

HCV ADVOCATE WEEKLY NEWS REVIEW

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

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Difficult Obstacles for SciClone

<http://www.fool.com>

By Brian Lawler

With all the new technologies and discoveries, some drugmakers are undoubtedly going to be left in the dust. SciClone Pharmaceuticals (Nasdaq: SCLN), with its lead drug **Zadaxin**, might be one such drugmaker.

On Thursday, SciClone announced that patients in a large phase 3 trial testing Zadaxin as a treatment for hepatitis C had completed dosing and that top-line clinical trial data would be announced in the fourth quarter.

Zadaxin has been tested for a range of indications including hepatitis B, melanoma, and hepatitis C. In February, SciClone released "blinded" data from one point in this phase 3 study showing that 31% of patients who had failed with other hepatitis C therapies had no detectable levels of the virus in their bloodstream at the end of 48 weeks in the trial.

The most commonly used hepatitis C standard-of-care drugs from Schering-Plough (NYSE: SGP) and Roche have cured up to 16% of patients in clinical testing. The catch with comparing the Zadaxin phase 3 data with this data is that the interim look at the Zadaxin trial contains both placebo and drug-treated patients -- that's what "blinded" means -- so the high response rate could theoretically be mostly placebo patients (or vice-versa, if you are a SciClone optimist). Also, this 31% response rate was at the end of treatment, so we'll need to wait for the full results to see where the long-term hepatitis C cure rates from this study will fall.

There are other potential issues for Zadaxin as well. But the bigger problem is that even in a perfect-case scenario -- it makes it onto the market at this point (despite significant hurdles) -- data from other compounds like Vertex Pharmaceuticals' (Nasdaq: VRTX) protease inhibitor telaprevir show them to be extremely effective in similar patients. So they may be ahead in the race to be the next hepatitis C drug onto the market. Being second on market and potentially inferior to the competition is not a winning recipe for commercial success with a drug.

Zadaxin is already approved for marketing in hepatitis B in China, which is undoubtedly the Wild West of pharmaceuticals, so who knows how Zadaxin will fare over there. But its potential as a treatment for hepatitis C in the U.S. and European Union looks rough at this point because of formidable competition.

Federal money for hepatitis C outbreak will have to wait another day

<http://www.lasvegassun.com>

By Lisa Mascaro

WASHINGTON — Funding for the investigation into the Hepatitis C outbreak in Las Vegas was stripped from the final war supplemental bill passed by the Senate last night, though Senate Majority Leader Harry Reid has tacked the request in a new bill making its way through Congress.

Almost half the Republican senators, including Sen. John Ensign, as well as fiscally conservative Democrats in the House, had balked at extras in the bill last month.

Reid's request had included \$21 million for the Centers for Disease Control and Prevention to investigate the problem nationally and \$5 million for the Southern Nevada Health Center to cover unexpected costs.

As many as 50,000 patients of an outpatient clinic in Las Vegas may have been exposed to hepatitis C or HIV after nurses reused syringes, an improper health care practice. Seven patients have been diagnosed with hepatitis C, as has one patient from a related clinic.

The CDC director has said what happened in Nevada may be the "tip of the iceberg" of similar problems nationwide. The CDC wants to conduct a public education campaign, staff training on proper techniques at outpatient and research the development of safer medical devices.

Locally, the health district would have used the funds to test patients and cover costs associated with the scare.

But to strike an agreement on the war funding bill, Congress eliminated much of the domestic spending from the package, which still preserved extended unemployment benefits and expanded education benefits for post-Sept. 11 vets under a new GI Bill.

In voting against the package last month, Ensign questioned whether the Southern Nevada Health Department needed the money. He voted for the bill last night.

Reid has since tucked a smaller funding request in another bill going through Congress. On Thursday, a committee approved \$5 million for the CDC and \$550,000 for the Nevada health district in the Labor, Health and Human Services bill.

"Reid definitely thinks the money is needed," his spokesman said. "He's going to work as hard as he can to get the funding this year."

Call for action now to cut Hep C burden

<http://www.theaustralian.news.com.au>

Adam Cresswell, Health editor

THE number of hepatitis C patients receiving treatment needs to double within five years just to stop the existing flow of cases of liver cirrhosis and liver cancer from turning into a flood, an official review has concluded.

Hepatitis C -- a viral disease that attacks the liver, and which is most often transmitted via sharing needles -- ranks as the most commonly notified infectious disease in Australia over the past 10 years. It is estimated that over 260,000 people in Australia carried the infection in 2005.

But a long-awaited review of treatment services commissioned by NSW Health has concluded that if the numbers of people receiving treatment remains at its 2005 level of 2000 patients, "the

number of people living with chronic HCV and more advanced-stage liver disease or cirrhosis are projected to increase by around 38 per cent by 2015".

The report says the number of patients treated each year would need to reach 6000 to prevent the expected increases in people with advanced liver disease.

Although treatment rates have risen since 2005, it is now estimated that about 3500 people a year are being treated for HCV infection in Australia -- meaning the number still has to rise substantially to ensure hospitals are not overwhelmed by patients needing treatment for liver failure that could have been prevented.

Stuart Loveday, executive officer of the Hepatitis C Council of NSW, says the most pressing need is to recruit more nurses and psychologists to help HCV patients get through the arduous year-long treatment.

"The side effects can be exceptionally debilitating. They can cause massive mood swings," Loveday said. "Hepatitis C itself causes depression, but the treatment can worsen that, and suicides have occurred on a number of occasions on hep C treatment. Really, it's the nurses who are in demand."

Greg Dore, head of the viral hepatitis clinical research program at the National Centre in HIV Epidemiology and Clinical Research, says although commissioned in NSW, where 40 per cent of the country's new HCV cases are reported, the report's findings apply to every other state except Queensland.

Although more patients had been coming forward for treatment since a requirement to first have a liver biopsy was lifted in 2005, capacity in the system has not been increased and "clinics are full at the moment", he says. "Apart from Queensland, where they have injected a fair bit of money into (recruiting more) clinical nurse consultants, things are pretty much the same in other jurisdictions," associate professor Dore said.

As well as recruiting more nurses and psychologists, other doctors -- such as sexual health physicians and doctors working in methadone clinics -- could also be used to deliver hepatitis C treatments, he said. Acting chief medical officer of NSW Health Kerry Chant says the department is "looking at how best to respond and implement the recommendations in the report".

Chant says NSW Health has already agreed to boost health service budgets by an extra \$800,000 in recurrent funding to support HCV patients. An extra \$250,000 in recurrent funding has also been given to the Hepatitis C Council of NSW for health promotion initiatives, and \$290,000 to the Australasian Society for HIV Medicine to train GPs to prescribe hepatitis C drugs.

Work has also begun on developing a revised model of care for hepatitis C treatment, in line with the recommendations, including the funding of pilot sites to trial provision of hepatitis C treatment through alcohol and other drug services.

Doctors with prescribing rights for hepatitis C treatment will also get free supplies of hepatitis B vaccine -- a three-dose vaccine that normally requires one or more doses to be bought on private prescription -- "to improve broader health outcomes for people with hepatitis C".

The 120-page report found most HCV treatment services reported having no spare capacity to increase numbers of patients receiving treatment, and most funding came from multiple sources and was non-recurrent -- a point that hinders recruitment efforts, because candidates are deterred by the reduced job security.

The report also found treatment services were scarcer in rural areas, and a number of groups -- including prisoners, children and indigenous people -- found it harder to access treatment.

Helen Tyrrell, CEO of Hepatitis Australia, says the report is "to my knowledge the first really comprehensive review of the treatment and care services in any of the states" for at least five years. As NSW accounts for nearly half of all HCV cases, "if NSW can make some inroads here, it's going to have some impact on the national figures".

"Unless we get numbers of new transmissions per year below the number who are treated and cured every year, we are not really winning," Tyrrell said.

"It's one thing for area health services to focus on treatment, but unless we are giving the same degree of scrutiny to what we are doing in prevention, we are only looking at half the picture."

June 28, 2008

Body-snatch ringleader Michael Mastromarino, gets 18-54 years

<http://www.nydailynews.com>

BY SCOTT SHIFREL

DAILY NEWS STAFF WRITER

Convicted body-snatch ringleader Michael Mastromarino was sentenced Friday to 18-54 years in prison.

A woman who developed hepatitis after surgery with contaminated human tissue blasted body-snatch ringleader Michael Mastromarino Friday as he was finally sent off to jail.

"Mr. Mastromarino's sick, disgusting, appalling actions, all in the name of greed, have devastated my family to the point where we can never recover," Dayna Ryan told a Brooklyn Supreme Court justice as the 44-year-old former dentist was sentenced to 18 to 54 years as part of a plea deal.

"I now stand before you...totally and permanently disabled at the age of 44," said Ryan, of Ohio, who suffered from a degenerative spine when she had her surgery in 2004.

The "substandard quality" of the cadaver bone fused to her spine left her in pain and unable to sit or stand for long, she said.

Mastromarino and his partners looted hundreds of bodies - many that regulations deemed too old or diseased to use - without permission, including "Masterpiece Theatre" host Alistair Cooke, and sold the parts for medical use.

They made millions off his Biomedical Tissue Services by the time accounting discrepancies at a funeral home came to light in 2003 and revealed the fiendish plot.

Mastromarino copped a plea in March and was to be sentenced June 12, but a glitch postponed the actual sentencing to Friday. He weakly apologized to Ryan and others before Justice John Walsh packed him off to jail.

"He fully recognizes the gravity of his actions," defense lawyer Mario Gallucci said. A co-defendant, Christopher Aldorasi, 36, was sentenced earlier this month to nine to 27 years in prison. Cases are pending against two others: Joseph Nicelli, 52, and Lee Cruceta, 35.

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June 29, 2008

Bicyclists hope trip took them closer to the cure

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

Emily Garber • egarber@pnj.com

Friends use cross-country ride to raise Hepatitis B awareness

John Ellis and his best friend, Jamaal Warren, were greeted with a round of applause as they wheeled their bicycles into Finnegans Wake Irish Pub for their homecoming party Saturday.

But riding their bikes to Finnegans was nothing compared to the 1,287 miles they bicycled from Tate High School to Philadelphia, dubbed the "2008 'Believe in the Cure' Cycling Tour."

The trek spanned three weeks, from June 2 to June 23 and raised nearly \$22,000 for Hepatitis B awareness.

Preparation

Shortly after Ellis was diagnosed with chronic Hepatitis B in 2006, he started bicycling to and from school every day to stay healthy and began forming a plan on how to raise money to promote awareness about the disease.

"John and Jamaal just came in one day looking for some help," said Robby Mott, manager of Bikes Plus, the sponsor for the trip. "What they have just accomplished is huge."

Rough conditions

Ellis and Warren rode 40 to 80 miles per day on their fundraising trek, and the conditions sometimes were rough. Along the way, they endured 107 degree heat, bone-jarring highways and forest fires in North Carolina.

At one point, the Tate High School graduates almost got run over when a senior citizen got distracted at a green light.

"We started riding and he started veering into us," Warren said. "He hit the shoulder and actually hit a few traffic cones."

Ellis' mother, grandmother and aunt followed the riders in a van that stopped every 15 miles so the boys could eat, rehydrate and rest.

"We weren't on the interstate," Ellis' grandmother, Pat Morrow-Johnson, said. "We were on these rinky-dink little roads."

In the end, the long trip was worth it.

The payoff

When Ellis and Warren arrived in Philadelphia, they were greeted by Dr. Baruch Blumberg, who received a Nobel Prize in Medicine in 1976 after discovering the Hepatitis B virus in 1967.

The city of Philadelphia also proclaimed June 23, Ellis' birthday, "John Ellis Day."

At the end of the homecoming party Saturday, Ellis and Warren received a scholarship, raised by all their friends, family and sponsors, for each of their freshman years at Pensacola Junior College. The scholarship will be enough to cover the cost of tuition and books.

June 30, 2008

Early Results from Ongoing Clinical Study of Hepatitis C Vaccine Delivered by Inovio Biomedical's Electroporation System Show Increased T-Cell Responses and Reduced Viral Loads

<http://biz.yahoo.com>

SAN DIEGO--(BUSINESS WIRE)--Inovio Biomedical Corporation (AMEX:INO - News), a leader in enabling the development of DNA vaccines using electroporation-based DNA delivery, announced today that its partner, Tripep AB, reported additional interim results from its ongoing phase I/II clinical study of its **ChronVac-C®** therapeutic DNA vaccine, which is delivered using Inovio's electroporation-based DNA delivery system. These preliminary results are from the first two patients in the intermediate dose group to complete treatment against hepatitis C virus infection. Samples taken before, during and after treatment showed that the viral levels in blood decreased up to 87% and 98%, respectively, during treatment. Simultaneous activation of the patients' T-cell responses to the hepatitis C virus was recorded in conjunction with the viral load reductions. Inovio's electroporation delivery technology is intended to enhance the potency of DNA vaccines against cancers and infectious diseases.

ChronVac-C® is a therapeutic vaccine given to individuals already infected with the hepatitis C virus with the aim of clearing the infection from the liver by boosting the body's immune response against the virus. This clinical study is being conducted at the Infectious Disease Clinic and Center for Gastroenterology at the Karolinska University Hospital in Huddinge and Solna,

respectively, in Sweden. The intended enrollment of 12 patients is being divided into three dose groups with increasing doses of ChronVac-C. Each patient receives four vaccinations one month apart. After the last vaccination, patients are followed for another six months. The study's main purpose is to assess safety. It is also testing whether the treatment boosts the immune response (immunogenicity) to HCV and its effect on virus replication in the liver. If the patient is completely virus-free six months after completing treatment, he/she will be considered cured.

In the group treated with the low dose of ChronVac-C, transient activation of T-cell responses was recorded but no reduction of viral load. In the group treated with the intermediate dose, T-cell responses were recorded simultaneously with clear reductions in the serum levels of hepatitis C virus, suggesting that the therapy is dose-dependent. No severe adverse events have been recorded. All three patients in the high dose group have started therapy and we expect results from this group during the fall.

Avtar Dhillon, MD, Inovio's president and CEO, stated: "Recognizing that this is still a very limited patient population and data set, we are encouraged by the results of this hepatitis C virus phase I/II clinical study. Existing treatments are hard on patients, often described as being similar to chemotherapy, and are only effective in roughly half of patients treated. We are pleased that to date this therapy has not produced these chemotherapy-like side effects nor serious adverse events and, without yet reaching the highest dose levels, is producing positive results. The fact that there may be a dose-dependent correlation between T-cell responses generated and reduction in hepatitis C viral load may position ChronVac-C, in which we have partial ownership, to potentially play a role as a first-line therapy or as an adjunct to existing therapies. We look forward to the continuing clinical assessment of this promising DNA vaccine candidate."

The total market for therapies against hepatitis C infections was estimated by Rodman & Renshaw to be around \$3.5 billion in 2005 and to grow to more than \$8.0 billion in sales by 2012.

About Inovio Biomedical Corporation

Inovio Biomedical (AMEX:INO - News) is focused on developing multiple DNA-based immunotherapies and DNA vaccines. Inovio is a leader in developing human applications of electroporation using brief, controlled electrical pulses to increase cellular uptake of a useful biopharmaceutical. Human data has shown that Inovio's electroporation-based DNA delivery technology can significantly increase gene expression and immune responses from DNA vaccines. Immunotherapy partners include Merck, Wyeth, Vical, University of Southampton, Moffitt Cancer Center, the U.S. Army, National Cancer Institute, and International Aids Vaccine Initiative. Inovio's technology is protected by an extensive patent portfolio covering in vivo electroporation. More information is available at www.inovio.com.

Staying straight while in dire straits

<http://thechronicleherald.ca>

By SHERRI BORDEN COLLEY Staff Reporter | Faces of Poverty

After decades of substance abuse, an addict faces a daily struggle to turn his life around

EDITOR'S NOTE

Today, The Chronicle-Herald publishes its second profile of a person struggling with poverty. On Mondays this summer, we will bring you stories of people trying to escape — or merely cope with — the challenges that poverty presents, even inside a society as rich as Canada's.

KEN BROWN's addiction to hard drugs started long after he became an alcoholic. As a teen he used marijuana and LSD, but he only got hooked on opiates about 16 years ago after he needed pancreatic surgery because of his problem with the bottle.

"I was an alcoholic for years and my pancreas went and they put me on long-term morphine for the pain, and it just snowballed from there and before I knew it I was addicted to morphine, I was into OxyContin," the 48-year-old Glace Bay native said in a candid interview about his addiction, the poverty that accompanied it and his efforts to break free.

"It got to the point where it was just crazy, so I came up here (to Halifax) to get off of them."

Brown's addiction had already taken a toll on his family life. He remained alienated from his brothers and sisters, who understood alcohol use but not drug-taking. But that has made him work all the harder to nourish family ties to the children and grandchildren who are the most important part of his life.

So, seven days a week, Brown shows up at Direction 180 for his daily 250 milligrams of methadone. He has been going there for six years.

"Down in Cape Breton, there were no programs like this at the time; there is one in Sydney now," Brown said.

But it's not easy to stay straight "hanging around a place like this," Brown says of the clinic's location in a mixed-income central Halifax neighbourhood where drugs are plentiful. "It's hard. You see it on the street right out front. This is Gottingen Street; if you can't find drugs on this street, you're in trouble."

Established in February 2001 in the Mainline Needle Exchange, Direction 180 helps addicts cope while getting off drugs and gives them regular contact with nurses, peer support counsellors, a doctor and a social worker. Eighteen people are on staff. Of the annual \$600,000 operating budget, \$400,000 comes from the province, the rest from grants and fundraising.

Methadone, the drug that Brown and others use in their battle against drugs, is a synthetic narcotic that addicts drink mixed with orange juice. When they're on a stable dose, they enjoy about 24 hours of relief from withdrawal symptoms and cravings to shoot drugs like heroin.

"Most people, by the time they get here, they're not getting high anymore — they're just getting normal," said Cindy MacIsaac, the clinic's program director. "Their addiction to their drug is so great that using just helps them feel normal."

For Direction 180 clients, success is not only about staying away from needles; it's also about regaining custody of their children, finding stable housing, eating healthy meals, staying out of jail: rediscovering the desire to live.

"Success is coming here daily despite all of the challenges and the barriers," Ms. MacIsaac said. "Success is people becoming employable or returning to the workforce."

Methadone sometimes finds its way out of the clinic and onto the street; clients and staff both try to keep dealers away from the door. Clients "are trying to stay straight and coming in, and it's a trigger to see people out there," said Brown. "It's supply and demand. They're not going to go to a straight neighbourhood and try selling drugs."

But without this program, Brown said, he would either be dead or in jail. "When you're using, you wake up in the morning and the first thing you do is you go steal to get money if you don't have any. When you're on a cheque, you might have money one day a month; that's it."

"When you wake up in the morning you're sick, so you gotta go do something if you don't have a pill there to shoot right away. You get diarrhea, you puke; every muscle in your body is aching, so you gotta get going for the day. You're making money for drugs for the rest of the day."

"It's endless. You're buying drugs, using them or doing something to get the money to get it. It's a 24-hour thing."

When Brown was scoring OxyContin, used to treat intense pain but also a popular and highly addictive street drug, an 80-milligram pill cost \$50, while 40s went for \$25 and 20s cost \$15. An 80 could keep him going for a couple of hours. "So it gets expensive, and you get that sick that you'll do whatever you have to do to get it."

There's a vicious circle involved for many opiate addicts: They kick the habit only to turn to crack cocaine. This has happened to Brown, but he says he's not using crack now. "If I went and bought one stone right now, I'm going to spend every cent I've got in my pocket." And that would just lead to more stealing.

Crack is the worst drug Brown says he's ever done. "It will take you to places where no other drug would, and quick." With his daily methadone treatment, he could do any opiate he wanted and get nothing out of it. "So if you want to get a buzz, you have to do something like crack. You can't get high on the opiates anymore."

Brown's girlfriend is also in the program. "She knows what I am going through and I know what she is going through. As long as we don't pick up that first stone, we're fine." And as long as there's no crack around him, Brown does well. "If it's there, I'm going to pick it up. With it being so plentiful in this area of town and everything, it doesn't bother me to see people selling it and that. It's if I see somebody smoking it, it's just, bang, you want it. It's an evil drug, though."

He might get two tokes from a \$20 stone of crack, but the kick would only last three to five minutes and then he would have to smoke another one. "It's an intense high but it doesn't last. Once you do it, it's gone and you're chasing it for the rest of that day, trying to get that buzz again."

When Direction 180 opened, 30 addicts showed up for help. "We opened in response to the increasing number of individuals who were addicted to opiates and the demographics of those individuals," MacIsaac said. "So they weren't just addicted to opiates; they had poly-drug

addictions. They were using other substances, they were homeless, they were engaged in sex work, they were at risk of hepatitis or had hepatitis C, hepatitis B, HIV, concurrent mental illnesses . . . living in substandard housing. So there needed to be a program that would meet them where they were."

The clinic workers set out to reduce the risk of crime, improve people's awareness of the dangers of misusing needles and help them improve the quality of their lives. It wasn't very long before 60 people were knocking on the clinic's doors; today there are 160 clients, 80 of whom visit daily for their methadone. Another 40 are on a waiting list.

By the time addicts arrive at Direction 180, most are poor. "They're bankrupt emotionally, spiritually, physically and mentally," MacIsaac said. "When they first make contact to get on the program, many are still holding on to jobs or still holding on to children or they're still holding on to their apartment. But because we can't get them in right away, by the time we do get them in, what they've had is gone."

Acceptance is based on a risk system, with priority for people who are HIV-positive or pregnant, or have other serious health problems. But people who use drugs in Direction 180 are not kicked out, as they are of other programs. "Our philosophy is that the change has to come from within," MacIsaac said. "We don't condone other drug use; however, we try to encourage people to stay as safe as possible and minimize the harms and the risks while they're still engaged in risk-taking behaviour."

Day after day, MacIsaac, a recovering cocaine addict, sees the consequences of addiction. "It tears families apart; people lose housing, they lose employment, they lose touch of what their morals or belief systems are in the process of that grip." Addicts often risk contracting other diseases or committing crimes that land them in prison. "People say, 'Why don't they just stop?' Well, they can't; it's not that easy. They're physically dependent and it's just not that easy."

There are also huge barriers because of society's attitudes toward addicts. "If you contracted hep C through blood transfusion, you're a victim. If you do it through a needle, you've victimized yourself, so people tend to have less tolerance."

Drug addicts are far from being all alike, MacIsaac said; some have been schoolteachers and pilots. "Addiction does not discriminate."

Added Brown: "A lot of them get hooked the same way I did, through prescription painkillers. They weren't drug addicts that were out on the street."

Much sacrifice comes with enrolling in a methadone program, he said. "Methadone should be your last resort because your whole life's got to revolve around it. Like when I get up in the morning, I've got to come here every day. If I wake up and I want to go to the beach, I have to come here first. It's the same thing on the weekends. This place is open every day."

Users can gradually work their way down to a lower methadone level, but Brown isn't ready for that. "For me, I know if I come off the methadone, I'm going to end up back on the (street) drugs."

Before Direction 180, he was stealing to support his habit. "I never had theft charges until I got into drugs. I was at the point where I couldn't keep going anymore." He has been jailed for theft, impaired driving and breach of probation.

The divorced father of two adult children and four grandchildren quit drinking about eight years ago when his granddaughter was born. "But then I got into the drugs. Now I want to stay away from all of it. I want to see (my grandchildren) graduate and hopefully get married someday. This is not going to happen if I had kept going the way I was going.

"My grandchildren are everything."

Brown said his alcoholism led to his divorce and to the bad feelings that persist between him and his three brothers and five sisters. "(For) my brothers and sisters, the drinking wasn't so bad but the drugs, they don't understand it. None of them were ever into drugs. To them if you smoke a joint, you're a drug addict. They don't understand drug addiction."

He came from a stable home, he said. His father was a painter, his mother a stay-at-home mom. Asked how his siblings' abandonment affects him, he said: "I'm used to it now."

Back at the clinic, once he finishes his treatment, Brown, who used to make \$21 to \$25 per hour as a general labourer, bricklayer and painter, volunteers as one of two client representatives who sort out disputes between clients and staff. "It helps keep me straight to stay off the drugs."

Social assistance pays \$600 a month for a bachelor apartment. He and his girlfriend jointly get \$712 per month, of which \$150 is for Brown's diet because he is a diabetic and has pancreatitis and hepatitis C, and \$120 pays for two bus passes. The Community Services Department also covers Brown's medication.

"Usually, if you don't have enough money to rent a nice apartment, then you're going to end up in a place where there's crack because that's all you can afford to live," he said. But getting a full-time job to supplement his income would not be worth it. "For every \$100 I'd make (Community Services) would take \$70. What initiative is that? I mean, why would you work when they're going to take \$70 from you?"

"They discourage people to work — poor people. The system is kind of geared to keep you down."

(sborden@herald.ca)

July 1, 2008

Liver Phase I Results Presented at WCIO 2008 & Best of ASCO

<http://www.therapeuticsdaily.com>

COLUMBIA, Md.--(BUSINESS WIRE)--Jun 27, 2008 - CELSION CORPORATION (NASDAQ: CLN) announced today that the interim results from its second Phase I liver cancer confirmation study of **ThermoDox** in combination with Radio Frequency Ablation (RFA) treating patients with primary and metastatic liver cancer were presented at both Oral and Poster

presentation at the WCIO 2008 and Best of ASCO(R) conference. The presentation provided Phase I interim results including safety, dosing and pharmacokinetic summaries supporting the company's global pivotal trial in Hepatocellular Carcinoma, which is currently enrolling patients.

This annual WCIO (World Congress of Interventional Oncology) conference partnered with the Best of ASCO to present novel therapies in the emerging field of interventional oncology in a unique multidisciplinary meeting. This conference was held from June 22 - 25, 2008 at the Hyatt Regency Century Plaza in Los Angeles, CA. <http://www.wcio2008.com/>

The abstract presentation, titled "Phase I Dose Escalation Study of Thermally Sensitive Liposomal Doxorubicin (ThermoDox(R)) in combination with Radiofrequency Ablation (RFA) of Primary and Metastatic tumors to the liver: Interim Report" was delivered by Dr. Thanjavur S. Ravikumar, MD, Professor and Chairman, Department of Surgery, North Shore Hospital, Albert Einstein Medical School. Dr. Ravikumar commented, "These phase I findings are encouraging in terms of safety, drug distribution and cancer activity. I am pleased to observe impressive early responses in a variety of liver tumors." Local return of cancer was seen in only 2 of 44 tumors treated with RFA plus ThermoDox, resulting in an impressive 4.5% local recurrence rate. In addition, 5 of the 10 evaluable patients demonstrated a complete response (CR), along with a single partial response (PR). The progressive disease (PD) patients were largely a result of extrahepatic or distal hepatic recurrence, both from not treated lesions. The majority of the patients were metastatic liver cancer patients, presenting with extrahepatic disease.

Additionally, Celsion's newly initiated *phase III* study of ThermoDox in patients with hepatocellular carcinoma (HEAT Study) was presented during the Clinical Trials Update Session. The presentation was given by HEAT European Lead Principal Investigator Dr. Riccardo Lencioni who reviewed the study objectives, design and patient criteria with the audience.

Michael H. Tardugno, Celsion's President and Chief Executive Officer, commented, "The results presented by Dr. Ravikumar re-validate our proof of concept in liver cancer and further confirm our single vial formulation with which we plan to enter the market. The selection for Oral and Poster presentation demonstrates the medical interest in the unique role that ThermoDox can play in the treatment of liver cancer."

The WCIO 2008, Best of ASCO presentation was the fourth time this year that Phase I results from ThermoDox trials have been presented at a major medical conference. In February, Dr. Ronnie T. Poon, Professor of Surgery at the Queen Mary Hospital, Hong Kong, presented our Phase I liver study results at the IHBPA conference in Mumbai, India, at the Oral Paper Awards Session. In March, Dr. Bradford J. Wood's abstract titled "Imaging Features in Patients undergoing Liver RFA plus Heat Deployed Nanoparticles" was selected for Oral presentation at Society for Interventional Radiology. Also in March, Dr. Zeljko Vujaskovic, Associate Clinical Professor at Duke University, on behalf of Dr. Ellen Jones, presented interim progress and evidence of safety and suggested efficacy from our second indication under study, Recurrent Chest Wall breast cancer, at ICHO Conference in Munich, Germany.

Mr. Tardugno concluded, "It's clear that the excitement for our Phase III HCC trial announced by Dr. Lencioni is supported by the promise of clinical activity - as reported in Phase I studies - and

is consistent with the potential for ThermoDox to provide an effective treatment for these two difficult-to-treat cancers."

About ThermoDox(R)

ThermoDox(R) is Celsion's proprietary heat-sensitive liposomal encapsulation of doxorubicin, an approved and frequently used anti-cancer drug used in the treatment of various cancers. Localized heat (at 40-42 degrees Celsius and above) releases the entrapped doxorubicin from the liposome. This delivery technology enables high concentrations of doxorubicin to be deposited preferentially in a targeted tumor.

About Celsion

Celsion is dedicated to the development and commercialization of oncology drugs including tumor-targeting treatments using focused heat energy in combination with heat-activated drug delivery systems. Celsion has research, license or commercialization agreements with leading institutions such as the National Institutes of Health, Duke University Medical Center, University of Hong Kong, Cleveland Clinic, North Shore Long Island Jewish Health System. (CLN-W)

For more information on Celsion, visit our website: <http://www.celsion.com> .

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July 2, 2008

Insulin Resistance, Diabetes Increase Liver Fibrosis in Patients With Genotype 1 HCV

www.medscape.com

NEW YORK (Reuters Health) Jun 25 - Insulin resistance is a major determinant of advanced hepatic fibrosis in patients with chronic hepatitis C resulting from genotype 1 (G1-HCV), especially in the presence of severe necroinflammation, according to study findings published in the May issue of the *American Journal of Gastroenterology*.

"Metabolic factors may affect the course of chronic hepatitis C," Dr. Salvatore Petta, of the University of Palermo, Italy, and colleagues write. "Insulin resistance (IR) determines steatosis, but its direct role in affecting progression of hepatic fibrosis is less clear."

In the present study, the researchers examined whether increasing degrees of IR, up to overt diabetes, were associated with steatosis and higher stages of fibrosis in patients with G1-HCV.

Of the 201 patients, 55 (27%) had liver fibrosis of grade 3 or higher by the Scheuer score. Moderate/severe liver necroinflammation was observed in 72.7% of patients. Overall, 99 patients (49.3%) had histological evidence of steatosis.

The team reports that 95 of the subjects (47.3%) were not insulin resistant (group 1), 77 (38.3%) were insulin resistant without diabetes (group 2), and 29 (14.4%) were diabetic (group 3).

Results of multivariate analysis revealed an association between severe fibrosis (Scheuer score of 3 or greater) and prevalence of IR (odds ratio 2.69, $p = 0.001$) and high necroinflammatory activity (OR 2.99, $p = 0.003$).

Overall, 59% of patients in group 3 had severe fibrosis, compared to 30% of those in group 2 and 15% of those in group 1.

"Our study has conclusively demonstrated that IR, with or without diabetes, is a strong independent risk factor for fibrosis," Dr. Petta's team concludes. "Whether correcting IR by lifestyle modifications and/or the use of insulin-sensitizing drugs will modify the effect of IR on liver fibrosis remains to be demonstrated by appropriate trials."

Am J Gastroenterol 2008;103:1136-1144.

Irbesartan Added to Propranolol May Improve Cirrhosis Therapy

www.medscape.com

NEW YORK (Reuters Health) Jun 20 - Combination therapy with irbesartan and propranolol can produce greater sodium excretion than use of propranolol alone in certain patients with cirrhosis, according to German researchers.

In the May issue of the *American Journal of Gastroenterology*, Dr. Michael Schepke of the University of Bonn and colleagues note that angiotensin II type-1 receptor antagonists such as irbesartan have been shown to lower portal pressure in some cirrhotic patients but may cause severe adverse events.

Standard therapy for portal pressure is propranolol, but less than half of patients achieve adequate pressure reduction. To evaluate the use of the two drugs together, the researchers studied 32 patients with cirrhosis.

All of the patients received 20 mg propranolol twice daily, and were randomized to irbesartan titrated up to 300 mg per day or placebo.

At 8 weeks, portal pressure declined in the two groups.

The average daily dosage of irbesartan by the end of the study was 272 mg and the treatment was well tolerated.

In patients given the combination therapy there was a significant increase in urinary sodium excretion from 122 nmol to 230 nmol per 24 hours, while sodium excretion remained unchanged in the propranolol plus placebo patients.

"Although such a combination treatment is not particularly useful for its portal hypotensive effects as compared to propranolol alone," the researchers conclude, "it expands the

pharmacologic armamentarium in the management of selected patients with chronic liver disease by offering potential antifibrotic and natriuretic benefits."

Am J Gastroenterol 2008;103:1152-1158.

GlaxoSmithKline, Novartis Ordered to Pay \$114 Million in Price Fraud Case

<http://www.therapeuticsdaily.com>

Associated Press WorldStream

MONTGOMERY, Alabama_A jury in Alabama on Tuesday found two major pharmaceutical companies defrauded Alabama in a long-running drug pricing scheme affecting a federal health care program for the poor, and ordered the firms to pay more than \$114 million in damages.

The state court jury found that GlaxoSmithKline should pay the state \$80.8 million in compensatory damages and that Novartis should pay about \$33.7 million in similar damages. But it declined to order any punitive damages.

The state had asked for as much as \$800 million in total damages in what its attorneys claimed was a scheme to overcharge for Medicaid prescription drugs from 1991 to 2005.

The companies had denied any fraud, contending they followed proper procedures in setting drug prices.

GlaxoSmithKline is a London-based health care company with U.S. headquarters in Philadelphia and Research Triangle Park, North Carolina. Novartis is the U.S. affiliate of a Swiss company with U.S. headquarters in East Hanover, New Jersey.

The jury returned the verdict on its second day of deliberations.

It was the second trial of the state's lawsuits accusing more than 70 drug companies of Medicaid drug pricing fraud. In the first trial in February, a jury awarded the state \$215 million against AstraZeneca Pharmaceuticals LP. Price, who also was the judge in that case, later reduced that verdict to \$160 million.

Govt names 1,825 hospitals on tainted coagulant fears

<http://www.yomiuri.co.jp>

The Yomiuri Shimbun

The Health, Labor and Welfare Ministry announced Tuesday the names and addresses of 1,825 medical institutions that might have administered blood coagulation factor VIII and IX products to patients that are not hemophiliacs.

The ministry's move came in light of the recent cases of people becoming infected with the hepatitis C virus through the administration of tainted blood products. The ministry made a

similar announcement in 2001 regarding facilities that might have administered nonheated blood products, but reexamined the matter, this time including heated blood products in its investigation.

To date, 1,622 people who did not have hemophilia have been confirmed to have been administered with such products at 185 institutions.

"People that have had operations or been treated at the named institutions could be infected, and should go for a checkup," a ministry spokesman said.

Hemophilia is a group of genetic disorders in which blood coagulation factors are deficient, impairing the body's ability to control blood clotting. It is treated with the administration of coagulation factor products.

Hemophilia A, the most common form of the disease, is caused by a lack of blood coagulation factor VIII. Hemophilia B is caused by a deficiency of factor IX.

Contaminated fibrinogen blood product is the main cause of hepatitis C infection in Japan. The names of medical institutions that have bought the product have already been announced.

An estimated 10,000 people are thought to have been infected with the hepatitis C virus after fibrinogen was used in surgical operations involving 280,000 people, according to medical sources.

Stanislaus civil grand jury: Needle exchange could curb HIV, hepatitis C

<http://www.modbee.com>

By ADAM ASHTON

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Stanislaus County should create a needle exchange program to reverse a trend of rising hepatitis C infections, the civil grand jury recommended Monday.

The county is on pace to record 620 new hepatitis C cases this year, up from 519 in 2007, according to the grand jury report.

The grand jury advised the county that a needle exchange program could decrease the number of hepatitis C and human immunodeficiency virus infections while diminishing the threat to public employees who come in contact with discarded syringes.

Hepatitis C is a debilitating liver disease spread through contact with an infected person's blood.

Stanislaus County formed a committee to study hepatitis C in 2002. In 2006, the county's police chiefs wrote a letter saying "there may be merit in a needle exchange program."

"Both the public health and law enforcement approaches can coexist with the common goal of harm reduction in Stanislaus County ... by providing new syringes to injection drug users in exchange for dirty syringes," the grand jury wrote.

The grand jury suggested Stanislaus County follow the guidelines of a 2006 state law that recommends needle exchange programs as a public health benefit.

The report also points to a needle exchange program in Fresno that is administered through private contributions.

The hepatitis C report was one of two investigations the grand jury published Monday. The other focused on the county's correctional facilities.

It urged the county to:

- Demolish the county's downtown jail and the honor farm, both of which are in poor condition and have outdated buildings
- Increase staffing at the honor farm
- Develop more programs for young people at the juvenile detention center
- Consider separating mentally unstable inmates at the county's Public Safety Center on East Hackett Road

Volunteers make up the panel that is charged with investigating government agencies each year. They published six reports this year.

Bee staff writer Adam Ashton can be reached at aashton@modbee.com or 578-2366.

July 3, 2008

Movetis' Second Most Advanced Product Progresses to Phase IIb Trial Following Positive Results in Cirrhotic Ascites

<http://biz.yahoo.com>

TURNHOUT, Belgium, July 3 /PRNewswire/ -- Movetis NV, a European specialist pharmaceutical company, today announced that **M0002** is progressing to **phase IIb** following positive results of a phase IIa multiple-dosing trial for the treatment of ascites, the accumulation of fluid in the abdomen in patients with liver cirrhosis resulting from liver conditions such as hepatitis C, hepatitis B or alcoholism.

M0002 is an orally-active selective vasopressin 2 receptor antagonist and a member of a new class of compounds, known as aquaretics, which inhibit water reabsorption from the renal collecting duct. The compound induces free water clearance without loss of sodium.

The randomized, double blind, placebo controlled, dose-titration study explored the safety, tolerability, pharmacokinetic profile and efficacy of M0002 in cirrhotic subjects with ascites and hypo- or normonatremia. It was conducted in Belgium at multiple centers and enrolled 15 patients who were treated once daily with drug or placebo for 15 days.

"The data are encouraging," states Prof Dr. F. Nevens, Chief of Hepatology at the University Hospital in Leuven and principal investigator of the trial. "M0002 was very well tolerated and proved to have a good safety profile. No unexpected side-effects were seen in these very ill patients. The pharmacokinetic profile was in line with expectations."

Although a small number of patients were included in the study, a trend towards more stabilized and normalized plasma sodium levels was seen in those treated with M0002.

Remi Van den Broeck, Chief Development Officer of Movetis, said, "We are delighted with the promising results from the dose-titration trial. We will begin patient recruitment shortly for a Phase IIb dose-finding study. At Movetis we are committed to improving the lives of patients with ascites and we believe that M0002 may eventually offer hope to many who suffer from the condition."

About cirrhotic ascites

Cirrhosis is a consequence of chronic liver disease, most commonly caused by alcoholism and hepatitis B or C. It is characterized by replacement of liver tissue by fibrous scar tissue as well as regenerative nodules, leading to progressive loss of liver function. Ascites, the accumulation of fluid in the peritoneal cavity, is a major complication of cirrhosis. The development of ascites is a significant marker in the progression of cirrhosis as it is associated with high mortality over two years, and signifies the need to consider liver transplantation as a therapeutic option.

Dr. F. Wong, Associate Professor of Medicine at Toronto General Hospital, when asked for comment on the disease and on the therapeutic options, said:

"The development of ascites, or fluid in the abdominal cavity, is a common complication of liver cirrhosis. Its onset signifies the progression of liver cirrhosis into the decompensated stage with worsening of prognosis to 50% survival in 2 years. The treatment of ascites includes the use of dietary sodium restriction, diuretics (loop diuretics and or spironolactone) and large volume paracentesis. The continued use of diuretics is limited by the development of complications such as electrolyte abnormalities, and many patients eventually become diuretic resistant, that is, the use of diuretics is no longer resulting in a reduction of ascites. Such patients are totally dependent on large volume paracentesis as a means of controlling the ascites. The use of paracentesis is inconvenient to the patient and requires significant medical manpower."

Both Prof. Wong and Prof. Nevens agree that there is an urgent need for newer and effective drugs to better manage cirrhotic patients with ascites.

About M0002

M0002 is a selective vasopressin 2 receptor antagonist and is a member of a new class of compounds - aquaretics - that produce significant diuresis without the loss of electrolytes. Conventional diuretic drugs, which are currently used to treat ascites, have the drawback that they promote the excretion of both salt and water, leading to possibly symptomatic hyponatremia (abnormally low concentration of sodium in the blood). In contrast, M0002 primarily increases free water clearance. This important differentiation could potentially offer clinical advantages in the treatment of cirrhosis and other disorders caused by water-retention.

About Movetis

Through a clear focus on gastroenterology (GI), Movetis seeks to improve the lives of millions of patients - both adults and children - by discovering, developing and ultimately commercialising innovative treatments targeting GI conditions with a high unmet medical need. Movetis NV - founded in Belgium in December 2006 - aims to become a leading European specialty pharmaceutical organisation focused on GI diseases. Movetis has a broad GI portfolio with one product in preregistration, two products in clinical development, one product ready to move into clinical development and four in preclinical development, all addressing important areas including chronic constipation, ascites, paediatric reflux in infants, diabetic gastroparesis, specific subgroups of patients with severe forms of irritable bowel syndrome or dyspepsia. In addition, Movetis has rights to a large library of qualified lead compounds with potential for development in different GI indications and access to know how for compounds in secretory diarrhoea. The current portfolio has been licensed from Janssen Pharmaceutica NV, Belgium and Ortho-McNeil Pharmaceutical Inc., two Johnson & Johnson (J&J) companies.

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Source: Movetis NV

Medicare proposes hospital outpatient pay rates

www.reuters.com

WASHINGTON (Reuters) - The U.S. government proposed a 3 percent inflation increase in 2009 Medicare rates for outpatient services at about 4,000 U.S. hospitals, which will also impact medical imaging, diagnostic and other health care services.

The Centers for Medicare and Medicaid Services, which spends billions on Medicare health insurance for 44 million elderly and disabled people, proposed the payment rates on Thursday for services done on an outpatient basis at hospitals, a rapidly growing segment in the industry.

The biggest publicly traded hospitals include Tenet Healthcare Corp, Community Health Systems Inc, Universal Health Services Inc, LifePoint Hospitals Inc and Health Management Associates Inc.

CMS expects to spend \$29 billion on outpatient services for Medicare patients in 2009.

It will also set up new billing codes to pay for multiple imaging services, which will impact big imaging companies like General Electric Co, Siemens and Philips. The growth of imaging services such as ultrasound, three-dimensional CT scans and magnetic resonance imaging has been a target for Medicare and private insurance payers seeking to rein in escalating healthcare spending.

The government is also proposing new quality requirements, and will strip 2 percentage points off the inflation increase for hospitals that don't comply with reporting requirements. Such quality measures include such things as screening for fall risk and cancer care.

Comments on the proposal will be taken until September and a final rule will be issued by November.

More information on the Medicare proposal is posted online here and at www.cms.hhs.gov/ASCPayment/

(Editing by Braden Reddall)

Number of teenagers being treated for hepatitis has quadrupled

<http://www.newsandstar.co.uk>

By Steph Johnson

The number of teenagers being sent out of county to be treated for Hepatitis B and C has more than quadrupled over the last year.

Shared needles are one way in which hepatitis can be passed on. Unprotected sex is also behind the increase in cases

The region's Health Protection Unit was notified about nine North Cumbrian youngsters who tested positive for the liver diseases, a rise of seven on 2006.

They need to be monitored at specialist clinics in London, Birmingham and Leeds because of their age.

But the actual number of teenagers who have to get help away from home is likely to be higher.

The clinics do not directly report to the HPU and its data only reflects information passed on from GPs.

Hepatitis B and C are both transmitted through blood, sufferers can end up with liver failure and cancer in the most serious cases.

The most likely way to catch the viruses is through shared needles or medical and dental treatment in countries where procedures are not up to UK standards. Those who had blood transfusions before screening was introduced in 1991 are also vulnerable because it can take years for symptoms to appear.

Having unprotected sex puts people at high risk for Hepatitis B as it is also passed on through bodily fluids and is more infectious than HIV.

Since 2005, there has been a 28 per cent increase in Hepatitis C diagnosis for adults in north Cumbria, from 70 new cases a year to 90.

In south Cumbria there were no new cases reported in 2005 and just one in 2007. Lead hepatology nurse Ruth Harrison says this is because the specialised hepatitis programme only serves north Cumbria and therefore the data for the south is not as comprehensive.

The Hepatitis C Trust says four out of five carriers are unaware they have the illness, meaning there are hundreds in north Cumbria risking the deterioration of their health and of those they unwittingly infect.

Ms Harrison, who is treating about 450 Hepatitis C patients, admits she is alarmed by the rates of infection.

Especially since the rise is not thought to be due to an increase in the number of people being tested.

Ms Harrison began running hepatitis clinics at Cumbria Infirmary in 2003 and over the last five years she has noticed a particularly worrying trend emerge.

The numbers of women who contract Hepatitis C through sex has gone up, even though it not considered to be a high risk area for this strain of the disease.

Although there are fewer people with Hepatitis B than C, the figures still give cause for concern.

Ms Harrison has less than 50 cases on her books, but this is three times as many Hepatitis B patients as she was seeing 18 months ago.

Again only the north of the county has a recorded increase.

The symptoms of Hepatitis B are vague and can be confused with a flu like illness.

Ms Harrison wants those susceptible to get tested if they are in doubt about the cause of any ill health they are suffering.

She is also calling for more resources for hepatitis services and improved support from employers when their staff need to take time off for treatment.

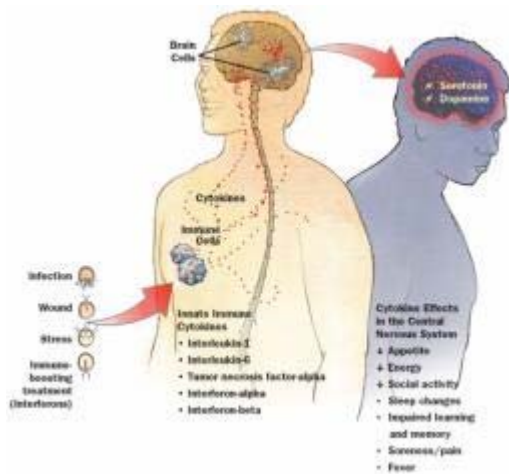
Sick and down

<http://www.sciencenews.org>

By Amy Maxmen

To fight off an infection or illness, the body shifts into a slow-down mode that mirrors some symptoms of depression. In fact, scientists now think the immune response itself may even cause the mood disorder.

From Sick to Down



Immune cells secrete cytokines (shown as red dots in this simplified drawing, click on image to see larger version) that trigger inflammatory responses. But when cytokine levels in the brain stay high for too long, people susceptible to mood disorders may develop depression. Cytokines released in the body may enter the brain directly, by passing through leaky areas in the blood-brain barrier, or indirectly by initiating a chain reaction of "middlemen" that lead to brain cells called microglia releasing cytokines. Cytokines may alter mood by changing brain processes and levels of brain chemicals such as serotonin and dopamine. Synthetic version of interferon-alpha and interferon-beta, used to treat cancers, hepatitis C and multiple sclerosis, may engage the same pathway. Amadeo Bachar

When one of psychiatrist Andrew Miller's patients asked about receiving the best drug available for treating hepatitis C, Miller said: "No way." The patient — in his early 20s and accompanied by his mom to the appointment — had no job, few friends and a history of depression. While Miller knows that hepatitis C patients often benefit from the new generation of immune-boosting treatments, he's keenly aware that those same immune therapies have a strong tendency to bring people down — and, in people predisposed to depression, dangerously down.

Certain immune proteins in the body appear to mess with the minds of otherwise healthy, but depressed people as well. Those who suffer from major depression have higher levels of cytokines, immune proteins the body makes to fend off infections and to patrol the body for disease, and which laboratories mimic. Excess cytokines have also been found lurking in the postmortem brains of suicide victims. "It raises the issue, how much of how we feel — how much of who we are as people — is dictated in terms of our immune system?" says Miller, a researcher at Emory University in Atlanta.

Though the connection between the body's immune response and depression has only gained firm support in the last five years, it's already catalyzing a revolution in antidepressant drug development. In hindsight, an emotional reaction to surging immune molecules does not seem so surprising. Cytokines are among the first immune proteins to respond to infection. Some direct swelling and fevers. Others order the body to rest, and so the sick take to the bed and decline party invitations, showers and even homemade dinners. The powerful molecules influence wants and needs by altering levels of substances like serotonin in the brain. Essentially, cytokines command the body to conserve energy when it's sick. "A little depressed behavior is a survival mechanism in that sense," Miller says. But when inflammation is artificially or erroneously

triggered, prolonged sickness behavior may morph into depression and do more harm than good.

Figuring out the biology behind depression should help doctors combat the disorder, which strikes an estimated 14.8 million American adults each year, according to the National Institute of Mental Health. More than one in six individuals will experience major depression in their lifetime. And when depression coincides with chronic diseases like multiple sclerosis, cancer or diabetes, patients' conditions are less likely to improve.

Psychiatrists and pharmaceutical companies have noted the downpour of evidence linking inflammation to depression. Miller says he and his colleagues have considered creating a new diagnostic category: Major Depressive Disorder with Increased Inflammation. To combat this depression, he says, researchers must find a way to alter the body's immune response. It is a risky strategy but one that offers hope to the nearly 30 percent of all depressed patients who don't respond to the antidepressants currently on the market.

Jekyll-and-Hyde changes

Cytokines emerged as the primary suspects for what's since become known as inflammation-induced depression after Miller and others noticed that cancer patients became inexplicably upset during treatment with synthetic type 1 interferons, cytokines that block viral replication in infected cells. One of these, interferon-alpha, is among the most effective drugs for patients battling cancer and the hepatitis C virus. Yet the treatment has become notorious for causing major depression and other behavioral changes in more than half of these patients, depending on the dose of the immune booster.

Miller describes a "Jekyll-and-Hyde— type change" in one of his patients after interferon therapy. Eight weeks into it, the patient dumped his girlfriend, began dressing in black and grew a goatee. And there was another woman, Miller recalls, who took a drastic downward turn. "One of my most positive patients had been battling cancer for years, yet four weeks into the cytokine therapy she was distraught," he says. "She told me, 'I love my husband and my children, but I don't want to be around them. I want to be left alone, and I don't know why.' "

As observations of sadness, irritability, insomnia, fatigue and loss of appetite — all classic symptoms of depression — mounted in patients treated with immune boosters in the 1990s, papers published nearly a decade earlier in veterinary journals resurfaced. Benjamin Hart had been writing about the behavior of sick animals since the mid-1980s. "Depression was the first sign we had that an animal was sick," says Hart, an animal behavior researcher at the University of California, Davis. In a seminal 1985 paper in the *Journal of the American Veterinary Medical Association*, he put forth the argument that animal malaise serves a purpose.

"People would call in and say that the dog is sleeping more than usual. They give the dog its favorite treat, and it only nibbles at it and then drops it, or they'd say the cat looks scruffy," Hart explains. "Cats usually groom all the time." He says that when he ran blood and urine tests on such animals, he usually discovered signs of bacterial or viral infection. Instead of assuming the pet acted sad because it wasn't feeling well, he suggested that the pet's behavior was part of its immune response. Fido's body forced the animal to devote its energy to battling illness, instead of to chasing squirrels.

Furthermore, since all mammals act similarly when sick, Hart suggested that the behavior had

been inherited from a common ancestor who survived infection better than other animals who had not evolved the behavioral response.

In the 1990s, researchers in the Netherlands reported that patients with major depression showed signs of inflammation, with elevated levels of cytokines in their blood and cerebrospinal fluid. And in 2001, Robert Dantzer, now at the University of Illinois at Urbana-Champaign, injected rats with cytokines. Sure enough, Dantzer says, the rats lost interest in previous pleasures and activities: They didn't care for sugary water, they didn't run on the wheel and, when placed in a pool of water they swam lethargically, barely keeping their heads above water.

Miller compares this sickness behavior to "holing up in a cave." Although the animal has little drive to do much of anything, it does stay alert to major threats. "While in the cave, the organism rests but keeps one eye open," he says. That may explain why people with the flu, as well as people with depression, neither leave the couch nor get the deep sleep they crave.

Connecting body to mind

Like army generals, innate immune cytokines order inflammatory molecules to prepare for war when the body is under threat from invasive bacteria or viruses, or under perceived threat in the form of stress or chronic disease. In these situations, cytokine levels rise. "It's a good thing if you're running from a tiger," explained psychiatrist Dominique Musselman in May at a meeting in Washington, D.C., of the American Psychiatric Association. "You'd want to rev up your immune system to prepare for an injury." Nowadays, however, angry bosses, aggressive creditors and disappointed spouses have replaced vicious predators, she said. And as those stressors are less likely to bite, the subsequent immune response, which had evolved to heal injuries and fight infection, seems a vestige of the distant past.

"The fact that stress can activate the innate immune response has been a major breakthrough," Miller notes. Add this to one more piece of the puzzle: Stress often leads to depression. The immune system may explain why.

In mapping out the molecular pathway between elevated cytokines in the body and chemical changes in the brain, scientists aim to provide targets for drugs intended to treat depression caused by inflammation. In the last few years, researchers have identified primary suspects. Many cytokine proteins, including tumor necrosis factor-alpha, interleukin-6 and the type 1 interferons (IFN-alpha and IFN-beta), have been accused of being the principal perpetrators in sickness behavior. They respond rapidly to foreign intruders, circulate in the bloodstream and initiate a response in the central nervous system.

Cytokines manufactured in the body can send messages through the central nervous system to induce production of cytokines in the brain. That message may be relayed when cytokines sneak into the brain through leaky regions in the blood-brain barrier, a series of structures that block most substances. In the brain, cytokines activate inflammatory middlemen who tag-team their way to affecting emotion-regulating neurotransmitters. As neurotransmitter levels change, so can mood. "Among other things, we see a drop in levels of serotonin, the feel-good chemical," Miller says.

Attempts are underway to treat depression by blocking specific cytokines or the messages they send. A 2006 clinical trial funded in part by the biotech company Amgen found that depressed

patients who suffered from psoriasis, an autoimmune skin disease associated with increased levels of cytokines, felt happier after taking the cytokine blocker etanercept (brand name Enbrel), which affects tumor necrosis factor-alpha. Another TNF-alpha blocker, infliximab (Remicade), is being tested for use in depressed patients who don't respond to antidepressants such as the selective serotonin reuptake inhibitors Prozac and Zoloft. Those results should be ready by 2010, says Charles Raison, a research psychiatrist at Emory University who heads the project.

Anti-inflammatory drugs like aspirin and ibuprofen haven't been shown to affect mood. But another anti-inflammatory, celecoxib (Celebrex), that more specifically blocks the inflammatory molecule COX-2, helped heal depression in a small clinical trial in Germany. Norbert Müller, a psychiatrist on that study from Ludwig-Maximilians-University Munich, suggests that a high dose of aspirin would be needed to inhibit COX-2 as strongly as celecoxib. And that, he says, "would provoke a high rate of side effects, mainly gastrointestinal pain and possibly bleeding."

Developing these types of treatments isn't easy, warns Dantzer. Compounds that interfere with immune responses have the dangerous potential to compromise the body's resistance to infection. The goal is to temper inflammatory molecules in the brain, not the body.

Researchers will have to identify safe points to alter along the molecular pathway that runs between bodily cytokines, molecular middlemen and neurotransmitters in the brain. "The further upstream you go towards the cytokines, the more far-reaching the effects on the body. If you move downstream to block cells that are activated by the inflammation, you may have a drug that is less toxic," Miller says.

Custom-made meds

Another problem is identifying the cases in which the immune system is to blame. "The evidence is clear at this point that inflammation events can lead to a depressed mood," says neuroscientist Steven Maier of the University of Colorado at Boulder. "The issue is how often this is the case."

Not all people are sensitive to surges in cytokines. Some recover from the side effects of interferon therapy as gracefully as some lovers rebound from heartbreak. Variations in a couple of genes may help doctors to predict who is most susceptible to immune-related depression. Miller and collaborators found that patients with hepatitis C were more resistant to interferon-induced depression if they possessed a slight variation in the gene encoding the serotonin transporter 5-HTT, which is known to be involved in psychiatric disorders, as well as another small variation in a gene that codes for the cytokine interleukin-6. The fact that the interleukin-6 gene, involved with inflammation, has an emotional impact provides more evidence of how the body and mind interact, the researchers report in the May 6 *Molecular Psychiatry*.

Identifying these genes is part of a larger effort by doctors to tailor treatment to the individual. "Ideally there could be a drug where one size fits all, but that doesn't seem to be the case," Miller says. He thinks that while serotonin reuptake inhibitors like Prozac work for certain people, others might need an immunological approach to combat depression. "We want to bring to people's attention the interaction between factors," he says. "This is the idea behind personalized medicine."

Others agree that depressed patients unaided by standard treatments may be good candidates for an immune approach. "People who don't respond to those [therapies] seem to have increased

levels of inflammatory markers,” Raison says.

As logic, and misfortune, would have it, depression caused by inflammation is most prevalent in patients who have diseases associated with increased inflammation. Rates of depression are five to 10 times higher than average in patients with disorders that involve the immune system, including infectious diseases, cancer and autoimmune disorders, say Miller and Raison in a March report that appeared online in FOCUS. Inflammation is also a risk factor for diabetes and cardiovascular disease. When these diseases coincide with depression, patient outcomes can worsen.

Sickness behavior leads to grumbling under the covers. And grumbling under the covers hinders the hope and drive that patients need to follow doctors’ orders. Depressed patients are more likely to skip appointments and stop taking their medication, Musselman said at the APA meeting. And depressed smokers are more likely to continue smoking after bypass surgery.

By treating those susceptible to depression early on, doctors may increase their patients’ chances of surviving disease. “The idea,” Maier says, “is to cut depression off at the pass.”