While cancer treatments targeting specific mutations are very much in vogue, a U.S. based team has developed an innovative treatment which holds great promise in clinical application.

**Recent Clinical Trials**

Conducted on patients at high risk of colorectal cancer, these trials have reaped landmark findings which could establish a new paradigm in efforts to harness effective methods of preventing colorectal and other cancers. Developments within the field are often marred with questions regarding the safety of new applications and approaches. However, results reported by a team led by Drs Frank Meyskens (University of California, Irvine) and Gene Gerner (University of Arizona) hold genuine hope in alleviating the number of individuals who fall victim to colorectal cancer every year, without inflicting pernicious side effects.

The trials involved administering two drugs, in tandem, to patients with a history of resected colorectal adenoma. The results indicated that the drugs caused a dramatic reduction in the number of polyps and, even more strikingly, an almost complete prevention of the appearance of advanced and multiple adenomas, which are a major precursor and risk factor for the development of colorectal cancer. These promising results mark a seminal demonstration of the clinical validity of the concept of ‘combination chemoprevention’, a form of treatment first postulated as far back as 1980, but which has not, up to this point, been corroborated.

Both drugs used in Meyskens’ trial were first synthesised over 30 years ago. One was synthesised to inhibit a very specific enzyme important in early cancer formation; the other was considered multifunctional but was subsequently found to affect the pathway in a particularly important way, in a manner that markedly enhanced the effect of the first drug.

While Meyskens and his colleagues’ work has yielded remarkable results, their achievements have not sprung from sudden events; rather, their findings have stemmed from dedication, patience and industry in the laboratory. Indeed, the clinical trials were based on extensive animal, in vitro and translational studies, which Meyskens and his collaborators have conducted over the course of the last 20 years.

**Alternative Approach**

Colon cancer is a highly prevalent form of cancer; in the U.S., it is the leading cause of cancer-related death in people under 74 years, and among the population as a whole, is the second most common cause of cancer-related deaths. While there is general consensus among the oncology community that the onset of colorectal cancer can be thwarted by eliminating precursor adenomas found in colonoscopy screening, pharmaceutical intervention had – prior to Meyskens’ results – been very modest. Although diet is often linked to colorectal cancer, a series of clinical trials involving dietary supplements have proven largely ineffective in preventing the incidence or recurrence of colon polyps.

Meyskens was cautious not to overplay the association between colorectal cancer and diet. Instead, his team employed combination chemoprevention strategies in rodent models; this approach illustrated that using two or more drugs in tandem is often more effective in stemming the onset of colorectal cancer.
Dr Frank Meyskens speaks to International Innovation about the development of a revolutionary therapeutic prevention for colorectal cancer, and the encouraging results of associated trials thus far.

What is the overall aim of your project?

The project started around 20 years ago with the aim of preventing colorectal cancer using what we call therapeutic prevention, which has been traditionally known as chemoprevention.

Could you explain the motives behind initially focusing on the high risk populations, and then producing treatments for the wider population? Which groups are you specifically targeting?

Initially, we began with patients at moderate risk. Because the results of the trial were so positive, we were hopeful that a pharmaceutical company would pick it up and run with it. That was not to be, so we decided to set up a company, Cancer Prevention Pharmaceuticals. One trial is focused on individuals with familial adenomatous polyposis, which is driven by the absence of a particular gene, and in which thousands of polyps develop. Previously, most patients would die of cancer before the age of 20; now they live longer due to prophylactic colectomy, usually during the teenage years, and intense surveillance. They have thousands of polyps which develop into cancer. This condition is now our target population; there is only one approved medical treatment for this – Celebrex – which at lower doses is used for management of arthritis. However, its effects in FAP are modest at best and has long-term repercussions in that it increases the risk of cardiovascular disease.

In a larger trial, the second set of patients are individuals with stage I, II or III colon cancer, who have had surgery and, in some cases, chemotherapy. One year later we will randomise them into treatments consisting of a placebo, difluoromethylornithine (DFMO), sulindac, or the combination.

Could you elaborate on the lifestyle recommendations that you will be promoting? How will these differ from other medical advice and what difference will this make to the patient?

These fall in-line with those promoted by American Cancer Society and the National Cancer Institute: keep your weight down, eat a healthy diet with moderate calorie intake, and do a moderate amount of exercise; the only other thing we look at is that we have some evidence that eating a diet high in polyamines may not be beneficial. Yet while the data looks good, more studies need to go into this area before making a general recommendation. Researchers in France are, however, doing extensive studies in this particular area of diet and cancer.

How soon do you believe these treatments could be used in clinical application?

We hope to start the FAP trial later this Fall; if all goes well, we hope to have a definitive clinical result in 3-4 years. The other trial will probably take 6-7 years to finish; that is a much larger and harder trial to execute, but we have an excellent team of investigators and scientists on hand.

What are the greatest challenges in working with multiple forms of cancer and will you utilise your colon cancer model as the basis for further research?

It takes an enormous amount of energy to study one pathway, and it takes an enormous amount of energy to study one human tumour. History dictates that you dedicate yourself that way.

Dr Frank Meyskens reflects on the body of evidence accumulated in this regard: “A very large amount of data was generated in animals – and in vitro – that indicated that combining drugs with different mechanisms of action would be much more effective than employing each individual agent alone”. Around this time, one agent in particular, an inhibitor of polyclamine synthesis known as difluoromethylornithine (DFMO), had delivered very promising results in preclinical results in prevention models, most notably colon and prostate cancer models. In animal and in vitro studies, the combination was highly effective, and, subsequently, the team initiated a series of translational pilot, phase IIa and phase Iib trials in patients with prior colorectal adenomas.

A series of studies in patients ensued, and Meyskens and his colleagues found that DFMO was very successful in controlling a key pathway by preventing the synthesis of polyamines, a key molecule in the growth of tumours. At this point, the team found themselves at a crossroad, with one question on their lips: what compound should be added to DFMO to improve the efficacy of the treatment? Meyskens recalls this somewhat vividly: “There was a lot of debate at that point, and people were somewhat surprised that we decided on an older drug, sulindac, which is among a class of drugs of non-specific anti-inflammatory agents to which aspirin belongs”.

PHASE III TRIALS

The team’s highly favourable results led to a randomised, placebo-controlled phase III trial.
PHASE III COLON CANCER PREVENTION TRIAL

OBJECTIVES
This study was a randomised, double-blind placebo-controlled trial to test whether the combination of a low dose of DFMO plus a low dose of sulindac reduces the recurrence of colorectal adenomas detected by standard colonoscopy. The trial involved seven clinical sites in the U.S., and an independent Data and Safety Monitoring Board reviewed safety and efficacy data twice yearly.

KEY COLLABORATOR
Dr Eugene Gerner, University of Arizona

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DR MEYSKENS is an active medical oncologist and tumour biologist. He is Associate Director for Control and Prevention of the Southwest Oncology Group, the largest cooperative cancer group for clinical trials in the world. Since 1993 he has been Director of the Chao Family Comprehensive Cancer Center, University of California, Irvine. He has published over 400 papers in scientific and medical journals. Dr Meyskens is also an expert in the biology of cutaneous melanoma and is developing a new therapeutic prevention approach to this malignancy, which, after premenopausal breast cancer, is increasing faster in incidence than any other cancer. He is also a published poet with his first book ‘Aching for Tomorrow’ (2007, Fithian Press) focusing on patient-healthcare givers’ interactions. Dr Meyskens co-founded Cancer Prevention Pharmaceuticals in 2008.

The drug combination inflicted very few side effects, with little additional toxicities. Crucially, results from the trial also indicated that the low doses of the two agents cause no significant toxic side effects.

Dr Meyskens and his team then conducted follow-up colonoscopy to compare the rate of adenoma recurrence between the two groups of patients, and their findings are incredibly promising: within the placebo group, the recurrence of one or more adenomas stood at 41.1 per cent, compared to 12.3 per cent among the test patients; furthermore, 8.5 per cent of placebo patients contracted advanced adenomas, with the corresponding figure representing only 0.7 per cent of those afforded DFMO-sulindac.

The landmark results of the phase III trial – highly promising in terms of both suppressing adenomas and causing little toxicity – are testament to the dedication and innovation of Meyskens and his team, and mark a major development in improving the risk-to-benefit ratios associated with chemoprevention.

NON TOXICITY
A major aspect of the treatment that warrants attention is that the drug combination inflicted very few side effects, with little additional toxicities. Invariably, the risk-to-benefit ratios regarding new or novel treatments permeate the minds of both oncologists and patients. Crucially, results from the trial also indicated that the low doses of the two agents cause no significant toxic side effects. This can be attributed to an informed decision made on the part of Meyskens. Eschewing conventional approaches in which drug doses are escalated to determine maximum tolerated doses before a full-scale treatment protocol, the earlier clinical trials were uniquely subject to dose-deescalation, in which the dose of DFMO is reduced to the lowest possible, demonstrating an effect on polyamine content in the colon.