

COLORECTAL CANCER RESEARCH

Week Ending August 8, 2008

The following colorectal cancer research update extends from July 26 – August 8, 2008 inclusive and is intended for informational purposes only.

**DRUGS**

**1. Potential Anti-Cancer Activity of the Antidepressant Sertraline in Human Colon Cancer Cell Lines and in Colorectal Cancer-Xenografted Mice** (Jul 30/08)

Evidence has been provided of the anti-cancer activity of certain antidepressants, sertraline. The effect of different antidepressants on cell viability and proliferation of human colorectal cancer cell lines were tested and when compared to chemotherapeutic agents such as doxorubicin, vincristine and 5FU, the antidepressants showed comparable activity or a superior effect. In particular, sertraline, significantly inhibited tumour growth in nude mice. The investigators concluded the following: "Collectively our results suggest that the widely-used antidepressant, sertraline, possesses a potential anti-tumour activity, which circumvents the MDR mechanism. Since SSRI therapy is frequently indicated in cancer patients, the use of sertraline in colon cancer patients with co-morbidity of depression seems attractive."

Gil-Ad I., et al., Evaluation of the potential anti-cancer activity of the antidepressant sertraline in human colon cancer cell lines and in colorectal cancer-xenografted mice. *Int J Oncol.* 2008. Aug ; 33(2): 277-86

**2. Biweekly Cetuximab and Irinotecan in Advanced Colorectal Cancer Patients Progressing After At Least One Previous Line of Chemotherapy: Results of a Phase II Study** (Jul 31/08)

Data from a phase II institutional exploratory trial of biweekly irinotecan and cetuximab administration in metastatic colorectal cancer patients progressing to at least one previous chemotherapy regimen revealed some rather promising results. A total of 40 patients were treated between November 2005 and November 2007 with irinotecan 180 mg/m<sup>2</sup> and cetuximab 500 mg/m<sup>2</sup> every 2 weeks, in every 21 day cycles, until unacceptable toxicity or progressive disease. Overall, the results turned up very similar both in terms of toxicity and efficacy to those obtained in weekly and biweekly administration regimens.

Martorell, P M, et al., Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *British Journal of Cancer* (2008) 99, 455-458

**3. Kras Status Doesn't Impact Treatment with 5FU** (Aug 1/08)

Research has demonstrated that mutated Kras genes do not respond to treatment with anti EGFR therapies such as erbitux or vectibix. Investigators wanted to determine if 5FU (fluorouracil), which is the backbone of most colorectal cancer treatment, given alone or in combination with other drugs, was dependent on Kras status. Researchers analyzed tumour tissue from patients who had 5FU treatment only and whose cancer had spread to their liver and whose liver mets could not be surgically removed. Investigators found the following:

- 38.7% of the patients had a Kras mutation in their tumours
- Kras mutations in liver tumours matched exactly with those in primary tumours in the colon
- There was no significant difference in the percentage of liver tumours that got smaller with 5FU treatment
- There was no difference in survival between the group of patients with mutated Kras and those with normal or wild type Kras

Hence, treatment with 5FU is not impacted by Kras status and other research has found that avastin treatment outcomes are not affected by Kras status either.

Etienne-Grimaldi, et al., Kras Mutations & treatment Outcome in Colorectal Cancer Patients Receiving Exclusive Fluoropyrimidine Therapy. *Clinical Cancer Research*, Volume 14, Number 15, August 1, 2008

#### **4. YM BioSciences Reports Phase II Data for Nimotuzumab Metastatic Colorectal Cancer**

(Aug 4/08)

YM Biosciences, an oncology company situated in Mississauga, Ontario, announced preliminary results obtained from its open-label, phase II study (ymb 1000-015) of nimotuzumab in patients with irinotecan-refractory, metastatic colorectal cancer. The data are based on 58 evaluable patients of the 61 enrolled in the trial. The trial was conducted at 10 centers across Canada and consisted of treatment with 400 mg of nimotuzumab weekly plus irinotecan in patients refractory to irinotecan alone, with patients remaining on nimotuzumab until disease progression. The overall survival and disease control rate for patients receiving nimotuzumab compare well with published results in similar patient populations treated with cetuximab, a currently available EGFR monoclonal antibody. Investigators report that nimotuzumab also continues to display a safety profile unequalled in its class for nimotuzumab was administered without premedication, and, in contrast to cetuximab, no infusion reactions were observed. No subjects discontinued treatment or required dose reductions due to nimotuzumab-related adverse events. Only 22% of patients were reported with rash, all of which was graded I/II. In contrast, grade I/II rash was reported in 80% and grade III/IV in 9.4% of patients in the cetuximab/irinotecan trial known as BOND I. Neutropenia, asthenia and diarrhea were all lower in the nimotuzumab trial than in the BOND I trial.

[www.drugs.com/clinicaltrials/ym-biosciences-reports-phases-ii-data-nimotuzumab-tetastatic-colorectal-cancer-5236.html](http://www.drugs.com/clinicaltrials/ym-biosciences-reports-phases-ii-data-nimotuzumab-tetastatic-colorectal-cancer-5236.html)

#### **5. Adjuvant Treatment Does Not Have Negative Impact On Elderly Quality of Life** (Aug 5/08)

Colorectal cancer patients 75 years and older who are treated with chemotherapy or radiation don't report any poorer quality of life than older patients who don't have such therapy. Patients who had chemotherapy said that their physical functioning was better than that reported by those who did not receive chemo. French patients who were at least 75 responded to questionnaires about their quality of life and emotional health three, six and twelve months after their diagnoses. Overall health and emotional functioning improved between the first questionnaire at three months and the twelve month survey for people with colon cancer. For rectal cancer patients, scores improved between six months and twelve months. The lead investigator comments: "To the author's knowledge, the current study is the first to examine trends over time with regard to the influence of adjuvant treatments for colon and rectal cancer on quality of life (QoL) in a general aged population. Providing evidence that adjuvant chemotherapy for colon cancer has no negative impact on the QoL of elderly patients is of great significance in encouraging clinicians to treat this population."

*Bouvier. AM., et al., Adjuvant Treatmebt Does Not Have Negative Impact on Elderly Quality of Life, Cancer, Volume 113, Number 4, August 5, 2008*

## **SURGERY**

#### **6. Rectal Cancer Patients Benefit From Minimally Invasive Surgery** (July 28/08)

A group of Houston colorectal surgeons have conducted one of the largest studies to date of the patient benefits of minimally invasive laparoscopic surgery for rectal cancer, leaving behind no markers for cancer. Some 100 consecutive surgical cases were analyzed and the results reported at the international meeting of the American College of Colon & Rectal Surgeons in June. A minimally invasive laparoscopic approach to colon and rectal surgery offers significant advantages that change the patient's experience of surgery and recovery, according to Eric Haas, MD, of Colorectal Surgical Associates in Houston. Surgeons used a digital camera and specialized instruments allowing them to use a dime-sized incision where the patient benefits from a shorter hospital stay, a smaller scar, and quicker recovery. In the study conducted by CSA, the average hospital stay was 4 days compared to nine days with traditional surgery. Patients were mobile, walking, eating and drinking within days of surgery. Additionally, the surgeons studied the lymph nodes which were removed and found they were able to extract more than with traditional surgery, leaving the patients with no trace of cancer. The patient also benefits from a minimally invasive approach because it avoids the need for a permanent colostomy thus having a better quality of life after minimally invasive surgery according to the investigators.

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

## **RADIATION**

### **7. Clinical Trial Testing Ultrasound System for Painful Bone Mets** (Jul 26/08)

Mets to the bones can be quite painful. Current treatments consist of radiation therapy or opiate drugs but these are not always successful in relieving the pain. A system that combines magnetic resonance imaging (MRI) with ultrasound treatment to destroy bone tumours and treat pain is being evaluated in a randomized phase III clinical trial at a number of centers in the United States, Israel and Canada (Toronto, Ontario – Toronto General Hospital). BM004: is a pivotal study designed to evaluate the effectiveness and safety of ExAblate treatment of metastatic bone tumours for the palliation of pain in patients who are not candidates for radiation therapy and is sponsored by InSightec Ltd. ExAblate 2000, magnetic resonance guided focused ultrasound (MRgFUS) was developed by Insightec and has been used to treat uterine fibroids since 2004. Magnetic resonance imaging focuses high-intensity ultrasound waves on tumour tissue to destroy it and relieve pain. Doctors can measure and adjust increasing temperature in tumours being treated during therapy. Patients eligible for the trial include those:

- With 1-3 painful metastases to their bones
- Whose pain has not improved despite radiotherapy or who are unable to use radiotherapy
- With pain scores at least 4 or higher
- Whose bone tumours are less than 8 cm
- Who are able to communicate sensations during the ExAblate treatment
- Have tumours clearly visible on MRI and accessible to MRgFUS

More information on the trial is available at:

<http://www.clinicaltrials.gov/ct2/show/NCT00656305?term=NCT00656305&rank=1>

[www.C3:Research&TreatmentNews.com](http://www.C3:Research&TreatmentNews.com)

## **OTHER**

### **8. GeneNews Launches World's First Blood Test For Colorectal Cancer Screening** (Jul 21/08)

GeneNews Limited announced the launch of ColonSentry, the world's first blood-based molecular test for colorectal cancer screening. ColonSentry is a blood test that assesses a patient's current risk of having colorectal cancer, identifying those in the asymptomatic general population with increased risk who might benefit from further more invasive diagnostic testing such as colonoscopy. This risk stratification approach allows for a more targeted application of colonoscopy which could increase the detection rate of crc by as much as 3 fold in an asymptomatic general population. The test requires a simple blood sample. 7 specific genes are measured at the molecular level by quantitative RT-PCR which results in an assessment of the patient's current risk. ColonSentry will be performed at the Company's lab facilities in Richmond Hill, Canada and is the first in a series of blood-based molecular tests based on the company's platform technology, the award winning Sentinel Principle.

[www.prnewswire.co.uk/egi/news/release?id=233021](http://www.prnewswire.co.uk/egi/news/release?id=233021)

### **9. Colon Cancer Patients with a family History of CRC Have Lower Risk of Recurrence & Death** (Jul 29/08)

According to a study, which looked at the link between inherited crc and survival, patients with stage III colon cancer who had a family history of crc in a first degree relative had a lower risk of recurrence and death than those without. Studies have shown that a history of crc in a first-degree relative nearly doubles the risk of developing the disease. However, the influence of family history on cancer recurrence and survival has previously been unclear. The current study followed up 1087 patients with stage III colon cancer who were taking part in a clinical trial of chemotherapy. Rates of recurrence and death were compared over a follow-up of 5.6 years in the 195 patients with a family history of crc in a first-degree relative with the 892 patients without a close relative with the disease. Results showed that cancer recurrence or death occurred in 29% of the patients with a family history of crc, compared to 38% of those without a first-degree

relative with the condition. The risk of recurrence was 26% lower in patients with a family history of crc, while their risk of death was 25% lower.

*Chan, JA, Meyerhardt, JA, Niedzwiecki, D, et al. Association of family history with cancer recurrence and survival among patients with stage III colon cancer. JAMA 2008; 299: 2515-2523*

## **9. Journal of Clinical Oncology Article Highlights CellSearch Circulating Tumor Cell Test in Treatment of Metastatic Colorectal Cancer** (Aug 1/08)

An international, prospective clinical trial found the number of circulating tumor cells (CTCs) is a strong indicator of progression-free and overall survival among metastatic colorectal cancer patients, according to a report published in the July 1 of the Journal of Clinical Oncology. The study found that metastatic colorectal cancer patients with fewer than three circulating tumor cells in their bloodstream had significantly better overall survival than patients with more than three CTCs. The CellSearch System is the first diagnostic test to automate the process of identifying and counting circulating tumor cells (CTCs) in a blood sample. This system helps physicians to predict disease progression and patient survival any time during therapy through its ability to locate minute numbers of circulating tumor cells in the approximately 40 billion cells contained in a 7.5 ml sample of blood – an achievement never before documented in any diagnostic tool. In this particular study, researchers counted the number of circulating tumor cells in the peripheral blood of patients at baseline and after starting first-, second-, or third-line therapy. Given the variety of cancer drugs available today, the ability to monitor CTCs in conjunction with radiological assessment may help physicians and patients make more informed and timely treatment decisions. Obtaining measurements of CTCs for patients with metastatic colorectal cancer beginning a new therapy can provide additional information about their prognosis, and may also be followed serially to assist with clinical management.

*Cohen, Steven, J. et al., Relationship of Circulating Tumor cells to Tumor Response, Progression Free Survival & Overall Survival in Patients with Metastatic Colorectal Cancer, Journal of Clinical Oncology. Vol 26, No 19 (Jul 1) 2008: pp 3213-3221*

## **NUTRITION**

### **10. A New Study Reports That Morning Cup of Coffee is Still OK** (Jul 29/08)

A new study published in the Annals of Internal Medicine suggests that those people who regularly indulge in their favorite coffee beverage may live longer than those who don't. The authors of this study reviewed data from two large ongoing studies that have followed health professionals over more than twenty years, including their dietary habits and what they found was that people who drank at least five to seven cups of coffee per week had a significantly lower overall risk of dying from any cause compared to those who did not drink coffee; people who drank 4-5 cups per day or more seemed to have the strongest protection. Also, in this study, people who drank decaf coffee benefited as much as those who drank the "rock fuel", suggesting that there is something else in coffee besides the caffeine that is beneficial to our health. We do know that coffee is high in polyphenols – plant chemicals that are known to reduce inflammation. Polyphenols also have other positive effects on the heart, blood vessels, and blood sugar. Polyphenols act as anti-oxidants and may help to reduce blockages in the arteries; they help relax blood vessels, which can also lower blood pressure; and they seem to improve glucose tolerance and utilization, thus reducing the risk of diabetes.

[www.cancercompass.com/cancer-news/1,14533,00.htm](http://www.cancercompass.com/cancer-news/1,14533,00.htm)

### **11. Omega-3 Impact on Colon Cancer Prevention** (Jul 29/08)

In a 2006 project, Japanese researchers studied the link between omega-3 fatty acid and red blood cell membranes for people with colorectal cancer and in healthy people who were cancer free. Research controls were matched by age and gender. Lead researcher Kiyonori Kuriki commented that omega-3 did show promise and suggested that the risk of colorectal cancer decreased by 85% when patients consumed omega-3 fatty acids.

[www.omega3healing.com/omega-3-and-cancer](http://www.omega3healing.com/omega-3-and-cancer)

### **12. Green Tea Shown to Reduce Risk of Ovarian & Colorectal Cancers** (Jul 30/08)

Recent studies reveal green tea's benefits as an antioxidant, promoter of glucose tolerance, protector of the liver and detoxification system, and benefactor of the cardiovascular system.

Two recent studies show that green tea is also a powerful agent in the prevention and cure of cancers. Specifically, a study from Cancer Biology and Therapy, researchers from the Fourth Military Medical University in Xian China, reported progress in identifying the underlying mechanism by which green tea possesses therapeutic cancer effects through induction of cell death in colorectal cancer. Two different lines of colorectal cancer cells were treated with different concentrations of green tea, which led to repression of cell proliferation and induction of cell death in both cell lines. The results suggest that green tea may be a factor for inducing cell death in colorectal cells, thereby acting as both a preventative and a factor in the cure for this cancer.

*Green-tea-facts.blogspot.com/2008/07/Green-tea-can-reduce-ovarian-and-colorectal-cancers*

### **13. Marinating Meat Can Reduce Carcinogens From Grilling** (Aug 3/08)

Research that appears in the Journal of Food Science is suggesting that marinating meat before grilling can reduce some carcinogens that are connected with colon polyps and cancer and this research emanated from Kansas State University. Food technology researchers marinated round steaks in three different commercial marinade mixes containing different spice blends including Caribbean, southwest, and herb. They then grilled the steaks at 400 degrees F. Grilling meat at high heat produces heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), both of which have been associated with an increase in CRC polyps (adenomas). The Caribbean spice mixture reduced the level of HCAs by 88%, the herb marinade by 72%, and the southwest by 57%. HCAs were reduced due to the presence of antioxidants in the marinades, the highest levels of which were found in the Caribbean mix (ie herbs such as rosemary, oregano, and sage). Marinades are therefore recommended before grilling meat to reduce the production of carcinogens.

*Smith, J.S., et al., Journal of Food Science, Vol 73, No 6, Jul 14, 2008.*

### **14. Growth Inhibition of Human Colon Cancer Cells by Plant Compounds** (Aug 1/08)

Current treatments for colon cancer are not always totally effective in all patients. In addition, these treatments, (chemotherapy, surgery, and radiation) are frequently toxic to normal host cells. Many plant-derived phytochemicals have been shown to be beneficial to human health. In the present study, researchers sought to determine the effect of 3 phytochemicals on colorectal cancer cell growth. Cinnamaldehyde is a naturally occurring product found in the bark of cinnamon trees; piperine is a compound found in black pepper; and resveratrol, an anti-carcinogenic found in red grapes and peanuts. Their anti-proliferative effects were analyzed using a colon cancer cell line, DLD-1. The rationale of the study was that if phytochemicals exert inhibitory effects on cancer cell proliferation, then foods rich in these agents will help prevent colorectal cancer. **The results in the current study indicate that anti-proliferative effects on human colon cancer cells were identified for resveratrol, piperine, and cinnamaldehyde.** Hence, researchers suggest that the intake of foods with high levels of these phytochemicals may be a preventive approach to cancer treatment.

*Duesse., Sharon Heuertz, et al., Growth Inhibition of Human Colon Cancer Cells by Plant Compounds, Clin Lab Scienc, 2008; 21(3): 151*

### **15. Dietary Patterns As Identified by Factor Analysis & Colorectal Cancer Among Middle Aged Patients** (Aug 3/08)

Although diet has long been suspected as a contributing factor for colorectal cancer, studies of single foods and nutrients have provided inconsistent results. The current study looked at associations between dietary patterns and colorectal cancer in middle aged Americans. Three primary dietary patterns were identified: a fruit and vegetables diet, a diet foods, and a red meat and potatoes pattern. 2151 incident cases were examined between men and women. Men with high scores on the fruit and vegetable pattern were at decreased risk. Both men and women had a similar risk reduction with high scores on the diet food factor. And high scores on the red meat factor were associated with increased risk for men and women. The results suggest that dietary patterns characterized by a low frequency of meat and potato consumption and frequent consumption of fruit and vegetables and fat-reduced foods are consistent with a decreased risk of CRC.

*Flood, Andrew, et al., Dietary Patterns as identified by factor analysis and colorectal cancer among middle-aged Americans. American Journal of Clinical Nutrition. Vol 88, No 1, 176-184*

## 16. Exercise Lowers Risk of Colon Cancer (Aug 6/08)

Physical activity can reduce the risk of colon cancer, but not all doctors are informing patients of this simple preventive approach. A sedentary lifestyle accounts for as many as 14% of all colon cancer cases in the US. People who get lots of exercise have a 30% to 40% lower risk of developing colon cancer, according to this current study performed at Fox Chase Cancer center in Cheltenham, PA. Several factors may contribute to the lack of knowledge about the link between exercise and colon cancer risk. Patients may not be learning the information from their health-care providers and information regarding colon cancer prevention is not as well publicized as it could be. Sedentary people can greatly benefit from starting a modest exercise program, such as gardening or walking 2-3 hours a week and then gradually increase the goal.

[www.health.usnews.com/articles/health/healthday/2008/08/06](http://www.health.usnews.com/articles/health/healthday/2008/08/06)

## 17. Vitamin C Shows Promise as Cancer Treatment (Aug 6/08)

New research with mice suggests that intravenous doses of vitamin C could one day reduce the size of cancerous tumours in people. It's not necessarily being recommended as a cure, but may one day likely be used in combination with other drugs. Vitamin C has long been one of the most respected of all vitamins, lauded for its supposed powers to treat many ills, from colds to heart disease. The late scientist Dr. Linus Pauling increased the vitamin's profile by touting it as a cancer treatment. But getting heavy doses of vitamin C into the body is a challenge, though it's virtually impossible for people to overdose on vitamin C since the body only ingests a certain amount through the mouth and then stops allowing it to build up. Researchers have found that they can disrupt the body's tight control over vitamin C levels by giving the nutrient intravenously and bypassing the digestive system. In this study, researchers found that intravenous vitamin C produced hydrogen peroxide, which proceeded to reduce cancerous tumours in the mice by 43% to 51% and **normal cells are unharmed by the therapy**. Furthermore, researchers, claim that it is possible to boost levels of vitamin C in humans to the levels used in the mice but caution that the treatment isn't ready for prime time with humans.

*Mark Levine, MD, chief, Molecular and Clinical Nutrition Section, and senior staff physician, US National Institutes of Health, Bethesda, MD.' Len Lichtenfeld, MD., Deputy chief Medical Officer, American Cancer Society, Atlanta; Aug 4-8, 2008, Proceedings of the National Academy of Sciences*

## 18. Higher Plasma Folate Associated with Lower Colorectal Cancer Mortality (Aug 8/08)

In a study that was undertaken to address concerns that folic acid supplements promote tumor growth in patients with a history of crc, researchers found that in fact higher plasma folate levels are associated with a lower risk of crc-specific and overall mortality. High levels of plasma folate, such as those that can be seen with supplementation, did not appear to be harmful among the participants in the study. Using data from participants in two prospective cohort studies, researchers analyzed the influence of prediagnostic levels of plasma folate on patients diagnosed with colorectal cancer. According to their report in the July 1 of J of Clinical Oncology, patients with plasma folate levels in the top quintile had a 58% lower risk of colorectal cancer-specific mortality and a 54% lower risk of overall mortality compared with patients having plasma folate levels in the bottom quintile, the authors report. Instead of a harmful effect, a statistically significant inverse relationship was observed between plasma folate and the risk of crc specific and overall mortality.

*Wolpin, Brian, M., et al., Higher Plasma Folate Associated with Lower Colorectal Cancer Mortality, J Clin Oncol, 2008; 26: 3222-3228*