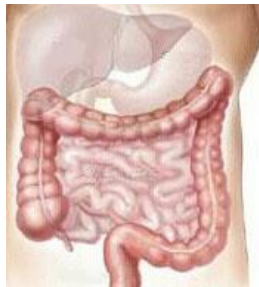


## COLORECTAL CANCER RESEARCH UPDATES

Month Ending May 18th, 2017



The following colorectal cancer research update extends from March 17<sup>th</sup> to May 18th, 2017 inclusive and is intended for informational purposes only.

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#### **DRUGS / SYSTEMIC THERAPIES**

1. Dual HER2 targeting of HER2-positive metastatic colorectal cancer shows clinical benefit

The final results from the phase II HERACLES-A trial demonstrated positive results among patients who normally did not respond well to any available therapies for HER2-positive metastatic colorectal cancer (mCRC). The combination of trastuzumab (Herceptin) and lapatinib (Tykerb) achieved clinical benefit in 70% of patients and an overall response rate of 30%. Trastuzumab is an anti-HER2 antibody and Lapatinib blocks EGFR and HER2 expression. While HER2-positive patients make up only 3% of all CRCs, with the projected CRC incidence in 2035 believed to be 2.4 million, about 70,000 patients will have HER2-positive CRC by that time. The HERACLES-A researchers aimed to identify treatment targets in mCRC by investigating biomarkers or molecular indicators in the genome that suggested the presence of mCRC. Using CRC mouse models, the researchers treated mice with the standard treatment of cetuximab (anti-EGFR antibody) and

then studied the gene environment in non-responsive cases. Among mouse models that demonstrated amplified levels of the HER2 gene (at least 50% of the tumour cells overexpressing the HER2 gene), researchers found that they were sensitive to blockade by lapatinib plus trastuzumab but not to either drug alone. Disease control was achieved among 70% of patients, 30% of patients achieved objective response, and 6% had a complete response. With respect to other third-line therapies (therapies that are given when both initial treatment (first-line) and subsequent treatment (second-line) do not work or stop working), the combination therapy did almost as well as immunotherapy (30% and 35% overall response rates, respectively). The combination therapy well exceeded response rates of 15% for anti-EGFR therapy, 12% for anti-BRAF combinations and 5% for chemotherapy as third-line treatment options. Researchers found that when the tumour is truly “addicted” to HER2, i.e. HER2 expression is very high among tumour cells, radiology scans demonstrated impressive and long-lasting responses to the lapatinib plus trastuzumab therapy. The drug combination was well-tolerated, with low rates of grade 3 toxicity and no patients were forced to stop treatment due to adverse effects.

<http://www.ascopost.com/issues/april-25-2017/dual-her2-targeting-of-her2-positive-metastatic-colorectal-cancer-shows-clinical-benefit/>

## **2. Reducing debilitating symptoms of advanced colorectal cancer (March 25/17)**

MABp1 is an antibody that targets interleukin 1 (a signalling molecule involved in the production of inflammation) and is involved in antitumour activity. A recent phase III trial demonstrated that treatment with MABp1 was linked to improvements in stabilizing and improving lean body mass (body mass that is not fat, i.e. muscle, bones, organs) and debilitating symptoms in patients with advanced colorectal cancer (CRC). 333 patients from outpatient clinics in Europe and Russia were randomly assigned to receive intravenous MABp1 every 2 weeks for 8 weeks. Patients had metastatic or unresectable CRC, systemic inflammation, weight loss and other CRC-related conditions that were associated with a poor prognosis. Their CRC was also resistant to standard chemotherapy treatments of oxaliplatin and irinotecan. The primary endpoint was a stable or increased lean body mass and improvement in at least two of the three symptoms of fatigue, pain and anorexia at week 8 compared to pre-treatment conditions. Primary endpoint was reached in 33% of patients who received MABp1 compared to 19% of patients in the non-treatment group. Stable or improved lean body mass occurred in 51% vs. 45%, stable or improved symptoms occurred in 45% vs. 44% for pain, 45% vs. 45% for fatigue and 55% vs. 48% for anorexia for the treatment group and non-treatment group, respectively. After 8 weeks of treatment, 17% vs. 12% of patients experienced stable disease and median overall survival was 6.1 months in the MABp1 group compared to 2.4 months in the non-treatment group. The most common grade 3 or 4 adverse events in the MABp1 group were anemia, increased alkaline phosphatase (indicator of damaged liver cells and liver conditions), fatigue and increased aspartate transaminase (indicator of liver or other organ damage). Serious adverse events occurred in 23% vs. 32%, among the treatment and non-treatment group respectively. These results suggest that MABp1 represents a promising new strategy in the management of advanced CRC.

<http://www.ascopost.com/issues/march-25-2017/reducing-debilitating-symptoms-of-advanced-colorectal-cancer/>

## **3. Novel immunotherapeutic vaccine studied in colorectal cancer (March 25/17)**

A study presented at the 2017 Clinical Immuno-Oncology Symposium reported that a combination of low-dose cyclophosphamide and an experimental vaccine induced highly beneficial antitumour immune responses, resulting in significant survival benefits among late-stage colorectal cancer (CRC) patients without major adverse effects. It was found that low-dose cyclophosphamide alone produced strong antitumor immune responses that were linked to longer cancer remission. The experimental vaccine combines 5T4, an antigen or marker found on 90% of CRCs with a highly weakened strain of the vaccinia virus Ankara. The researchers used low-dose cyclophosphamide to stimulate an immune response by blocking the regulatory T cells which are responsible for downregulating the immune response. Study participants who experienced the greatest reduction in regulatory T cells after cyclophosphamide treatment had a disease progression-free survival advantage. In the study, vaccination with the 5T4 CRC antigen induced a more than double increase in the subsequent immune response, and patients experienced a significant prolonged median progression-free survival compared to the non-treatment group (5.6 vs. 2.4 months) and overall survival (20.0 vs. 11.2 months). It was observed that while cyclophosphamide can boost immune response to the vaccine, the combination of the low-dose cyclophosphamide and the vaccine was not significantly superior to either agent alone. Researchers emphasize that patients undergoing no treatment was by far the most detrimental factor, and low-dose cyclophosphamide with or without the vaccine produced better survival rates in late-stage, previously treated CRC.

<http://www.ascopost.com/issues/march-25-2017/novel-immunotherapeutic-vaccine-studied-in-colorectal-cancer/>

## **4. Hepatic Artery Infusion Pump (HAIP) Chemotherapy Program – Sunnybrook Odette Cancer Centre (May 2017)**

The HAIP program is a first-in-Canada for individuals where colon or rectal cancer (colorectal cancer) has spread to the liver and cannot be removed with surgery. The program involves a coordinated, multidisciplinary team approach to care, with close collaboration across surgical oncology, medical oncology

(chemotherapy), interventional radiology, nuclear medicine, and oncology nursing. The Hepatic Artery Infusion Pump (HAIP) is a small, disc-shaped device that is surgically implanted just below the skin of the patient, and is connected via a catheter to the hepatic (main) artery of the liver. About 95 percent of the chemotherapy that is directed through this pump stays in the liver, sparing the rest of the body from side effects. Patients receive HAIP-directed chemotherapy in addition to regular intravenous (IV) chemotherapy (systemic chemotherapy), to reduce the number and size of tumours.



Presently at Sunnybrook Odette Cancer Centre, HAIP is only being used in patients with colorectal cancer that has spread to the liver that cannot be removed surgically, and has not spread to anywhere else in the body. Patients who have few (1-5) and very small tumors in the lungs may be considered if the lung disease is deemed treatable prior to HAIP. If you believe you may benefit from this therapy and/or would like to learn more about the clinical trial, your medical oncologist or surgeon may fax a referral to **416-480-6179**.

<http://sunnybrook.ca/content/?page=colorectal-colon-bowel-haip-chemotherapy>

### **5. Chemo pump implant after resecting colorectal liver metastases improves survival (May 8/17)**

A new study shows that adjuvant chemotherapy directly delivered to the liver via the implanted hepatic artery infusion (HAI) pump is associated with improved survival among colorectal cancer (CRC) patients following a complete resection of liver metastases. In the study, the use of HAI chemotherapy in CRC patients given with adjuvant systemic chemotherapy was associated with an overall survival of 2 years longer than patients receiving adjuvant systemic chemotherapy alone. The HAI pump uses the hepatic artery (the major artery supplying the liver) to deliver drugs at a stronger dose to the organ without causing toxicity to the rest of the body. To date, HAI chemotherapy has not been widely accepted despite studies suggesting that it does improve survival following liver resection. In the study, patients who received HAI chemotherapy had more advanced disease compared to patients who did not receive HAI chemotherapy. Nonetheless, it was found that patients receiving HAI chemotherapy achieved a greater median overall survival than patients who did not receive the treatment. Both 5-year and 10-year overall survival rates were significantly greater among those who received HAI chemotherapy. Researchers state that this is the first study to demonstrate adequate numbers of patients with dramatically improved outcomes with adjuvant HAI chemotherapy, with the inclusion of 10-year overall survival which basically equates with cure in this patient population (10-year survival was 38% in patients treated with HAI chemotherapy vs. 24% in patients not treated with the therapy). Researchers note that applying the study results in a practical setting remains a challenge, as HAI chemotherapy requires expertise in hepatobiliary surgery, medical oncology, interventional radiology, nuclear medicine and nursing.

<http://www.medscape.com/viewarticle/879602>

## **SURGICAL THERAPIES**

### **6. Stents effective as bridge to surgery for left-sided malignant colon obstruction (April 19/17)**

According to a recent systematic review, stents can be an effective tool to permit surgery among patients with obstruction in their left-sided colon. In cases of left-sided malignant obstruction of the colon, emergency surgery is risky and complicated by a high rate of anastomotic leakage, or opening of the surgical wound in the intestine (up to 33% leakage rate). Self-expandable metallic stents (SEMS) have been used in these cases, but their clinical effectiveness has not been convincing. To determine whether stents as bridge to surgery (SBTS) provides any clinically relevant advantage over emergency surgery in the treatment of left-sided colonic obstruction, researchers examined data from 251 patients in the SBTS group and 246 in the emergency surgery group. Overall mortality at 60 days was 9.6% in the SBTS group and 9.9% in the emergency surgery group. Overall morbidity, or conditions of the disease, was significantly improved (33.9%) compared to the emergency surgery group (51.2%). Tumour recurrence rates were reported in only 4 of the studies examined, and were non-significantly higher in the SBTS group than in the emergency surgery group (40.5% vs. 26.6%). In contrast to this study, Korean researchers recently compared colonic stenting with complete removal of the colon for obstructive left colon cancer. They found that a complete removal of the colon is a clinically safer, one stage, surgical strategy compared to SEMS as a bridge to surgery. The researchers report that technical failure rate of SBTS remains high, up to 30-50%. They urge patients who are considering SBTS to consider its clinical and oncologic consequences.

<http://www.medscape.com/viewarticle/878769>

## **SCREENING**



## **7. Germline cancer susceptibility mutations in early-onset colorectal cancer (March 10/17)**

A recent study in JAMA Oncology found that 16% of patients with early-onset colorectal cancer (CRC) had particular mutations in their genes that predisposed them to the disease. 450 patients with early-onset CRC (i.e. diagnosed with the disease at age <50 years) were involved in the study from January 2013 to January 2016. The patients were assessed for mismatch repair deficiency, and their genomic DNA was examined for 25 different known mutations. Mismatch repair deficiency is a syndrome which predisposes someone to mutations throughout the genome and especially in regions of DNA known as microsatellites, giving rise to the phenomenon of microsatellite instability (MSI). Overall, 75 mutations were found in 72 patients, or 16% of the patients. 10.7% of patients had mismatch repair-deficient tumours, and 83.3% had at least 1 gene mutation. A total of 402 patients (89.3%) had mismatch repair-proficient tumours, with 32 (8%) with at least 1 mutation. Researchers found that 33.3% of patients who tested positive for mutations did not meet established genetic testing criteria for the gene with the mutations. The researchers concluded that given the high frequency and wide spectrum of mutations, genetic counselling and multigene screening could be considered for all patients with early-onset CRC.

<http://www.ascopost.com/issues/march-10-2017/germline-cancer-susceptibility-mutations-in-early-onset-colorectal-cancer/>

## **8. Patients with positive fecal screening test, sooner is better for colonoscopy (April 25/17)**

A recent study revealed that the risk of colorectal cancer (CRC) increased dramatically when colonoscopy was delayed by more than nine months after a positive fecal screening test. The study evidence strongly supports that a colonoscopy should be performed within a few months following a positive fecal test. The fecal immunochemical test or FIT, detects microscopic amounts of blood in the stool which can be an early sign of CRC. If blood is found, a colonoscopy is performed to detect and remove cancerous or pre-cancerous polyps before symptoms arise. The study followed 70,124 individuals in California between the age of 50 and 75 years with an average risk for CRC who had a positive FIT result. 40% of individuals received follow-up colonoscopies within one month, 64% within two months and 74% within three months. No significant differences in risk for any CRC or advanced cancer with colonoscopy follow-up times of two, three, four, six, seven or nine months. By ten to twelve months, however, the risk of any CRC increased by about 50% and the risk of an advanced cancer almost doubled. Waiting longer than 12 months conferred twice the risk for any CRC and triple the risk for an advanced cancer. Physicians realize that it can be a lot of effort for patients to arrange a colonoscopy, including taking the time off work and having someone accompany them. The study reinforces that while the colonoscopy should be done as soon as it is possible, it is reasonably safe to get one within a few months following a positive FIT result.

<https://www.sciencedaily.com/releases/2017/04/170425110811.htm>

## **9. Single-cell analysis reveals subtypes of colorectal tumours (March 20/17)**

Advances in tumour gene sequencing have improved how tumour subtypes are classified, allowing for more precise cancer treatments and improved patient outcomes. Beyond specific genetic mutations, however, tumours typically contain a variety of cancerous and noncancerous cells that are also important contributors to the unique tumour makeup. The most up-to-date technologies enable scientists to dissect tumours based on their cellular composition and further divide tumours into subgroups. Each of these subgroups has a different survival probability, and such cell-type classification of tumours can help oncologists predict disease outcomes more accurately and suggest treatment options that are better tailored to the patient's unique disease. Researchers at the National Cancer Centre Singapore led a study that screened 626 randomly selected individual cells from colorectal tumours and adjacent normal cell samples via single-cell RNA sequencing. The messenger RNA record of each cell was examined and researchers were able to identify two distinct subtypes of cancer-associated cells (cancer-associated fibroblasts or CAFs). These cells are associated with cancer cells' ability to metastasize, suggesting that their presence contributes to a worse prognosis in colorectal cancer patients. Researchers suggest that these findings show promise for more refined classification of colorectal and other tumours in the future.

<https://www.sciencedaily.com/releases/2017/03/170320143818.htm>

## **10. New alternative to colonoscopy is as easy as swallowing a pill (March 15/17)**

Loyola Medicine's digestive health program in the Chicago area has designed the PillCam™ Colon 2, which is a capsule containing two miniature cameras on each end. As the capsule makes its way through the digestive tract, it takes pictures and wirelessly transmits them to a recorder that the patient wears on a belt. Like a colonoscopy, the system can help to identify cancerous and pre-cancerous growths in the intestine. A standard colonoscopy is safe and has been proven to be the gold standard for colorectal cancer (CRC) screening. The procedure, however, is not well-tolerated by all patients. With the PillCam, the patient swallows the pill with water. After the capsule is excreted from the body, it is flushed down the toilet. The patient returns the recorder belt to the doctor and if a polyp is found, the patient arranges a colonoscopy for its removal. To date, the video capsule system is the only alternative screening method that is comparable to the colonoscopy in its ability to directly visualize the polyps. Early detection of the disease is essential to reducing mortality, and the video capsule provides a convenient and non-invasive method of screening especially for those who are unable to have a regular colonoscopy. Similar to a routine colonoscopy, the

patient must complete the same bowel-cleansing regimen prior to the screening. Unlike a standard colonoscopy, however, the pill system is painless and does not require sedation or anesthesia. Patients also do not have to take time off work or arrange for someone to drive them to and from the procedure. To date, the US Food and Drug Administration has approved the capsule screening system for patients who are poor candidates for colonoscopy due to anatomical difficulties of their colon or due to increased risk of complications due to age, lower gastrointestinal bleeding, or other reasons. Loyola Medicine is currently performing a clinical trial to determine the safety and effectiveness of the capsule system for a wider population of patients who could tolerate a colonoscopy but would rather swallow a capsule.

<https://www.sciencedaily.com/releases/2017/03/170315144501.htm>

### **11. Cancer cells shown to co-opt DNA ‘repair crew’ (May 8/17)**

A new study uncovered a link between chronic inflammation and epigenetic factors that influence cancer cells’ ability to metastasize. Scientists focused their attention on a protein known as CHD4, which is associated with DNA damage repair. A series of experiments were designed to determine the mechanism behind CHD4’s DNA repair. Human colon cancer cells were first exposed to hydrogen peroxide, which damages DNA in a way that resembles the inflammatory process. It was observed that within minutes of DNA exposure to hydrogen peroxide, CHD4 was present and was quickly accompanied by a “repair crew” of proteins that rapidly attached methyl groups to genes in order to silence or turn them off. In the next experiment, a laser beam was used to cause DNA damage in the colon cancer cell lines and again, CHD4 and its crew of repair proteins were quick to arrive at the sites of damage. When the scientists blocked the production of CHD4 in the colon cancer cells, the repair crew proteins never arrived at the damage sites, suggesting that CHD4 is crucial in initiating the repair process.

The repair mechanism exists in order to turn off specific genes in damaged regions while the DNA is being repaired. The scientists noticed that the repair team, however, sometimes kept certain genes turned off even after the DNA repair is completed, and that the types of genes that were kept silenced were linked to cancer. Indeed, the research team found that 8 genes most likely to be methylated and therefore silenced in colon cancer cells are potential tumour suppressors. It was found that these genes were already enriched with CHD4 protein, and when these cells were prevented from making CHD4, the 8 tumour suppressor genes lost their methylation and became reactivated, producing proteins that prevented the spread of cancer cells.

The researchers also performed a set of experiments to examine the behaviour of colon cancer cells with high CHD4 and genetically modified cells with reduced levels of the protein. It was found that in colon cancer cells with high expression of CHD4, the cells were able to easily migrate and penetrate other cell membranes to create new tumours, indicating high metastatic abilities. On the other hand, cells in which CHD4 was deactivated, no such metastatic abilities were observed. Researchers concluded that CHD4 and the resulting methylation is an important event that is associated with the cause of colon cancers and likely other cancers as well. They suggest that further research to reduce the amount of CHD4 in tumours could aid in the better understanding of cancer recurrence.

<https://www.sciencedaily.com/releases/2017/05/170508140746.htm>

## **NUTRITION/ HEALTHY LIFESTYLE**

### **12. Moderate activity may improve overall and progression-free survival in patients with metastatic colorectal cancer (March 25/17)**

The CALGB/SWOG 80405 trial is the first study that demonstrates a clear association between physical activity and survival in metastatic colorectal cancer (mCRC). Patients who engaged in at least 5 hours of non-vigorous physical activity per week had a 25% reduction in mortality from any cause. Walking 4 or more hours per week was associated with a 20% improvement in mortality from any cause. In the study, it was observed that greater walking duration but not walking pace were associated with improved overall survival among patients with mCRC. These associations remained statistically significant even after adjusting for other predictors. While researchers indicate that exercise is not a substitute for chemotherapy, it can significantly improve benefits to patients with as little as 30 minutes per day. The study reinforces the fact that even a small amount of exercise can improve survival in patients, regardless of the stage of their disease.



Image from: <http://www.dailymail.co.uk/health/article-2773365/Walking-superfood-fitness-experts-say.html>

### **13. Rice bran, bean powder might reduce colorectal cancer risk (April 7/17)**

New research presented at the American Association for Cancer Research (AACR) 2017 annual meeting suggests that increased daily intake of dietary fibre through the addition of rice bran and navy bean powder alters gut bacteria in a way that might be protective against colorectal cancer (CRC). Dietary rice bran and navy beans are foods that contain high dietary fibre and other phytochemicals that have been shown to inhibit colon cancer development in animal and human studies. A pilot project part of the Beans/Bran Enriching Nutritional Eating for Intestinal Health trials (BENEFIT) trial aims to boost community knowledge about the benefits of simple foods on gut health. 29 CRC survivors were recruited for the study and randomly selected to receive either 4 weeks of a diet containing 30g of rice bran and 35g of navy bean powder per day or a control diet without these foods. Significant increases in various species of bacteria and overall increases in bacterial richness and diversity were detected in the stool microbiota of participants assigned to the fibre-supplemented diet compared to those on the control diet. Through examination of plasma, urine and stool substances, numerous microbial, host and diet-derived metabolites or breakdown products such as fatty acids, amino acids, bile acids and small molecular by-products of carbohydrate metabolism were found in greater quantities in the supplemented group compared to the control group. When CRC cells were exposed to these metabolic extracts 4 weeks after participants had received the supplemented diet, cellular growth was diminished. Despite the protective effect that the supplemented diet appears to confer against CRC, how to convince people to eat sufficient amounts of these foods on a daily basis remains a challenge. Researchers suggest that just as you need to take a specific dose of a drug in order to see the benefits, you need to reach intake levels and consume increased amounts of these foods in order to reap the cancer protective effects.

<http://www.medscape.com/viewarticle/878333>

## **OTHER**

### **14. Expect questions about colorectal cancer among younger adults (April 10/17)**

Recent studies have pointed to a sharp increase in colorectal cancer (CRC) among young people, even among those in their 20s. Among people aged 20-39, CRC rates have increased 1% to 2.4%, and rectal cancer rates have increased 3.2% per year. Physicians are stressing the importance of both the patient's and the physician's responsibility to be on high alert to CRC symptoms. The American Cancer Society states that "many of the symptoms of CRC can also be caused by something that isn't cancer, such as infection, haemorrhoids, irritable bowel syndrome, or inflammatory bowel disease". Due to the increasing incidence of CRC among young people, it is necessary to raise the suspicion that a symptom could indicate CRC and should not be dismissed merely because a patient is young.

<http://www.ascopost.com/issues/april-10-2017/expect-questions-about-colorectal-cancer-among-younger-adults/>

### **15. Olfactory receptors: new molecular targets detected in colorectal cancer cells (March 23/17)**

Researchers have detected the olfactory (related to the sense of smell) receptor OR51B4 in tumour cells extracted from rectal and colon cancer cell lines. They examined which odor molecule activates the receptor, and in what way the activation affects the tumour cells. The florally-scented molecule troenan was identified as an activator of the olfactory receptor OR51B4. The researchers treated cancerous cells and colorectal tumour tissue samples with the troenan molecule. They discovered that the activation of this receptor caused cell proliferation to slow down and the cancer cells were observed to move far more slowly than before, suggesting that the activation of the receptor induced inhibition of tumour growth and metastasis. The experiments were later performed in mice models with the same results. Researchers suggest that the study results may open a new approach to colorectal cancer therapy, where troenan could be orally or rectally administered to the inner cavity of the intestine to reach colorectal tumours in effective concentrations to elicit an anti-tumour effect. Clinical trials in humans will be necessary to further examine this potential new approach to colorectal therapy.

<https://www.sciencedaily.com/releases/2017/03/170323141329.htm>

### **16. Long-term antibiotic use in early to midlife linked to colorectal adenomas later (April 5/17)**

A new study published in *Gut* journal suggests that antibiotic exposure in early to midlife may increase one's risk for colorectal adenoma (the precursor for the majority of colorectal cancer (CRC)) after 60 years of age. Researchers evaluated data on antibiotic use and subsequent disease outcomes from 16,642 women 60 years or older who had undergone at least one colonoscopy. The researchers found 1195 cases of adenomas and found that women who used antibiotics for 2 months or longer between the ages of 20 and 39 were 36% more likely to develop colorectal adenoma compared to women who did not use antibiotics. It was

found that women who used antibiotics for 2 months or longer between the ages of 40 and 59 years were 69% more likely to develop colorectal adenoma. Recent exposure to antibiotics (within 4 years of their colonoscopy) was not linked to an increased risk for colorectal adenoma. The study is limited in that it does not include information on the types of antibiotics used, nor does it examine these trends in men and other racial or ethnic groups. Indeed, while the role of an altered gut bacterial population remains unclear, the study findings suggest that there is a need to limit the use of antibiotics which appears to be linked to tumour formation in later life.

<http://www.medscape.com/viewarticle/878242>