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Cancer Prevention Network

CPN Highlights

Spotlight on Gary Falk, MD, MS!

Inside This Issue

Dr. Gary Falk, University of Pennsylvania, was the PI for the first Barrett's esophagus study conducted by the CPN Consortium, MAY04-4-01, "Randomized, Double-Blinded Phase II Trial of Esomeprazole versus Esomeprazole + Two Doses of Aspirin in Barrett's Esophagus Patients" — better known as "The Falk Study."

Dr. Falk grew up in New York, NY. He completed his undergraduate degree at the University of Rochester in Rochester, NY, and his medical degree at the University of Rochester School of Medicine and Dentistry. His residency training in internal medicine led him to George Washington University Medical Center in Washington, DC, followed by a Clinical Fellowship in Gastroenterology and a Research Fellowship at the University of Michigan Medical Center in Ann Arbor, MI.

The University of Pennsylvania has a translational research team actively involved in Barrett's esophagus translational research with an emphasis on cell of origin. They are funded by the National Institutes of Health (NIH) and have a team of basic scientists who focus on the pathogenesis of Barrett's esophagus and esophageal cancer, multiple postdocs, outstanding interventional endoscopy colleagues and a superb research coordinator. UPenn also has a newly developed Barrett's esophagus registry that is integrated with their cancer center. Their NIH funding includes the U54 BETERNET program with Mayo Clinic and Columbia University, and their grant for the Molecular Studies in Digestive and Liver Diseases and Intestinal Stem Cell Consortium. This provides them with a wonderful collaborative research environment.

On a personal note, Dr. Falk has been married for 29 years to Lynn Shesser, who runs Children's Hospital of Philadelphia (CHOP) homecare programs. Together they have two children: Amy, age 24, who is completing a master's degree in social work at Simmons College in Boston; and David, age 22, who is applying to medical school and will spend his post-graduation year teaching adaptive skiing to people with disabilities at Breckenridge, CO.

In his "free time" (ha) Dr. Falk enjoys playing golf ("badly"), skiing, exercising, visiting his elderly mother on the east end of Long Island, theater, Philadelphia restaurants, and the Philadelphia Orchestra. Dr. Falk and his wife enjoy traveling and have done extensive ecotourism in such places as the Galapagos, Baja California, Tanzania, and South Africa. They also enjoy seeing their two children who "left them with a lonely, empty nest," and reconnecting with friends on the East Coast after almost 30 years in the Midwest.

Dr. Falk also invented the "Falk-O-Meter," a fun tool distributed bi-monthly to participating sites to provide accrual updates. "It was developed to enhance trial recruitment, just like various fundraising campaigns, to give all a sense of where we stood with our study," said Dr. Falk. "I am glad it continues to be used by CPN but cannot take credit!"

The study manuscript, "A Combination of Esomeprazole and Aspirin Reduces Tissue Concentrations of Prostaglandin E2 in Patients with Barrett's Esophagus" was published in *Gastroenterology* in 2012.

Thank you, Dr. Falk, for your many contributions to the CPN Consortium! It is a pleasure to work with you and your team.

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CPN Biospecimens: Team Members at the Heart of the Resource

Among CPN's greatest assets is its collection of biospecimens. CPN studies contain specimen banking components in the hope that the specimens will be used for pre-clinical work crucial to the development of novel chemopreventive strategies. The specimens themselves would be worthless without the careful collection, documentation, labeling, accessioning, and inventory management provided by two individuals—Roxann Neumann, Biospecimens Resource Manager, and Tabitha Hanson, Pathology Quality Assurance Specialist.

Roxann Neumann, RN, BSN, CCRP, grew up on a hobby farm near Stewartville, MN, and currently resides in the Rochester, MN, area. Roxann and her husband, who is a dairy farmer, have been married for 35 years and have four children and six grandchildren. Their oldest son passed away at the age of 25 from complications resulting from an episode of acute viral myocarditis he contracted as an infant.. Although this has been very difficult for Roxann's family, they take comfort in knowing that his death has made a difference in the way Mayo Clinic cares for patients with pacemakers.

Roxann loves to bake, cook, read and crochet. She finds that "working the dough" to make homemade bread, rolls and pasta is a great stress reliever.

Roxann has been at Mayo Clinic for 25 years. Past positions include urology nurse coordinator and project manager for clinical trials and anatomic pathology. She has been in her position with the Biospecimens Accessioning and Processing (BAP) lab for about five years. Her time is split among CPN and other departments. Roxann's duties as Biospecimens Resource Manager include design of blood and tissue collection kits; collaborative writing of lab protocol sections; providing budget information for correlative studies; and assisting sites with specimen collection, shipping and processing questions. Roxann enjoys the fact that no two days are ever the same.

Tabitha Hanson has lived in Rochester, MN, her whole life. She has three children, all living at home, and three grandchildren. Tabitha enjoys fishing, biking, and hiking during her rare free time.

Tabitha has worked at Mayo Clinic for 24 years. Her first job was a unit secretary at Saint Marys Hospital, followed by desk attendant in Neurology and later in Medical Genetics. She joined the Mayo Clinic Cancer Center in 2006 as a Quality Assurance Specialist (QAS) and joined the CPN team about a year ago.

In her role as Pathology Coordinator, Tabitha is responsible for receiving tissue and ensuring its timely delivery to the pathologist for review. She builds the forms for specimen collection, submission and pathology review. She also builds the tissue tracking systems for each clinical trial and accessions specimens as they are received. She makes sure the correct specimens or slides are reviewed and the results reported efficiently and correctly. Tabitha is the go-to person whenever specimens need to be tracked down.

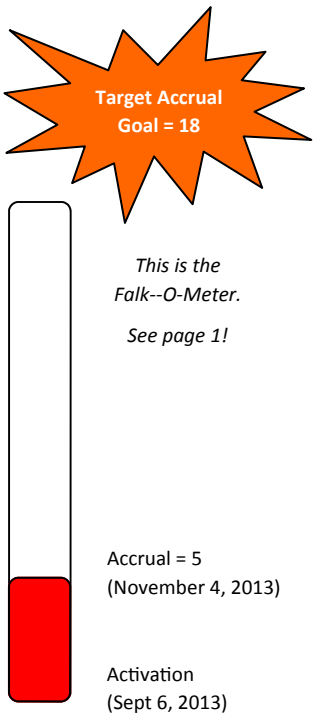
Featured Clinical Trial: MAY2012-00-01

MAY2012-00-01, "Phase 1, Randomized, Placebo-Controlled Trial of Linaclotide to Demonstrate Colorectal Bioactivity in Healthy Volunteers," was originally proposed in 2009 by Dr. David Weinberg, Fox Chase Cancer Center, and Dr. Scott Waldman, Thomas Jefferson University. The study was finally activated in September 2013, after successfully negotiating huge hurdles related to budget, study agent, legal agreements, and logistics. The current study is jointly sponsored and managed by CPN, NCI Division of Cancer Prevention and Ironwood Pharmaceuticals, Inc.

The study agent, linaclotide, is a guanylate cyclase C (GCC) agonist that is FDA-approved for the treatment of irritable bowel syndrome (IBS). Chemically, it is very similar to the hormones guanylin and uroguanylin, which are the most commonly lost gene products in colorectal cancer. If their activity can be replaced, and if linaclotide or its active metabolites can reach and effect the distal colon and rectum, then it may be an effective chemopreventive agent for colorectal cancer.

The current study involves seven days of linaclotide with colon and rectal biopsies pre- and post-intervention; the primary endpoint is pharmacodynamic. Are there detectable changes in cyclic guanosine monophosphate (cGMP) in the colon and rectum that would indicate activation of GCC?

All participants are being enrolled and treated at Thomas Jefferson University. As of early November, five participants had been enrolled and four have completed treatment. Enrollment was halted briefly during the government shutdown.



Feature Article: Cancer Immunoprevention

Asad Umar, DVM, PhD

Cancer immunoprevention or achievement of cancer prevention via immune response modifiers is a combination of strategies for utilizing immunological means such as vaccines, immune modulators or combination of small molecules to achieve a synergy in overall efficacy. Cancer immunoprevention is conceptually different from immunotherapy, which aims at stimulating immunity in patients only after tumor onset, however the same immunological means can be used both in immunoprevention and in immunotherapy. Cancer immunoprevention approaches like vaccines either are prophylactic or therapeutic when targeting the initiating factors like infectious agents (prophylactic vaccines, *e.g.,* HBV/HPV vaccines). Different from other forms of cancer preventive approaches the primary mode of action is to modulate host responses; the host response in turn mediates cancer prevention through a variety of mechanisms. The advantages of cancer immunoprevention are that immune response can be specific in its utmost form and it can be exquisitely targeted. In addition, most immune responses are long-term, well past the time of initial administration.

Vaccines are prominent among the approaches aimed at harnessing an individual's immune system against cancer, showing greater success in cancer prevention than treatment. The preferential success of preventive vaccination is attributable largely to a minimal or tumor burden. In addition, candidates for preventive vaccination still have fully competent immune systems capable of developing robust anti-tumor responses leading to eradication of abnormal cells and/or preventing disease onset and recurrence.

Immunoprevention of Cancers Caused by Viruses

Immunoprevention of tumors caused by viruses or other infectious agents aims at the prevention or cure of infection before the onset of cancer. Effective vaccines are available for human use. Some tumor types in humans and animals are the consequence of viral infections. In humans, the most frequent viral tumors are liver cancer (or hepatocellular carcinoma), which arise in a small proportion of patients with chronic infection by hepatitis B or hepatitis C Virus (HBV or HCV), and carcinoma of the uterine cervix (or cervical cancer), caused by human papilloma virus (HPV). Combined, these two tumors represent approximately 10% of all human cancers, affecting approximately one million new patients each year around the world. Moreover, immunoprevention of tumors caused by infectious agents is already implemented at the population level for HBV-related hepatocellular carcinoma and for tumors caused by HPV, like cervical carcinoma [3]. The HBV vaccine, now in worldwide use, has been shown to reduce the incidence of liver carcinoma. Clinical trials have likewise shown that HPV vaccines can prevent HPV infection and carcinogenesis quite effectively. These results have led to vaccine approval by regulatory agencies, including the FDA in the USA and other agencies in Europe.

Immunoprevention of Cancers Caused by Mutations

Furthermore, the current challenge is to develop immunological strategies to prevent the bulk (>80%) of the human cancer burden, unrelated to infections. Specifically, the challenge is to predict for each individual the risk of specific cancer types and to design immune strategies targeting these cancer types. Both immune response modulators and vaccines against tumor antigens can prevent cancer onset in cancer-prone mice.

Effective immunoprevention of various types of cancer was obtained in murine models of cancer risk, particularly in transgenic mice harboring activated oncogenes. Therefore, it was demonstrated that activation of the immune system in healthy hosts could prevent carcinogenesis. Both non-specific immune stimuli, like cytokines and other immune-stimulators, and vaccines containing a specific antigen were active in these mouse models. Therefore, combinations of both types of agents yielded the best results, up to an almost complete, long-term block of carcinogenesis in models of aggressive cancer development.

Continued……

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Immunoprevention continued from page 3

Similarly, a recent review outlined various studies that identified target antigens and the molecular and cellular mechanisms of cancer immunoprevention[3]. The findings indicated the following:

a. The best target antigens are surface molecules controlling tumor growth and progression (oncoantigens)

b. Combinations of potent vaccines and nonspecific stimuli (adjuvants) yield the strongest protection

c. Immunoprevention must start early in the natural history of tumors, before key progression events like the onset of carcinoma in situ

d. Lifetime protection requires repeated boosts, to maintain a strong and steady immune response;

e. Antibodies and helper, rather than cytotoxic, T cells mediate long-term protection from tumor onset;

f. Immunoprevention can be combined with chemoprevention. The development of agents like tamoxifen, which went from cancer therapy to chemoprevention, could be a model for the translation of cancer immunoprevention from mice to humans.

It is well established that evolution of most tumors occurs in the presence of inflammation even before any tumorigenic alterations are apparent...the tumor cells can be detected and eliminated by immune cells. Therefore, the evidence for the role of immunosuppression in cancer development is even stronger.

What Role Does the Immune System Play in the Control of Tumor Development?

Burnet and Thomas [1] proposed that immune cells like B and T cells recognize and eliminate continuously arising, nascent transformed cells. This ability of immune systems to control tumor development has been termed immunosurveillance. Cancer immunosurveillance might actually be the process that plays a critical role during early carcinogenesis when precancerous lesions spontaneously regress, maintaining a state of homeostasis for normal cells. The concept has been proven empirically, *e.g.,* immunosuppressive states or drugs lead to increased carcinogenesis. Furthermore, details of immunosurveillance indicate that there are distinct phases during carcinogenesis where nascent transformed clones constantly are in play, hence, immunoediting is ongoing, keeping normal and transformed cells in equilibrium until there is an escape from this immunosurveillance and invasion ensues. More recently, Hanahan and Weinberg acknowledged the importance of the immune system in cancer development in 2011, when they added immune evasion to their list of "*hallmark*" abilities that are essential for the transformation of normal into cancerous cells.

How Does Inflammation Support or Suppress the Development of Cancer?

Evidence suggests that the immune system recognizes the tumor cells by the virtue of tumor associated antigens as well as tumor microenvironment modulation due to stromal remodeling through processes like inflammation that is essential for the recruitment of immune system cells to the localized tumor site. As a consequence of inflammation, prostaglandin E_2 (PGE_2) is increased and is well known for its pro-tumorigenic capacity and ability to promote angiogenesis and tumor cell migration[2,3].

What Role Does Immunosuppression Play in the Development of Cancer?

Inflammation and immunosuppressive mechanisms are closely linked to the development of tumors. It is well established that evolution of most tumors occurs in the presence of inflammation even before any tumorigenic alterations are apparent. As outlined above the tumor cells can be detected and eliminated by immune cells. Therefore, the evidence for the role of immunosuppression in cancer development is even stronger. It is believed that many of the escape mechanisms are important for cancer development evidenced by propensity of cancers in immunosuppressed individuals. Similarly, a large number of cancer therapeutic vaccines have failed in the advance stages of cancer, while the same vaccines tested in an early disease burden have shown much better outcome in preclinical settings [4].

Foreign antigens are more likely to elicit a powerful immune response than tumor-antigens from spontaneously occurring cancers, making virally related cancers a better candidate for the use of cancer vaccines. However, even early on in persistent infections, before the development of cancer, there is inhibition of CD8+ T cell responses to viral antigens, resulting in viral immune escape. For example, hepatitis C

infection often becomes chronic, eventually leading to hepatocellular carcinoma in some cases. As in other persistent infections such as HIV, T cells in hepatitis C–infected patients demonstrate markers of exhaustion and decreased activation, such asimpaired cytokine secretion and stimulation of immune checkpoint markers.

Inflammation and downstream bioactive lipids (prostaglandins, and thromboxanes) have also been shown to exhibit immunoinhibitory properties. The immunosuppressive effect of PGE2 includes inhibition of antigen presenting cell maturation (dendritic cells), T cell proliferation and function, as well as the inhibition of pro-inflammatory chemokines and type 1 cytokines. In studies of some cancer patients, negative effects on dendritic cells and T cell function have been correlated with tumor expression of COX_2 and PGE_2 as well as an increase in T_{reg}-mediated suppression[5].

Recently, there is an increased interest in the development of cancer immune modulatory approaches to handle many of the cancers resistant to other intervention. As better understanding in immune surveillance, immune editing and immunosuppressive checkpoints have come into focus, and new immunotherapies have been approved by the FDA. However, significant challenges for effective prevention remain.

Immunologists are discovering that immunosuppressive signaling networks begin early in the progression of cancer. Hence this window of time before cancer has progressed provides an ideal setting for the use of immunotherapy while there is a role for the protective antitumor immune response. As the ability to detect and treat early stage cancers increases, interventions used in combination with traditional cancer preventives or vaccines should include agents that modulate the early suppressive events occurring in cancer development.

Moving forward, we must use other tools in our cancer preventive arsenal where small molecules like NSAIDs have given reasonable efficacy, and imagine combination strategies to induce potent CD8+ T cell responses that turn on mechanisms that more effectively eliminate precancers.

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For More Information:

Hanahan D and Weinberg RA. Hallmarks of Cancer: The Next Generation. Cell 144: 646-674 (2011). doi:10.1016/j.cell.2011.02.013

Limes Are Not So Limey!

Did you know that limes increase in weight after they've been picked? Limes, native to Southeast Asia, have been around since the 10th century when Arab traders introduced them to Egypt and Northern Africa and later to Spain. Columbus introduced limes to the New World where they eventually became the citrus of choice for the British navy; they were cheaper than lemons! A Scottish naval surgeon, Sir James Lind, observed that the dreaded scurvy could be kept at bay with a daily ratio of lime juice along with their daily ration of rum; hence British seamen became known as Limeys.

A Cuban Mojito traditionally is made with five ingredients:

- Rum to taste
- Sugar to taste
- 1/2 cup of lime juice
- 3/4 cup carbonated water
- 1 bunch of mint.

Remove the rum and you have a delicious non-alcoholic Mojito Limeade. The 'limey' combination of citrus lime and mint makes for a refreshing combination!

References

http://homecooking.about.com/od/foodhistory/a/limehistory.htm

http://www.todaysdietitian.com/newarchives/072709p74.shtml

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Cancer Prevention in the Kitchen: Butternut Squash Soup—The Food Network/Barefoot Contessa

Ingredients

- 3 to 4 pounds butternut squash, peeled and seeded
- 2 yellow onions
- 2 McIntosh apples, peeled and cored
- 3 tablespoons good olive oil
- Kosher salt and freshly ground black pepper
- 2 to 4 cups chicken stock, preferably homemade
- 1/2 teaspoon good curry powder

> "Life expectancy would grow by leaps and bounds if green vegetables smelled as good as bacon."
>
> - Doug Larson

Directions

Preheat the oven to 425 degrees F. Cut the butternut squash, onions, and apples into 1-inch cubes. Place them on a sheet pan and toss them with the olive oil, 1 teaspoon salt, and 1/2 teaspoon pepper. Divide the squash mixture between 2 sheet pans and spread in a single layer. Roast for 35 to 45 minutes, tossing occasionally, until very tender.

Meanwhile, heat the chicken stock to a simmer. When the vegetables are done, put them through a food mill fitted with the medium blade. Alternatively, you can place the roasted vegetables in batches in a food processor fitted with the steel blade. Add some of the chicken stock and coarsely puree.

When all of the vegetables are processed, place them in a large pot and add enough chicken stock to make a thick soup. Add the curry powder, 1 teaspoon salt, and 1/2 teaspoon pepper. Taste for seasonings to be sure there's enough salt and pepper to bring out the curry flavor. Reheat and serve hot with condiments either on the side or on top of each serving.

Clinical Trials Updates

In development: Two concepts were approved for development in June of 2013. The first version of the protocols and all related documents were submitted to NCI, DCP on September 30, 2013.
MAY2013-02-01, DNA Vaccine for Chronic Hepatitis C Virus (HCV) Infection. Dr. Jeff Jacobson - Drexel University
MAY2013-02-02, EGFR Inhibition with Erlotinib for the Prevention of Hepatocellular Carcinoma. Dr. Ken Tanabe - Massachusetts General Hospital

Also in development awaiting final approval:
MAY2013-01-01, MUC1 Vaccine in Newly Diagnosed Advanced Adenoma. Dr. Rocky Schoen - University of Pittsburgh

Open and enrolling:
MAY2012-00-01, Linaclotide for Colorectal Bioactivity. Dr. David Weinberg - Fox Chase Cancer Center

Closed, final participants are completing the study:
MAY06-8-01, Myo-Inositol in Smokers with Bronchial Dysplasia. Dr. Stephen Lam - British Columbia Cancer Agency

Closed, manuscripts in process:
MAY10-15-03, Barrett's Esophagus Chemoprevention with Metformin. Dr. Amitabh Chak - University Hospital/Case Medical Center
MAY10-15-02, Pioglitazone as a Pilot Chemoprevention Agent for Lung Cancer. Dr. Dennis Wigle - Mayo Clinic in Rochester

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