe that thymalfasin could represent an important advance in the treatment of non-responder hepatitis C patients and address a growing and acute need," said Friedhelm Blobel, Ph.D., President and Chief Executive Officer of SciClone Pharmaceuticals, Inc.

The treatment approach for HCV using a combination of thymalfasin together with pegylated interferon plus ribavirin is patent protected by SciClone in most major markets including the United States and Europe until 2021. Details of the thymalfasin triple therapy for HCV, the hepatitis C virus, and thymalfasin may be found in the press release from SciClone Pharmaceuticals dated February 11, 2008, at [www.sciclone.com](http://www.sciclone.com).

### **About SciClone**

SciClone Pharmaceuticals is a biopharmaceutical company engaged in the development of therapeutics to treat life-threatening diseases. SciClone's lead product ZADAXIN® is currently being evaluated in a late-stage clinical trial for the treatment of hepatitis C, and successfully completed a phase 2 clinical trial in malignant melanoma. ZADAXIN is approved for sale in select markets internationally, most notably in China where SciClone has an established sales and marketing operation. A key part of SciClone's strategy is to leverage its advantage and broaden its portfolio in the rapidly growing Chinese market by in-licensing or acquiring the marketing rights to other products, such as DC Bead(TM). For the U.S. market, SciClone's other clinical-stage drug development candidates are RP101 for the treatment of pancreatic cancer and SCV-07 for the treatment of hepatitis C. For more information about SciClone, visit [www.sciclone.com](http://www.sciclone.com).

### **About sigma-tau Group**

Sigma-tau Group is a leading research-based Italian pharmaceutical company with a consolidated 2007 turnover of approximately EUR 665 million (US\$ 920 million) and over 2500 employees worldwide. The therapeutic areas in which sigma-tau Group focuses its Research and Development include cardiovascular disease, metabolism, neurology, oncology and

immunology, totalling 48 projects. Over 30 indications are explored in clinical trials with 24 molecules of which 17 are proprietary and the majority of them (14) are NCEs. Sigma-tau Group has operating subsidiaries throughout Europe and the U.S. and is active in every major pharmaceutical market. For additional information about sigma-tau Group, please visit [www.sigma-tau.it](http://www.sigma-tau.it).

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## ***Fake virus could make safe new vaccines***

[www.reuters.com](http://www.reuters.com)

By Maggie Fox, Health and Science Editor

WASHINGTON (Reuters) - A "wimpy" artificial virus protected mice against polio, and the approach might be used to make a range of safer new vaccines against viruses, U.S. researchers reported on Friday.

The team at the State University of New York, Stony Brook, had created the first artificial virus, a synthetic version of polio, in 2002.

Reporting in the journal Science, they said they used it to vaccinate mice, and then infected the mice with what should have been a deadly dose of polio. The mice survived.

"Ultimately we created a wimpy poliovirus that can be customized and does not cause disease unless given at high doses," Bruce Futcher, a professor of molecular genetics and microbiology who worked on the study.

"These viruses are still far from suitable vaccines for humans, but there is a lot of potential for this approach," he added in a statement.

The researchers used a unique method to make their virus, relying on a built-in redundancy in DNA, the material that carries genetic instructions in organisms.

DNA's code is written using just four nucleic acids, represented by the letters A, C, T and G. These are combined in various ways to make amino acids, which in turn make proteins.

It is possible to make an amino acid with more than one combination of these letters -- for example, GCC and GCG both code for the amino acid alanine. For unknown reasons, organisms favor certain combinations.

### **SAFER VACCINES?**

Futcher's team made their polio virus using the less-favored combinations of the virus's genetic code.

They hoped these would stimulate the immune system in the same way as "wild-type" polio, without causing disease, and that is what appears to have happened, they wrote.

Each difference in the genetic code weakened the virus in a different way.

"This 'death by a thousand cuts' strategy could be generally applicable to attenuating many kinds of viruses," they wrote.

"Even for an inactivated rather than live virus approach, these features would allow a vaccine to be made from a safer starting material than the corresponding wild-type virus."

Polio vaccines have virtually eradicated the disease in most countries. But an oral vaccine that uses a weakened version of a live polio virus can sometimes get back into the water supply and mutate into a form that can infect people.

Doctors have been looking for a safer yet effective polio vaccine that is as easy to administer as the drops. Dr. Jonas Salk's original polio vaccine, which effectively rid the United States of the feared virus in the 1950s and 1960s, used a "killed" polio virus but had to be injected.

The letter-by-letter changes needed the help of a powerful computer, said computer science professor Steven Skiena, who worked on the project.

"Sophisticated computer algorithms are necessary to design the hundreds of changes to sufficiently cripple the virus for our 'death by a thousand cuts' approach," Skiena said in a statement.

"Because of the large number of changes, the weakened virus can never mutate back to wild-type."

(Reporting by Maggie Fox; Editing by Eric Walsh)