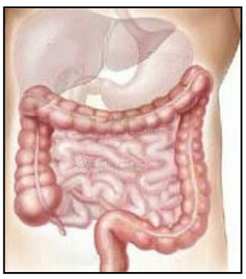
COLORECTAL CANCER RESEARCH UPDATES

Month Ending June 20th, 2014



The following colorectal cancer research update extends from May 24th, 2014 – June 20th, 2014 inclusive and is intended for informational purposes only.

CONTENT

DRUGS / SYSTEMIC THERAPIES

1. Patients With MCRC Respond to New Combination Therapy (May 31/14)

In an aggressive disease known for poor response rates, researchers from The University of Texas MD Anderson Cancer Center found patients with advanced colorectal cancer responded well to a combination therapy of the drugs **vermurafenib, cetuximab and irinotecan**. The phase I trial examines a specific mutation in the ***BRAF gene***, which is present in 5 to 10 percent of colorectal cancer patients. Previous research identified this mutation as a target for therapy, but response rates with single agent vemurafenib were poor, leading researchers to inquire about combining it with different drugs. "Patients with a BRAF mutation in colorectal cancer are recognized for having aggressive disease that doesn't typically respond to standard chemotherapy," said David Hong, M.D., associate professor, Investigational Cancer Therapeutics and lead author. "So when BRAF inhibitors initially started, there was excitement this could become the new standard of care, however we found they didn't work very well." In the trial, researchers combined escalating doses of vermurafenib (V), along with cetuximab (C) and irinotecan (I), two drugs previously used in the treatment of metastatic colorectal cancer. Twelve patients were enrolled at two dose levels including seven at dose level one (V-480 mg, C-250 mg and I-180 mg) and five at dose level two with vemurafenib increased to 720 mg. Radiographic images were evaluated every four cycles over the course of a 14-day cycle of treatment. Patients were assessed for adverse events with the most common including rash, diarrhea and nausea. Of the nine evaluable patients, partial responses or stable disease was seen in all eight patients with colorectal cancer who underwent restaging scans following the beginning of their treatment. The response rate for the eight colorectal patients was 50

percent, whereas response rates with single agent vemurafenib are less than 10 percent. "What's promising is the fact that we're seeing these high response rates in early studies which suggests this could become a new standard of care down the line," Hong said. "There's clearly some kind of synergistic activity with the combination." A U.S. cooperative randomized Phase II trial of this combination in BRAF-mutated colorectal cancer will begin later this summer led by Scott Kopetz, M.D., Ph.D., in Gastrointestinal Medical Oncology who's the senior author on the Phase I study. "While early, the exciting aspect is that we're seeing substantial response rates, but questions remain about the duration of these responses and what the mechanisms of resistance are," Kopetz said. "By expanding on our initial findings and moving to the cooperative group network we'll be able to rapidly perform studies that could lead to getting this combination approved."

University of Texas M. D. Anderson Cancer Center. "Patients with metastatic colon cancer respond to new combination therapy." ScienceDaily. 31 May 2014. www.sciencedaily.com/releases/2014/05/140531132310.htm

2. Avastin and Erbitux Extend Life of Patients With KRAS Wild Type Advanced Colon Cancer (Jun.2/14)

A large independent phase III study (CALGB 80405) designed to assess the superiority in overall survival of erbitux over Avastin when combined with either folfox or folfiri chemotherapy in people with previously untreated, KRAS wild type advanced colon cancer has failed to meet this primary endpoint. Instead the study found both medicines help give patients almost 30 months of extra life. The secondary endpoint of progression free survival was also similar between treatments. The study data addressed the question of which medicine is the most appropriate first line treatment for patients with kras wild type disease and reinforces the role of avastin as an efficacious and valid treatment option for advanced colorectal cancer patients regardless of kras status. Results of the study also highlight the significant progress made in improving outcomes for people with bowel cancer and are important news for the patients diagnosed with the disease every year. Results from the study reinforce that Avastin is helping some patients with advanced colon cancer live longer than ever before. While more than 10 years ago, the average survival for patients with newly diagnosed advanced bowel cancer was little over a year (15 months), median overall survival for patients without mutations in the kras gene (kras wild type patients) treated with avastin in this study was almost two and a half years (29 months). This study reinforces that avastin plus chemotherapy remains an efficacious and valid treatment option for the initial treatment for most patients regardless of biomarker (kras) status.

http://www.news-medical.net/news/20140603/Avastin-and-cetuximab-extend-life-of-patients-with-KRAS-wild-type-advanced-bowel-cancer.aspx

3. Role of Neoadjuvant Oxaliplatin Unclear in Early Rectal Cancer (Jun.3/14)

The role of oxaliplatin in early-stage rectal cancer may still be unclear, according to the differing disease-free survival results from two studies examining its use in preoperative chemoradiotherapy and postoperative chemotherapy regimens presented at the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting. Results of the first study CAO/ARO/AIO-04 trial showed that adding oxaliplatin to 5-FU-based neoadjuvant chemoradiation and adjuvant chemotherapy improved disease-free survival compared with treatment with 5-FU alone. In contrast, Hans-Joachim Schmoll, MD, of Martin Luther University Halle-Wittenburg, Germany, presented the results of an interim analysis of the EORTC-PETACC-6 trial that indicated that adding oxaliplatin to capecitabine plus radiotherapy did not improve disease-free survival compared with capecitabine plus radiotherapy alone. In his discussion of the results of these two studies, Carmen Joseph Allegra, MD, of the University of Florida said that the weight of evidence supports a lack of benefit for the addition of oxaliplatin to fluoropyrimidine-sensitized radiation therapy in the neoadjuvant rectal setting and is not recommended for use in clinical practice. The CAO/ARO/AIO-04 trial included 1,256 patients with clinically-staged T3-4 or any node-positive rectal cancer. Patients were randomly assigned to preoperative 50.4 Gy plus infusional 5-FU followed by total mesorectal excision surgery and 4 cycles of bolus 5-FU (n = 627), or preoperative 50.4 Gy plus infusional 5-FU and oxaliplatin followed by surgery and 8 cycles of oxaliplatin, leucovorin, and infusional 5-FU (n = 613).The primary endpoint was disease-free survival and the median follow-up was 50 months. Seventy-six percent of patients in both arms of the trial started adjuvant chemotherapy. There were 198 disease-free survival events in the 5-FU–alone arm and 159 in the 5-FU/oxaliplatin arm. The 3-year disease-free survival was 71.2% for patients assigned 5-FU alone compared with 75.9% for patients on combination treatment. No significant difference in overall survival was observed at 3 or 5 years. “We showed that a regimen of preoperative 5-FU/oxaliplatin chemoradiation therapy with 1 week chemotherapy gap was well tolerated and associated with a high compliance rate and an increased pathologic complete response rate,” said the study author. In the PETACC-6 trial, 1,094 patients with resectable rectal adenocarcinoma were randomly assigned to preoperative chemoradiation with capecitabine followed by 6 cycles of adjuvant chemotherapy with capecitabine with (537 evaluable patients) or without oxaliplatin (544 evaluable patients) before and after surgery. Only 79% of the patients assigned capecitabine plus radiotherapy and 63% of patients in the oxaliplatin arm started adjuvant chemotherapy. Sixty-nine percent of patients assigned capecitabine alone and 57% of patients assigned the oxaliplatin combination completed the full 6 cycles of treatment.“Interim results at a median follow-up of 2.6 years indicate no disease-free survival benefit for the addition of oxaliplatin to pre- and postoperative capecitabine,” Schmoll said during his presentation. At 3 years, 124 disease-free survival events occurred in the capecitabine alone arm and 121 occurred in the oxaliplatin combination arm. The 3-year disease-free survival in the intent-to-treat population was 74.5% for patients assigned capecitabine and 73.9% for

capecitabine plus oxaliplatin. Looking at the relapse rate at 3 years, the local relapse rate for capecitabine was 7.6% compared with 4.6% for capecitabine plus oxaliplatin; distant relapse was 19.2% for capecitabine compared with 17.6% for capecitabine plus oxaliplatin, both nonsignificant differences. Results were similar for the overall survival analysis as well, with patients assigned capecitabine having a 3-year overall survival of 89.5% compared with 87.4% for patients assigned the combination. Schmoll noted that this interim analysis was early with only 250 out of 440 expected events having occurred. At least 2 more years of follow-up will be needed for the final evaluation

http://www.cancernetwork.com/asco-2014-colorectal-cancer/role-neoadjuvant-oxaliplatin-unclear-early-rectal-cancer

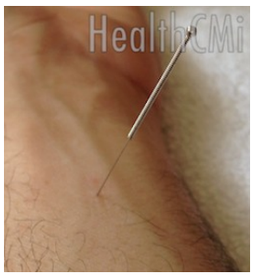
4. New mCRC Drug Combo Meets Phase III Endpoint (Jun.9/14)

Taiho Pharmaceutical Co., parent company of Taiho Oncology, announced recently that its combination drug for refractory metastatic colorectal cancer met its primary endpoint in a phase 3 global RECOURSE trial. The RECOURSE trial of the combined oral drugs trifluridine and tipiracil hydrochloride (TAS-102) is a global, randomized, double blind, placebo-controlled study of 800 people with refractory mcrc. Each participant had received at least two prior failed treatment attempts using standard chemotherapy and received either TAS-102 or placebo to establish the efficacy and toleration of the drug combination and improve overall survival. "We are very pleased by the results from the phase 3 RECOURSE trial in refractory mCRC, which support TAS-102 as a potential new treatment option for this patient population," **Fabio M. Benedetti, MD,** senior vice president and chief medical officer at Taiho Oncology, said in a press release. The company is preparing to submit its findings to regulatory agencies in the US and Europe. More study details will be presented at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer, June 25-28, in Barcelona, Spain.

http://www.healio.com/hematology-oncology/practice-management/news/online/%7Bfbb86e1e-6280-4c70-af7d-730bafbfdacc%7D/new-mcrc-drug-combo-meets-phase-3-endpoint

5. Acupuncture Lowers Chemo Side Effects, Ups Immunity (Jun.11/14)

According to the results of this study, acupuncture reduces chemotherapy side effects for colorectal cancer patients. New research confirms that acupuncture benefits the immune system and improves the psychological state for these patients. Blood samples prove that acupuncture enhances the immune system's NK (natural killer) cells for colorectal cancer patients. Subjective testing showed improved mental health scores after acupuncture. The research team commented that NK cells are "a first line of defence against the metastatic spread of tumour cells." Data shows that decreases in NK cell numbers and activity correspond to the progression of cancer. NK cells are immune system lymphocytes that are part of bodily responses to pathological concerns including tumors and virally infected cells.



Source: ***http://www.healthcmi.com/Acupuncture-Continuing-Education-News/1324-acupuncture-lowers-chemo-side-effects-ups-immunity***

The new study shows that acupuncture benefits NK cell numbers thereby supporting the immune system. The study used a randomized, controlled investigation model. The acupuncture group received acupuncture treatments twice a week starting one week prior to chemotherapy for a total of six acupuncture treatments. A standardized protocol was used in the administration of care. Normally, acupuncture point prescriptions are customized contingent upon an individual's differential diagnosis. In this case, a standard set of acupuncture points were used to eliminate variables. Lower extremity acupuncture points were: LV3, ST36, SP9, GB39. Upper extremity points were LI4, PC5, TB5, LU7. Moxibustion was applied to SI6, TB5, ST32 and CV6 for two minutes at each acupuncture point. Each acupuncture treatment lasted for a total of 45 minutes. Average needle depth was 10mm and manual acupuncture was applied until a de qi sensation was achieved. Disposable acupuncture needles of 36 gauge (Tewa brand) were used. The objective testing revealed benefits to NK cell levels while subjective testing revealed psychological and physical benefits to patients receiving acupuncture. Improvements included reductions of gastrointestinal disorders, urological disorders and male sexual dysfunction. The acupuncture group also reported fewer side effects due to chemotherapy. The acupuncture study group had significantly less depression reported when compared with the control group. The researchers discovered that acupuncture reduced both anxiety and depression and exerted "positive trends on the levels of WBC, ANC, B and NK cells…." In addition, "The increase on WBC and

ANC resulted in approximately a 1.5x reduction in leukopenia and neutropenia rates. The acupuncture group showed a twofold increase in NK cells rate compared to the control group." The team notes that this data indicates that acupuncture exerts an immunomodulatory effect in colorectal cancer patients receiving chemotherapy. No adverse events occurred as a result of acupuncture. As a result, the research team concluded that acupuncture is both "feasible and safe." The team notes that acupuncture may "stimulate anticancer immunity" and "promote a myeliprotective effect." The team notes that this data warrants continued investigation into the integration of acupuncture into colorectal cancer patient care.

Pais, Irene, Nuno Correia, Isabel Pimentel, Maria José Teles, Esmeralda Neves, Júlia Vasconcelos, Judite Guimarães4 Nancy Azevedo et al. "EFFECTS OF ACUPUNCTURE IN LEUKOPENIA, NEUTROPENIA, NK AND B CELLS IN CANCER PATIENTS UNDERGOING CHEMOTHERAPY: A RANDOMIZED PILOT STUDY." Evidence Based Complementary and Alternative Medicine.
http://www.hindawi.com/journals/ecam/aip/217397/

6. Merck to Collaborate with Sysmex Inostics on a Blood-Based RAS Biomarker Test (Mar.19/14)

Merck announced today that the company has signed an agreement to collaborate with Sysmex Inostics in Germany, for the development and commercialization of a **blood-based RAS biomarker** test for patients with metastatic colorectal cancer (mCRC). Blood-based biomarker testing is a faster and easier approach for determining the mutation status of tumors as it requires a small blood sample rather than a tissue biopsy procedure. The test has the potential to provide mutation status results within days, which in turn can help guide treatment decisions. In addition, it may become the method of choice where a tissue biopsy is difficult to obtain, for example in patients whose physical condition does not allow for a surgical procedure. A biomarker test is a simple way of looking at the type and status of particular genes of interest in a cancer. Biomarkers have been found for many different types of cancer such as colorectal, breast and lung cancer, and have an increasingly important role in helping physicians to tailor care and treatment for their patients, known as 'personalized medicine'. RAS - a predictive biomarker - is a group of genes that includes KRAS and NRAS and can be used to help select the most appropriate therapy for each individual mCRC patient. Currently, biomarker testing has been performed with tissue taken directly from the tumor itself, requiring an invasive biopsy, to ensure that the genes from the tumor can be isolated. However, recent technological advances embraced by Sysmex using blood samples allows very small amounts of circulating tumor DNA to be isolated and tested. "In mCRC, RAS has been identified as a key biomarker that can help predict how well mCRC patients may respond to particular treatments, making it important to know their RAS status as early as possible," commented Professor Sabine Tejpar, Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium. "As this test is potentially faster and easier to perform, this could mean quicker and more timely treatment decisions - supporting the ultimate goal of improved outcomes for patients." Approximately half of patients with mCRC have RAS wild-type tumors and half have RAS mutant tumors. Results from studies assessing RAS mutation status in patients with mCRC have shown that anti-epidermal growth factor receptor (EGFR) monoclonal antibody therapies, such as Erbitux(R) (cetuximab), can improve outcomes in patients with RAS wild-type mCRC.

http://www.marketwatch.com/story/merck-to-collaborate-with-sysmex-inostics-on-a-blood-based-ras-biomarker-test-2014-06-11

7. RAS Mutations Ready for Prime Time in mCRC (Jun.12/14)

A multitude of studies presented over the course of the past year have emphasized the importance of broader RAS mutational analyses outside of traditional KRAS testing for patients with metastatic colorectal cancer (mCRC). Until recently, KRAS mutation testing included only exon 2 at codons 12 and 13. However, a better understanding of the pathway and improvements in detection tools demonstrated that mutations in KRAS exon 3 and 4, including NRAS exon 2 and 3, are predictive of response to EGFR inhibitors in CRC. As a result of these findings, the number of patients with CRC who should receive EGFR inhibitors such as erbitux and vectibix has been reduced to approximately **40%** of the total population. "It appears that somewhere only between a third and 25% of patients who seem suitable for EGFR antibodies are receiving them," Alan P. Venook, MD, said in an online discussion. "So my hope would be that we'd be at 40%, which is probably the right percentage of patients, give or take, who should receive it of the total group." The collection of mutational analyses has provided ample evidence to begin utilizing the expanded RAS testing in the community setting. However, putting this new testing strategy into practice requires multidisciplinary collaboration, since pathologists generally order the tests, Marshall pointed out during the online talk. The current reflex for testing is KRAS exon 2 codon 12 and 13 alone, which should be expanded to include KRAS ***exon 3 and 4 and NRAS exon 2 and 3 mutations***, panelists agree. "In my practice, what I've been encouraging physicians to do within our centers, is to go ahead and order the expanded KRAS testing," Johanna Bendell, MD, said during the conversation. "I think what we do know is that from the data we've seen, there's a suggestion that if you treat those patients with KRAS mutation, especially with the expanded KRAS mutation, you could actually do harm to them by treating them with an anti-EGFR inhibitor." Despite the desire to adopt this approach today, future studies are still required to discover the optimal approach to RAS testing. With the increased sensitivity of testing, finite levels of alterations can now be detected. This places further emphasis on the study of functional heterogeneity within the RAS pathway, in order to identify meaningful criteria to use for predicting response to EGFR inhibitors. "I think where confusion comes in is how do we implement this

test. What technologies do we use, because with the standard technologies we can pick up probably 10 out of 100 cells or 20 out of 100 cells. Technology has now become available [that] is now detecting 1 out of 10,000," Lenz notes. "Now, the big clinical question is whether that is the same clinically meaningful mutation data or not." Outside of retesting for patients currently on EGFR inhibitors who were deemed eligible by standard KRAS testing, the appearance of a treatment-related skin rash could indicate whether or not a patient is responding to EGFR inhibition. If a rash has not developed, it may be safe to discontinue therapy or retest using the expanded criteria for patients who were already on EGFR inhibitors before expanded testing was available. "If they have a bad rash I'd probably continue the treatment. If they don't have a rash at all, I might stop it—again, the pharmacodynamics of the rash reflecting some biology," Venook notes. "I'm hoping we can get there with further information, really to drill down."

http://www.onclive.com/publications/oncology-live/2014/may-2014/ras-mutations-ready-for-prime-time-in-mcrc/1

SURGICAL THERAPIES

8. After Colorectal Cancer Spreads, Additional Imaging Adds Little Benefit (May 20/14)

For patients whose colorectal cancer has spread to the liver, and confirmed by computed tomography (CT), further imaging scans **before surgery** added little benefit when compared to patients who did not undergo further imaging. Principal investigators, Carol-Anne Moulton, MB, BS, and Steven Gallinger, MD, of the Ontario Clinical Oncology Group (OCOG) randomly assigned patients with colorectal cancer with surgically-removable metastases based on CT scans to either PET-CT (positron emission tomography) or no further imaging (control) to determine the effect on the surgical management of these patients. "To our knowledge, our study is the largest, based on high-quality imaging and reading of scans, to understand the role of PET-CT in selecting the best colorectal cancer candidates whose cancer has spread to the liver for surgery. We did not anticipate that PET-CT would have such a small impact on hepatic surgery in our patients," said Steven Gallinger, MD, professor of Surgery at the University of Toronto in release. Traditionally, patients with colorectal cancer undergo surgery to remove the cancer, but approximately 50% of patients experience liver metastases. Some patients with liver metastases are candidates for liver surgery, which can lead to long-term survival. However, unidentified metastases outside the liver at the time of surgery can render the operation non-curative and thus futile. Therefore, long-term survival following surgical removal of colorectal cancer liver metastases is relatively low, about 50 percent. The usual practice is to perform a CT scan before surgery to determine the extent of the cancer. PET scans combined with computed tomography (PET-CT) could help avoid non-curative surgery by identifying patients with hidden metastases. "There has been a tendency for expensive imaging tests to be adopted in practice without rigorous evaluation," said Mark Levine, MD, a co-author. Trials such as this one play "an important role to provide the evidence that ultimately helps to inform and change health policy," continued Levine in a release, who is also Professor and Chair of the department of Oncology at McMaster University. The study, conducted between 2005 and 2013, enrolled 404 patients and involved 21 surgeons at nine hospitals in Ontario. Researchers report that the median follow-up was three years. They found no significant difference in survival or disease-free survival between patients in the PET-CT group versus the control group. Of the 263 patients who received PET-CT scans, 159 had no new information on PET-CT; 49 had new abnormal or suspicious lesions on PET-CT and in 62 the PET-CT did not identify the lesion in the liver identified on the baseline CT. Change in management (canceled, more extensive liver surgery, or surgery performed on additional organs) as a result of the PET-CT findings occurred in 8.7% of cases; only 2.7% avoided non-curative liver surgery. ***Overall, liver resection was performed on 91% of patients in the PET-CT group and on 92% of the control group***.

Carol-Anne Moulton, Chu-Shu Gu, Calvin H. Law, Ved R. Tandan, Richard Hart, Douglas Quan, Robert J. Fairfull Smith, Diederick W. Jalink, Mohamed Husien, Pablo E. Serrano, Aaron L. Hendler, Masoom A. Haider, Leyo Ruo, Karen Y. Gulenchyn, Terri Finch, Jim A. Julian, Mark N. Levine, Steven Gallinger. Effect of PET Before Liver Resection on Surgical Management for Colorectal Adenocarcinoma Metastases.* JAMA*, 2014; 311 (18): 1863 DOI: 10.1001/jama.2014.3740

http://www.onclive.com/news/After-Colorectal-Cancer-Spreads-Additional-Imaging-Adds-Little-Benefit-

9. Rectal Cancer Surgery Outcomes Enhanced with Colorectal Surgeons (May 29/14)

A new Mayo Clinic study shows that the type of surgeon and the type of hospital have a significant influence on long-term outcomes for patients who undergo surgery for rectal cancer. The study looked at the characteristics of hospitals where people got their surgery, the surgeons who performed them and how those affect long-term survival. Most surgeries for rectal cancer in the United States are performed by general surgeons. Only a minority of patients have their operation performed by a surgeon with subspecialty training in colorectal surgery. The study found that patients who had surgery from a colorectal specialist had better long-term survival compared with those who had their operation performed by a general surgeon. Those patients who had their operations performed at National Cancer Institute designated Comprehensive Cancer Center also had significantly better outcomes. Researchers

looked at records of more than 6,400 Medicare beneficiaries treated in the U.S. at more than 830 hospitals. The study points out that choices regarding treatment are complicated and are not always directly related to an estimation of outcomes. The geographic distribution of colorectal surgeons and NCI designated hospitals is imperfect -- most are located in large urban centers. Patients who don't live in these areas are faced with a difficult decision, whether to receive care locally or travel to specialist surgeons or specialty hospitals. Study investigator reports: “The upshot of this study is that patients, providers and payers who are interested in better long term outcomes should be directed to surgeons and hospitals with a focused expertise in rectal cancer treatment”.

David A. Etzioni, Tonia M. Young-Fadok, Robert R. Cima, Nabil Wasif, Robert D. Madoff, James M. Naessens, Elizabeth B. Habermann. Patient survival after surgical treatment of rectal cancer: Impact of surgeon and hospital characteristics. **Cancer*, 2014; DOI: 10.1002/cncr.28746***

OTHER

10. Chronic Constipation Ups Colorectal Cancer Risk (May 27/14)

Chronic constipation significantly ups the risk of colorectal cancer over time, new research shows. People with chronic constipation were one and half times more likely to develop colorectal cancer and two and half times more likely to develop benign neoplasms over time compared to people without the condition, the retrospective observational study of almost 30,000 chronic constipation patients and almost 87,000 matched controls found. The risk increased with the level of severity of constipation reported the researchers. The association remained after adjusting for the number of colonoscopies per patient year, the study that analyzed data from a US claims database over one-year.

Guerin, A., et al., Risk of developing colorectal cancer and benign colorectal neoplasm in patients with chronic constipation. Alimentary Pharmacology & Therapeutics. Vol. 40, Issue 1: pp. 83-92.

11. How Streptococcal Bacteria Can be Used to Fight Colon Cancer (May 27/14)

Researchers have shown how the bacteria primarily responsible for causing strep throat can be used to fight colon cancer. By engineering a streptococcal bacterial toxin to attach itself to tumor cells, they are forcing the immune system to recognize and attack the cancer. The study found the engineered bacterial toxin could significantly reduce the size of human colon cancer tumors in mice, with a drastic reduction in the instances of metastasis. Researchers at Western University (London, Canada) have shown how the bacteria primarily responsible for causing strep throat can be used to fight colon cancer. By engineering a streptococcal bacterial toxin to attach itself to tumour cells, they are forcing the immune system to recognize and attack the cancer. The study showed that the engineered bacterial toxin could significantly reduce the size of human colon cancer tumours in mice, with a drastic reduction in the instances of metastasis. By using mouse models that are stripped of their immune system, they were able to create a 'humanized mouse' -- one that would not only grow human colon cancer cells, but would also support a human immune system, to test the anti-cancer immunotherapy. The work was directed by John McCormick, PhD, an Associate Professor in the Department of Microbiology and Immunology and Scientist at the Lawson Health Research Institute. "Our team has been studying these bacterial toxins called 'superantigens' for their role in bacterial infections. But we are now utilizing the power of these toxins to re-direct the immune system to go after cancer cells." McCormick says their research provides important pre-clinical evidence that this may work in humans. "This work represents a 'next-generation immunotoxin' that we hope will eventually lead to a new class of cancer therapeutic." The research was funded by the Canadian Institutes of Health Research. Jennifer Dixon Pittaro, Peter Bastedo, David Hess and Mansour Haeryfar all contributed to the paper entitled "Control of established colon cancer xenografts using a novel humanized single chain antibody-streptococcal superantigen fusion protein targeting the 5T4 oncofetal antigen." McCormick and his colleagues have now received a new grant from the Cancer Research Society to develop different toxin and antibody combinations to fight other types of cancer.

http://www.sciencedaily.com/releases/2014/05/140520120123.htm

NUTRITION & HEALTHY LIFESTYLE

12. Calcium Supplements May Prevent Colorectal Cancer (Apr. 2/14)

Biochemical and epidemiological studies reveal evidence to suggest calcium intake protects against incident colorectal cancer and clinical trials show calcium prevents adenomas, a precursor to colorectal cancer, according to this review. Studies suggest high intake of dietary calcium or supplemental calcium was associat4ed with reduced risk of colorectal cancer. Specifically, each 300 mg of total calcium per day increase was associated with an 8 reduced risk of colorectal cancer. The finding was based on 15 studies of 12,305 cases of colorectal cancer who had 250 to 1,900 mg of calcium per day and were

followed for 3.3 to 16 years. For supplementary calcium, each 300 mg per day increase was correlated with a 9% reduced risk of colorectal cancer. The finding was based on six studies of 8839 cases who had 0 to 1150 mg of calcium per day and were followed for 5 to 10 years. The study concluded "both dietary and supplementary calcium intake may continue to decrease CRC (colorectal cancer) risk beyond 1000 mg/day."

Keum N, et al., Calcium intake and colorectal cancer risk: doe-response meta-analysis of prospective observational studies. International J of Cancer. 2014 Mar 13. 86.

13. Six New Cancer Preventing Nutritional Guidelines (Jun.9/14)

Six dietary guidelines – more aggressive than previous cancer prevention advice - will be unveiled in the June 30 issue of the Journal of the American College of Nutrition. The cancer prevention guidelines, emphasizing a diet rich in plant-based foods, such as soy beans and cruciferous, allium, and carotenoid vegetables, are based on the principle that diet changes are justified, even when evidence on certain issues are up for debate. The recommendations urge the same kind of precautionary approach health experts took against tobacco decades earlier, before smoking bans were enforced, and warn about the association between cancer and alcohol, red and processed meats, dairy products, and carcinogens in well-cooked meats, including beef, poultry, and fish. The key recommendation is to build meals around fruits, vegetables, and legumes. Plant-based foods provide an antioxidant boost and help promote a healthy weight, reducing the risk for all types of cancer in the long run.

The six dietary recommendations to reduce risk of several types of cancer are:

1. Limit or avoid dairy products to reduce the risk of prostate cancer.

Findings: Consuming thirty-five grams of dairy protein each day, the equivalent of one and a half cups of cottage cheese, increases risk of prostate cancer by 32 percent. Drinking two glasses of milk each day increases risk of prostate cancer by 60 percent. Note: Calcium supplements appear to have the same effect as milk intake. Men who supplement with more than 400 milligrams of calcium per day increase risk for fatal prostate cancer by 51 percent.

2. Limit or avoid alcohol to reduce the risk of cancers of the mouth, pharynx, larynx, esophagus, colon, rectum, and breast.

Findings: One drink per week increases risk of mouth, pharynx, and larynx cancers by 24 percent. Two to three drinks per day increase risk of colorectal cancer by 21 percent. Note: The alcohol itself (rather than additives) appears to be the cause of cancer, and all types of alcoholic beverages (wine, beer, and spirits) are problematic.

3. Avoid red and processed meats to reduce the risk of cancers of the colon and rectum.

Findings: Each 50-gram daily serving of processed meat, equivalent to two slices of bacon or one sausage link, increases risk of colorectal cancer by 21 percent. Each 120-gram daily serving of red meat, equivalent to a small steak, increases risk of colorectal cancer by 28 percent. Note: The heme iron, nitrites, heterocyclic amines (HCAs), and overabundance of essential amino acids in red and processed meats are all believed to contribute to cancerous cell growth in the body.

4. Avoid grilled, fried, and broiled meats to reduce the risk of cancers of the colon, rectum, breast, prostate, kidney, and pancreas.

Findings: Four types of heterocyclic amines (HCAs) are associated with cancer of the colon and rectum. HCAs form from creatine and amino acids in cooked skeletal muscle, increasing with higher cooking times and higher temperatures. When ingested, HCAs can disrupt DNA synthesis. Note: In addition to the cancers listed above, HCAs are also associated, to a weaker extent, with cancers of the breast, prostate, kidney, and pancreas.

5. Consume soy products to reduce risk of breast cancer and to reduce the risk of recurrence and mortality for women previously treated for breast cancer.

Findings: Evidence from Asian and Western countries shows that soy products are associated with reduced cancer risk. Chinese women who consume more than 11.3 grams of soy protein, equivalent to half a cup of cooked soybeans, each day during adolescence have a 43 percent reduced risk of premenopausal breast cancer, compared with women who consume 1.7 grams. Research in Shanghai shows that women with breast cancer who consume 11 grams of soy protein each day can reduce mortality and risk of recurrence by about 30 percent. U.S. populations show similar findings: the higher the isoflavone intake from soy products, the less risk of mortality and recurrence in women with breast cancer. Note: When choosing soy products, opt for natural forms, such as edamame, tempeh, or organic tofu, as opposed to soy protein concentrates and isolates, common in powders and pills.

6. Emphasize fruits and vegetables to reduce risk of several common forms of cancer.

Findings: Fruits and vegetables, especially leafy greens, help reduce overall cancer risk. A high intake of cruciferous vegetables, such as broccoli, kale, and cabbage, is associated with an 18 percent reduced risk of colorectal cancer and reduced risk of lung and stomach cancers. Women who consume the most carotenoid-rich vegetables, such as carrots and sweet potatoes, lower their risk of breast cancer by 19 percent. Overall, women who consume the highest quantities of any kind of fruit or vegetable reduce breast cancer risk by 11 percent. A high intake of tomato products has been shown to reduce risk of

gastric cancer by 27 percent. Garlic and other allium vegetables, such as onions, significantly reduce risk for gastric cancer, while a Western diet (high amounts of meat and fat with minimal amounts of fruits and vegetables) doubles the risk. Note: Some components in soybeans, green tea, turmeric, grapes, tomatoes, and other plant foods have the ability to regulate apoptosis (a natural process for destroying unhealthy cells), an important pathway for cancer prevention.

"There's considerable benefit--and no harm--in loading up with plant-based foods," notes study author Susan Levin, M.S., R.D., C.S.S.D., director of nutrition education for the Physicians Committee. "Large bodies of research show fruits, vegetables, and legumes offer a variety of protective properties, so why not move these foods to the center of our plates?"

The World Health Organization states that a significant percentage of cancers can be prevented by following a healthful diet, avoiding tobacco, leading an active lifestyle, and limiting alcohol intake.

Gonzales, Joseph f., et al., Applying the Precautionary Principle to Nutrition and Cancer. J of the Amer College of Nutrition. DOI: 10.1080/07315724.2013.866527. May 28, 2014. Published online ahead of print.