

TREATMENT UPDATE

January - February, 2008

Welcome to the 18th Queensland Positive People (QPP) Treatment Update Newsletter!

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Contact Peter on (07) 3013-5505, or Toll-free 1800-636-241, or email: health@qpp.org.au

The information, comments and editing in this newsletter do not necessarily represent the views of those involved in direct primary medical care...

...Always seek the opinion & advice of your doctor.



QPP have commenced release a **NEW RESOURCE** for people with HIV who experience side effects from HIV treatments or other symptoms of HIV infection. The resource is published by AFAO and was initially developed by QPP along with supportive input from a range of clinical and community services around the state and interstate.

The booklet is intended as a guide to help identify the kinds of side effects that some people with HIV experience, and to provide information on how to prevent, manage, reduce or eliminate some common side effects through the use of medicines, complementary and supportive therapies or practical measures, along with any special precautions and considerations for each side-effect.

The resource covers side-effects such as diarrhoea, headache, peripheral neuropathy, fatigue, anaemia, night sweats, skin problems, blood sugar changes, cholesterol, and liver and kidney problems. Also included is an extensive glossary of terms and information about how to find a qualified practitioner in various complementary medicine modalities.

Content can be viewed at www.qpp.net.au/treatments.htm

Copies can be obtained by contacting QPP on (07) 3013-5555 or 1800-636-241. Clinical- and Community-Based Services throughout Queensland can order bulk copies by Faxback Order to QPP.

Efavirenz (Stocrin) 200mg capsules changing from capsules to tablets

Merck Sharp & Dohme (MSD) has announced – from 1st January 2008 – the availability of a new 200mg tablet form of Stocrin, which replaces the old 200mg capsule form.

Three (3) x 200mg tablets are to be taken once daily. Meantime, the single 600mg tablet (which most people will be on anyhow) is also taken once daily, and will still be continuously available. **Question?:** So what's the difference then? Why a 200mg tablet?...**Answer:** The 200mg tablet may be recommended and prescribed by your doctor when:

- 1) Side effects and drug levels are too high on the 600mg tablet formula (so the dose can be split morning and night, or reduced); or
- 2) drug interactions are occurring with other drugs you may be on, requiring a dose adjustment (...this is least likely in our Australian setting, as the main drug interaction is with an anti-tuberculosis drug...).

New HIV Drug Intelence (etravirine) approved in the US

A new, long awaited, non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (formerly TMC125) was granted approval by the US Food and Drug Administration (FDA) on January 18th this year. The drug – given the trade name "**Intelence**" by its developers, Tibotec – is currently only approved for treatment-experienced adults who have current treatment failure (viral replication) and HIV strains resistant to current NNRTIs and other antiretrovirals.

This represents an important breakthrough, as those who have developed some resistance to the existing NNRTIs of Stocrin (efavirenz) or Viramune (nevirapine), may have further options in that class now.



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Approval Studies

The drug's approval is based on information from the DUET 1 and DUET 2 studies, which included people with both NNRTI resistance and at least three primary Protease Inhibitor (PI) resistance mutations. Longer-term data will be required before the FDA can consider full traditional approval for etravirine, and this is the same case for Australian access to the drug.

The DUET study results suggest that an undetectable viral load can be achieved in these highly treatment-experienced people if they receive both etravirine along with Tibotec's other new PI darunavir (Prezista) and Roche's Fuzeon (T-20), and have only a modest level of resistance to the current NNRTIs.

Side Effects

Etravirine's most commonly reported side-effects are rash and nausea. However, rare cases of serious skin reactions such as Stevens-Johnson Syndrome (SJS) and *erythema multiforme* (a less extreme, often self-limiting, allergic skin condition) have been reported during etravirine's development. Overall, the side effects are considered to be low.

History & Resistance

Intelence is the first new NNRTI to be introduced in nearly 10 years. It is also the first NNRTI to show antiviral activity in patients with NNRTI-resistant virus. NNRTIs block reverse transcriptase, a key enzyme the HIV virus uses to replicate. NNRTI drug resistance occurs when HIV develops mutations that partially or completely stop the NNRTI from binding to the reverse transcriptase enzyme, causing the drug to lose effectiveness. As with other HIV medications, patients can develop resistance to Intelence.

A press release from Tibotec confirms that the presence of the most common NNRTI mutation (called the "K103N") did not affect the treatment response in the individuals on etravirine in the DUET studies.

However, the presence of other resistant mutations was associated with a decreased viral load response to etravirine. Doctors may not prescribe etravirine if they predict it will not work in the presence of three or more of these other associated mutations.

The company has advised that "cross-resistance to efavirenz and/or nevirapine is expected after viral load failure with an [etravirine]-containing regimen."

Comments:

Dr Martin Fisher from Brighton & Sussex University Hospital, has commented that cross-resistance to current (and possibly future) NNRTIs may be etravirine's most limiting factor. "When using etravirine one has to look very carefully at the degree of underlying non-nucleoside resistance," he said.

"What's become very apparent is that the more non-nucleoside mutations one has, broadly speaking, the less likely etravirine is to work. So, the critical message there is that if anybody is taking either nevirapine or efavirenz and is experiencing virological failure, you need to get off that non-nucleoside as soon as possible because otherwise you're scuppering your chances of etravirine working in the future." *Your doctor will assess this situation if needs be, so readers who are on efavirenz or nevirapine and **are doing well** need not concern themselves about this, beyond having a basic understanding about the circumstances in which your doctor might suggest a change of treatment to etravirine, if at all pending future experience with this drug.*

Martin Markowitz, Clinical Director of the Aaron Diamond AIDS Research Center in New York City, also says that "This requires drug-resistance testing and careful review of the results." *Currently in Australia drug –resistance testing is not Medicare Approved, and this drug clearly shows the need for more routine availability of resistance tests, notwithstanding other areas of current prescribing which may sometimes be better guided by resistance testing availability (e.g. commencing treatment to test for transmitted resistance).*

Current and Future Australian Availability

Currently in Australia (and elsewhere), since the end of 2006, etravirine has been available in an [expanded access programme](#) (EAP). The EAP requires that etravirine patients be at least 18 years old, who have limited treatment options either due to viral load failure or intolerance (side effects) to a range of existing anti-HIV drugs. They must have previously received existing treatments from each of the three major anti-HIV drug classes (NRTIs, NNRTIs, and PIs), and must have received at least two PI containing regimens. Long termers with HIV are more likely to have reached this point after trying many treatments over the years.

Currently in Australia there are well over 100 people taking etravirine under this present EAP, and this access program will continue until etravirine is fully approved and listed. The Australian drug regulatory authorities will consider the drug for broader Medicare approval and PBS (subsidised drugs) listings, and this is expected to become available sometime later this year to early next year.



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The drug is also being studied in treatment-naive people (starting treatment for the first time), but it is not currently approved for this in the EAP. It has not yet been studied in children, adolescents, or pregnant women with HIV either.

The NNRTI class of drugs has been one of the most popular for use in people who are starting treatment for the first time, other than using a Protease Inhibitor according to the treatment commencement guidelines. To improve all treatment options it is hoped that the drug will be accepted on all formularies in the future - not just for rescue treatment, but the treatment naive studies need to demonstrate this benefit yet.

Sources:

- 1) www.aidsmap.com Adapted from article by Edward J. Bernard, Monday, January 21, 2008.
- 2) www.hivandhepatitis.com Adapted from article by Liz Highleyman.
- 3) www.aidsmap.com Adapted from article by David Evans, January 15, 2008.

What's New in Pipeline?

The clinical trial and approval pathway for Gilead's anti-HIV Integrase Inhibitor, Elvitegravir, recently got harder following the approval of Merck's rival Integrase Inhibitor, Isentress, in October 2007 (in the US), and February 2008 in Australia under a *Compassionate Supply Program* (for people who need other drugs beyond the existing ones). Gilead now plans to test Elvitegravir head-to-head against Isentress in a non-inferiority study (which is an attempt to prove that it is just as good as Isentress). Actually having to match a similar active comparator drug raises the bar for the 48-week study's success...Watch this space for future notice if Isentress later becomes fully approved on the Australian *Pharmaceutical Benefit Scheme (PBS)* for wider subsidised access; and further down the track if the same may occur with Elvitegravir.

...So what are Integrase Inhibitors????

Integrase is an HIV enzyme that allows the virus to insert its genetic material into the DNA of human T-cells. Previous to the development of these drugs, there have been no treatments which can block this step in the viral life-cycle. Integrase Inhibitors therefore represent a new target site to further prevent the virus from replicating, in conjunction with other existing treatments which target other parts in the HIV replication cycle.

RNA Interference (Gene Therapy) Future HIV Drugs

Researchers at Harvard Medical School have used a promising new technology to identify over 200 proteins that HIV needs to live and reproduce inside human cells. While these findings need more research before directly impacting the lives of people living with HIV/AIDS, they offer hope for novel drug targets at a time when such approaches are badly needed.

The research, published in the journal *Science*, was done by a team of scientists including Drs. Stephen Elledge and Judy Lieberman. Using HIV grown in Lieberman's lab, Elledge used small molecules of RNA (ribonucleic acid) to tease out which human proteins HIV needs to use in order to function. The technology, called *RNA interference (RNAi)*, uses tiny strings of RNA, called *small interfering RNA (siRNA)*, which can turn off a cell's ability to make a particular protein.

Dr. Elledge exposed cells to many thousands of different siRNA molecules to see if HIV was able to survive and reproduce inside them. In all they tested over 20,000 cells and identified 273 human proteins that HIV needs to function. Research using other methods has already found 36 such proteins.

There are potential benefits and risks to targeting human proteins. HIV may be less able to mutate to overcome drugs that target a human protein, making the issue of drug resistance less likely. However, interfering with human proteins runs the risk of disrupting normal cell function. Some drugs used to treat cancer use this approach. Targeting human proteins to combat HIV is a new and largely untested strategy. There is only one HIV drug that works this way—the CCR5 antagonist Selzentry (maraviroc)—which was just approved in late 2007.

Researchers are now able to look at each of these proteins to see if it can be safely and successfully targeted to block HIV. This report is very timely, as the pharmaceutical industry has been slow in developing novel types of drugs to treat HIV. With a couple of notable exceptions, most of the recent drug development—including the drugs now in clinical studies—are new and probably improved versions of the same kinds of drugs used to treat HIV since 1996. While this has meant significantly better tolerability and convenience, better protease or reverse transcriptase inhibitors are unlikely to fully overcome the limits of their predecessors.

Project Inform [wrote about siRNA](#) back in 2003. At the time they focused on siRNA's potential as a drug itself. While this has yet to materialise, the use of the technology to further our understanding of HIV and suggest new drug targets is very welcome. With potent and tolerable HIV drugs



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keeping many people—at least those who can access them—healthy for long periods, there is a growing risk of complacency by scientists and drug companies, who may feel that the problems of living with HIV/AIDS are pretty much solved. Hopefully this research, which Robert Gallo has said was, ‘...destined to be one of the top papers in [HIV/AIDS] for the decade,’ can serve to reinvigorate the search for new and more effective treatments for HIV.

Footnote:

RNAi therapeutics is also currently being investigated in Hepatitis B with an experimental drug called “NUC B1000” by a company called Nucleonics.

Source: www.projectinform.org Article by Paul Dalton. January 11, 2008

Rethinking the Merck AIDS Vaccine Failure

In September last year Merck halted a study, called STEP, after an unanticipated finding: people who got the vaccine were more likely to contract HIV than those who didn't. The result has stalled human studies of similar vaccines, including one from the U.S. government that shares features with Merck's product.

The Merck vaccine was the most advanced of several preventatives against HIV, now estimated to have infected more than 33 million people worldwide. Now, Anthony Fauci, the U.S. government's top infectious disease scientist, is waiting for more data from Merck and an international network of HIV researchers to determine whether the US government's leading vaccine candidate, called VRC, will be safe enough to test. Professor Fauci says “No final decision has been made on whether the trial is going to go forward,” but “If it does, it will probably be a modified, truncated version” of earlier plans.

Scientists say the Merck fallout may set back vaccine research for years, and the other vaccines aren't as promising.

“There's a lot of disappointment,” said John Bartlett, a Johns Hopkins University HIV researcher. “Prevention is the biggest failure in the field, I think everyone agrees.”

Features in Common

The US government VRC vaccine contains a cold virus made by Gaithersburg, Maryland-based GenVec Inc. and a DNA vaccine made by San Diego-based Vical Inc. It has at least two features in common with Merck's. First, while most vaccines spur the body to make protective proteins called antibodies, the experimental AIDS shots stimulate

protective T-cells that the immune system uses to attack viruses.

Both vaccines also were built using the cold virus, called adenovirus-5. Proteins that can trigger a protective immune system reaction to HIV are packaged within the virus that delivers them throughout the body. Atlanta-based GeoVax is also testing a T-cell vaccine that contains a virus.

AIDS researchers are concerned because, in the Merck study, the people most likely to become infected with HIV were those who had high levels of immunity to the cold virus before the test began. If the U.S. trial goes ahead, it should probably enrol less than half the 8,000 or more people originally proposed, and exclude anyone with immunity to the cold virus, government science advisors said at a meeting in Potomac, Maryland, in December last year to discuss the vaccine's fate.

Studies Halted

Eight government-funded studies of vaccines against HIV, malaria and Ebola virus were halted or put on hold after the Merck results. The International AIDS Vaccine Initiative (www.iavi.org) has stepped up efforts to find a way to prevent the disease that doesn't depend on triggering protective T-cells.

At the December meeting of the government advisory group, the AIDS Vaccine Research Subcommittee, most researchers said they were in favour of going ahead with testing vaccines related to Merck's. The government's shot is sufficiently different from Merck's to be worth testing, said Gary Nabel, director of the Vaccine Research Center in Bethesda, Maryland, where the preventive was developed. He said “we're not giving up, but we need to be intelligent about the approach. We need to move forward in a way that's constructive.”

Are T Cell Vaccines Worth the Risk?

Salim Abdool Karim, a vaccine researcher at the University of KwaZulu-Natal in South Africa, where the VRC may be tested, said the information to be gained in the test is worth the potential risk. A small trial would establish whether the vaccine is safe and provokes an immune response to HIV, he said.

“Given that we know so much about what this vaccine does in animals, it would be useful to see what it can do in people,” he said in a telephone interview. “I don't think the T-cell vaccines are dead because of this.”

Geovax's vaccine contains a virus called poxvirus. The product has significant differences from the Merck vaccine, and has given good results in animal tests, said Harriett Robinson, chief scientific officer and developer of the vaccine. “You can't just say globally that T-cell vaccines won't protect against HIV,” she said in a telephone interview. “We know



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that T-cells are an important component of protection and they will continue to be."

Geovax expects to enter the second of three phases of human testing of its vaccine in mid-2008. The three levels of testing are required for sale in the U.S.

THE FUTURE OF VACCINES?

Comments from the recent 15th CROI Conference held in Boston

Conference cochair John Mellors, MD:

"The path forward is not clear. I think there is agreement on that. Anybody who talks about a timeline for a vaccine is being silly and uninformed. It will require an incremental process of knowledge, and experimentation, and testing of ideas."

www.medscape.com/viewarticle/569816

Scientific Obstacles to Effective HIV Vaccine Frustrate Researchers

Source: www.natap.org Edited from article by John Lauerman. Merck Aids Vaccine Failure Signals Doom for African, U.S. HIV Vaccine Projects

New Anti-Smoking Pill Linked to Depression

A new pill (called *Champix [varenciline]*) designed to help smokers quit has recently been listed on the Australian *Pharmaceutical Benefits Scheme (PBS)*, available from January 2008. The drug is causing some concern because of reports that it led to suicides and depression among some patients in the United States and in Europe, where it has been available for over a year.

As a result the European Medicines Agency has asked the pharmaceutical company Pfizer to update its product safety information. The safety information has been changed in Australia too, to include a warning that people with mental illness (such as depression) should take the drug with caution, and keep up discussion with their doctor via regular monitoring appointments during the course of the drug treatment.

A course of treatment with Champix is 12 weeks, requiring 2 prescriptions: the first for an initial 4 weeks of treatment (where the dose is gradually increased); and the second for a further 2 months of treatment. Clinical review (monitoring by your Doctor) is recommended within 2-3 weeks of starting.

The drug works by blocking the effect of nicotine on the brain, therefore the brain does not feel any of the usual stimulation effects of cigarettes. Secondly, the mind feels less like wanting to smoke, because the sorts of pleasure and satisfaction from smoking are removed. Withdrawal is therefore easier and any withdrawal

symptoms are therefore reduced or eliminated when people stop smoking.

In two studies, about a quarter of all Champix users were still off cigarettes a year after taking the drug. So we know it works!...However, there are growing concerns about the drug's possible side effects, but of the 20,000 Champix users in Britain, only 50 people reported depression and suicidal thoughts. That's only about 0.3% of total users of the drug. Whilst that is a very low incidence level, the severity of such side effects is a clearly an important concern. It is well known that sometimes depression can also lead to suicide or suicidal thoughts.

Comments:

Mood changes and depression are well known triggers related to smoking, even before a drug like *Champix* is taken to stop smoking. Some experts have estimated that about 40% of all cigarettes smoked in Australia are smoked by people with **existing** depression. In reality, it's too early to tell if Champix **causes** mental health side effects (such as depression or suicidal thoughts), or whether it **exacerbates (worsens)** these conditions - since it has not been used long enough in wide-scale use in people **with** a history of depression, or even in those **without** pre-existing depression. We can only consider the odds of this existing early information about the limited number of cases which have been reported.

Nonetheless, people with existing depression are less likely to attempt giving up smoking anyhow, so the better treatment for them is more likely to be treatment for the depression...and tackle the smoking habit later!

Some experts suggest that smoking itself causes depression. So, if depression also causes smoking, then it is a bit of a circular event! Paradoxically, it is also suggested that quitting smoking can worsen depression or be a symptom of withdrawal - *even though the drug is meant to stop withdrawal symptoms!* So much of the facts between drug use and depression links with smoking are at worst ambiguous, or at least interchangeable or permeated with each other. It's therefore hard to know if it's **'the chicken'** (depression/suicide) or **'the egg'** (the anti-smoking drug/smoking itself), until this drug is used for much longer. Time will tell pending whether doctors use this drug with suspicion or not.

For Further information about stopping smoking:

Government Programs:

- 1) Quitline on 131848 or visit the **National Tobacco Campaign** www.quitnow.info.au (also try the quit coach www.thequitcoach.org.au) or
- 2) Queensland Cancer Council on (07) 3258 2281 (toll-free 131120) or visit www.qldcancer.com.au

Private/Commercial Programs:



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- 3) **Smoke-Enders** Information and Help-line on 1800-02-1000 or visit www.smokenders.com.au/
- 4) **Martin St James Hypnosis Centre** (Broadbeach, QLD Gold Coast) on 1300-884-966 or visit www.martinstjames.com

Source: Adapted from news article www.abc.net.au/pm/content/2007/s2121136.htm Monday, 17 December, 2007. Reporter: Jennifer Macey.

Sense of Smell and Depression

Scientists have discovered a link between depression and the loss of a sense of smell. It is suggested that those who are clinically depressed lose sensitivity in their olfactory glands at the same time. Some research has touted the possible benefit that aromatherapy could be a powerful weapon against depression.

Aromatherapy is particularly effective in alleviating stress, by introducing a state of relaxation, sense of wellbeing, and providing a sense of revitalisation. Stress can lead to depression. However, 'depression' is a term which encompasses a wide spectrum of problems and symptoms which, in turn, can lead to more serious and chronic (persistent) illnesses which should be diagnosed and treated by a medical doctor and/or professional psychotherapist.

By helping relaxation and reducing stress, aromatherapy may help to **prevent** such conditions of **mild** depression and mood related disorders, but is unlikely to cure the more serious clinical forms of depression (although it may assist in certain cases as **additional** support). Depression-related disorders, such as digestive problems, headaches, insomnia, low energy, mental fatigue, and general anxiety, can be all be helped or treated by Aromatherapy. However, aromatherapy is more effective when used as a Complementary Therapy, assisting other therapies and treatments.

The essential oils used in Aromatherapy can be blended and applied in massages, baths, diffusers/oil burners and personal perfumes

There is very little evidence for all the claims made by aromatherapists regarding the various healing properties of oils, although some follow:

Studies on brain wave frequency have shown that smelling lavender increases *alpha waves* in the back of the head, which are associated with relaxation. Fragrance of Jasmine increases beta waves in the front of the head, which are associated with a more alert (but relaxed) state.

The following aromatherapy oils are useful to assist mind relaxation:

Essential Oils	Curative Properties
Clary Sage essential oil	It is used in treating insomnia, anxiety and depression.
Basil	Basil essential oil is used to lift fatigue, anxiety and depression.
Rose essential oil	Rose is great on the entire nervous system and disorders
Ylang-ylang	A great relaxer anxiety, depression and Insomnia.
Sandalwood	Sandalwood's sedative properties are good for treating depression and tension.
Lavender	Lavender essential oil is used for nervous system disorders such as depression, headache, hypertension, insomnia, migraine, nervous tension, stress related conditions.
Jasmine essential oil	Jasmine increase the beta waves in the front of the head which can give you a more alert and responsive state of mind.

...Other oils that have also been used in different blends to relax and relieve depression are:

- [Rosemary essential oil](#) - Rosmarinus Officinalis
- [Patchouli essential oil](#) - Pogostemon patchouli
- [Chamomile essential oil](#) - Anthemis Nobilib
- [Bergamot essential oil](#) - Citrus Bergamia
- [Orange Essential oil](#) - Citrus aurantium
- [Geranium essential oil](#) - Pelargonium Adorantissimum
- [Cinnamon oil](#) – Cinnamomum Zeylanicum

Source: www.depression-guide.com/aromatherapy.htm

Seaweed extract hailed as a promising natural medicine

A natural seaweed extract – which might help protect against inflammatory conditions such as inflammatory bowel disease and arthritis and assist in the breakdown of dangerous blood clots – is being studied by Southern Cross University researchers.

The research is being conducted on behalf of the Australian Centre for Complementary Medicine, Education and Research (ACCMER*). Professor Stephen Myers, head of Southern Cross University's NatMed Research Unit and ACCMER Research Fellow, said the studies, being done at the University's Centre for Phytochemistry and Pharmacology, had far-reaching potential in the rapidly expanding world market for nutraceuticals.

Nutraceuticals are natural compounds taken to promote good health and fight disease, as compared to pharmaceuticals, which are generally drug-based treatments. Professor Myers recently



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gave the opening address at the launch of a new Tasmanian seaweed processing plant which harvests and refines the seaweed. The plant is owned by Marinova, a Hobart biotechnology company. The research is being undertaken on behalf of the company.

"Fucoidan, the seaweed extract being processed by Marinova, has some very exciting properties which could lead to many medicinal uses," Professor Myers said. "Research shows it has broad-spectrum anti-viral properties, including against the HIV and herpes simplex (cold sore) viruses as well as tumour inhibiting properties.

"It also has cholesterol-lowering and anti-inflammatory properties and the ability to dissolve blood clots, so it has many potential uses in promoting cardiovascular health.

"There is already some epidemiological and animal evidence on its efficacy and at Southern Cross University we are involved in laboratory tests to further advance this research. "The results are strong enough to warrant human clinical trials as the next step to prove its value as a medicinal product."

Marinova business development manager Nick Falk said the company had begun harvesting the seaweed in 1998 off the Tasmanian east coast. The seaweed species, *Undaria Pinnatifida*, was not native to Australia but had arrived in the bilge water of foreign ships and was considered a noxious weed. However the same species is highly prized in Asia as wakame, an ingredient in foods such as miso soup.

"Over the last 15 years, with the observation that seaweed eating populations show lower rates of cancer, HIV and inflammatory conditions, there has been an increase in investigational and clinical trial activity focused on fucoidans," Mr Falk said. "Marinova has its own research and development program and our work stems from the existing body of fucoidan research.

"Following the completion of our new proprietary extraction facility in Tasmania, Marinova has the capacity to develop fucoidans at a higher purity than any of our competitors." Mr Falk said the company had been introduced to a major US-based international commercial partner by ACCMER and the extract was now being used extensively in many of their health products. He said the extract provided health benefits similar to the cardiovascular drug heparin without any of its known serious health risks. He hoped the research work at Southern Cross University would continue to provide evidence for the efficacy of the extract and lead to its use in many more nutraceutical and cosmetic products.

"Fucoidans are polysaccharides and naturally occurring components of certain edible seaweeds and echinoderms. They have been part of the

human diet for centuries and in countries such as Japan and Korea, are prized for their dietary and medicinal properties," Mr Falk said. "The term fucoidan describes a diverse family of molecules rather than a single chemical compound. Each type of brown marine algae or echinoderm yields a specific fucoidan, and each fucoidan varies in its clinical benefit.

"Our primary interest in fucoidans stems from their ability to act as immunomodulators, selectin antagonists, viral attachment inhibitors, enzyme inhibitors and receptor blockers. Fucoidans and their derivatives demonstrate considerable anti-viral, anti-coagulant and cholesterol lowering activity. "Through extraction and fractionation, these naturally occurring molecules can be utilized as high efficacy targeted therapeutics."

** The Australian Centre for Complementary Medicine Education and Research (ACCMER) is Australasia's leading centre for evidence-based research and post-graduate education in complementary medicine. ACCMER is a joint venture between the University of Queensland and Southern Cross University, establishing a world first collaboration between conventional and complementary medicine. Media contact: Zoe Satherley, Southern Cross University media officer, 02 6620 3144, 0439 132 095.*

Source: www.uq.edu.au/accmcer/ accessed 24/01/08.
www.uq.edu.au/accmcer/assets/docs/Marinova_Aug06.pdf



Australian Centre for Complementary Medicine
EDUCATION & RESEARCH

Researchers Show that Fibrosis of the Liver Can Be Stopped, Cured and Reversed

University of California, San Diego researchers have proven in animal studies that fibrosis in the liver can be not only stopped, but reversed. Their discovery, published in *PLoS Online* on December 26, opens the door to treating and curing conditions that lead to excessive tissue scarring such as viral hepatitis, fatty liver disease, cirrhosis, pulmonary fibrosis, scleroderma and burns.

Six years ago, the UC San Diego School of Medicine research team discovered the cause of the excess fibrous tissue growth that leads to liver fibrosis and cirrhosis, and developed a way to block excess scar tissue in mice. At that time, the best hope seemed to be future development of a therapy that would prevent or stop damage in patients suffering from the excessive scarring related to liver or lung disease or severe burns.

In their current study, Martina Buck, Ph.D., assistant professor of medicine at UCSD and the Veterans Affairs San Diego Healthcare System, and



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Mario Chojkier, M.D., UCSD professor of medicine and liver specialist at the VA, show that by blocking a protein linked to overproduction of scar tissue, they can not only stop the progression of fibrosis in mice, but reverse some of the cell damage that already occurred.

In response to liver injury – for example, cirrhosis caused by alcohol – hepatic stellate cell (HSC) activated by oxidative stress results in large amounts of collagen. Collagen is necessary to heal wounds, but excessive collagen causes scars in tissues. In this paper, the researchers showed that activation of a protein called RSK results in HSC activation and is critical for the progression of liver fibrosis. They theorized that the RSK pathway would be a potential therapeutic target, and developed an RSK inhibitory peptide to block activation of RSK.

The scientists used mice with severe liver fibrosis – similar to the condition in humans with cirrhosis of the liver – that was induced by chronic treatment with a liver toxin known to cause liver damage. The animals, which continued on the liver toxin, were given the RSK-inhibitory peptide. The peptide inhibited RSK activation, which stopped the HSC from proliferating. The peptide also directly activated the caspase or “executioner” protein, which killed the cells producing liver cirrhosis but not the normal cells.

“All control mice had severe liver fibrosis, while all mice that received the RSK-inhibitory peptide had minimal or no liver fibrosis,” said Buck. Buck explained that the excessive collagen response is blocked by the RSK-inhibitory peptide, but isn’t harmful to the liver. “The cells continue to do their normal, healing work but their excess proliferation is controlled,” Buck said. “Remarkably, the death of HSC may also allow recovery from liver injury and reversal of liver fibrosis.”

The researchers found a similar activation of RSK in activated HSC in humans with severe liver fibrosis but not in control livers, suggesting that this pathway is also relevant in human liver fibrosis. Liver biopsies from patients with liver fibrosis also showed activated RSK.

The study expands on work reported in 2001 in the journal *Molecular Cell* announcing that a team led by Buck had found that a small piece of an important regulatory protein called C/EBP beta was responsible for fibrous tissue growth, or excessive scar tissue following injury or illness. When normal scarring goes awry, excessive build-up of fibrous tissue can produce disfiguring scars or clog vital internal organs and lead to serious complications. Buck and colleagues developed a mutated protein that stopped this excessive fibrous tissue growth.

“Six years ago, we showed a way to prevent or stop the excessive scarring in animal models,” said Buck. “Our latest finding proves that we can actually reverse the damage.”



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Worldwide, almost 800,000 people die from liver cirrhosis each year, and there is currently no treatment for it. Excessive tissue repair in chronic liver disease induced by viral, toxic, immunologic and metabolic disorders all result in excessive scar tissue, and could benefit from therapy developed from the UCSD researchers’ findings.

Comments:

Until such stages as human studies are conducted using this agent, as well as testing it for safety issues, then unfortunately progression to liver fibrosis (scarring) from hepatitis may remain a concern. Regardless of the level of scarring of your liver, it’s never too late to try and improve your liver health. Studies have shown that, short of cirrhosis, it’s sometimes possible to actually reverse fibrosis if the source of the damage is no longer present. However, there are still things you can do to improve liver health and potential scarring, if you have Hepatitis:

- 1) Drink plenty of water, and limit alcohol consumption, to not more than one standard drink per day, with at least 2 alcohol free days (if you have Hepatitis B or C). Chronic excessive alcohol intake can greatly increase the rate of liver fibrosis (scarring). People with Hepatitis A are best advised to avoid alcohol altogether until the infection is treated and cleared.
- 2) Maintain a well-balanced diet comprising a wide variety of foods such as fruits, vegetables, legumes, lean meats (trimmed of fat), fish and dairy. Avoid adding salt, and excess sugar.
- 3) Antioxidant natural therapies, such as vitamin E, may assist liver health in certain circumstances. Certain herbs, such as Milk Thistle, may also assist. There are certain herbs which should be avoided which can cause liver damage.
- 4) Talk to Hepatitis Council for further information about ways you can improve liver health. Facts sheets and printed information are available. Contact the Queensland Hepatitis Council via phone (07) 3236 0610, Statewide Tollfree 1800-648-491, or via the web www.hepqld.asn.au/

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Source: <http://health.ucsd.edu/news/2007/12-27-fibrosis> *Researchers Show that Fibrosis Can Be Stopped Cured and Reversed (Modified Protein Developed by UC San Diego Researchers May Lead to First Cure for Cirrhosis of the Liver).* December 27, 2007. Media Contact: Debra Kain, 619-543-6163, ddkain@ucsd.edu

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