From Crops to Clinic: OSU at Forefront of Food-Based Cancer Prevention Research

Tomatoes, soybeans, raspberries and broccoli contain remarkable cancer-preventive compounds. Researchers at the OSU Comprehensive Cancer Center are finding ways to refine and repackage them as cancer prevention and treatment foods for the masses.

by Bob Hecker

If it's true, as the adage holds, that "You are what you eat," then it follows that you'd better be careful about what you put on your plate.

At The Ohio State University, interdisciplinary scientists interested in how diet and nutrition can help prevent cancer are pooling their energies to study certain vegetables and fruits filled with natural compounds, or phytochemicals, that a growing body of research suggests have chemopreventive properties.

The "Fight" in Phytochemicals

The scientists admit that much remains to be learned about the intricate interactions and biological benefits of these multifarious substances, but they all agree that Ohio State is perfectly positioned for collaborative phytochemical research that could profoundly affect approaches to human health in general – and cancer prevention in particular – in the new century.

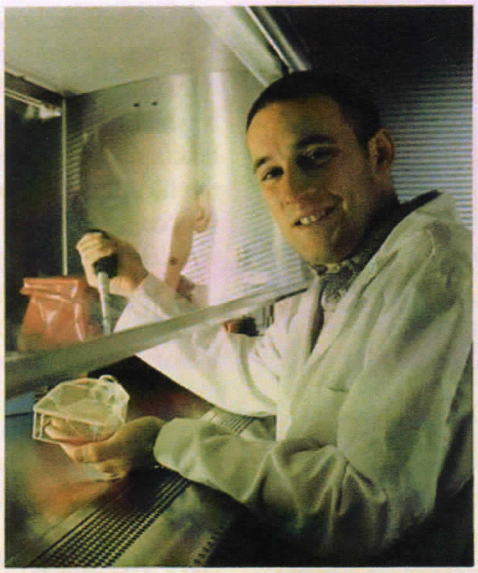
"Ohio State is one of the few universities that can claim to have, on the same campus: a college of agriculture; a college of medicine and public health; a comprehensive cancer center with its own hospital; pharmacology and analytical chemistry programs; a campus-wide nutrition program; and outstanding leadership in all of those areas," says Steven Clinton, MD, PhD, associate professor of hematology and oncology, and leader of the OSU Comprehensive Cancer Center's Molecular Carcinogenesis and Chemoprevention Program. "We have in place at OSU the kinds of talent and infrastructure that allow us to make major contributions in what we like to call 'crops to clinic' research."

"Nutrients and bioactive chemicals in foods represent important factors in the prevention and treatment of disease. They are Mother Nature's drugs, and we are trying to understand how they interact once they are ingested," says Mark Failla, PhD, professor and chair of the Department of Human Nutrition in the College of Human Ecology.

"More and more we're being guided by epidemiological studies that link consumption of certain plant products with inhibition of certain diseases," adds Steven Schwartz, PhD, professor of food science and technology in the College of Food, Agricultural and Environmental Sciences. "So it's important to identify components of these products that are biologically active, understand their absorption in the digestive system, and realize how food processing operations might enhance their biological activity.

"Collaboration is the key," he continues. "Our level of collaboration at OSU has the effect of a multi-institutional effort, making

us ideally suited for research grants that are focused on functional foods, or foods that provide health benefits beyond their contribution to nutrition requirements."



Joshua Bomser, PhD, is studying the cancer preventive benefits of combining soy and tomato products.

Tomato/Soy Combo

Drs. Schwartz, Failla and Clinton recently landed just such a grant: a $1.27 million, three-year award issued by the U.S. Department of Agriculture (USDA) Cooperative State Research, Education and Extension Service as part of its Initiative for Future Agriculture and Food Systems (IFAFS). The three scientists serve as principal investigators.

Their long-term goal is twofold: A) to devise a model system for studying functional foods and B) to apply it toward developing new foods that combine soy and tomatoes, both of which possess biologically active components that, when consumed, are associated with a reduced risk of cancer and heart disease.

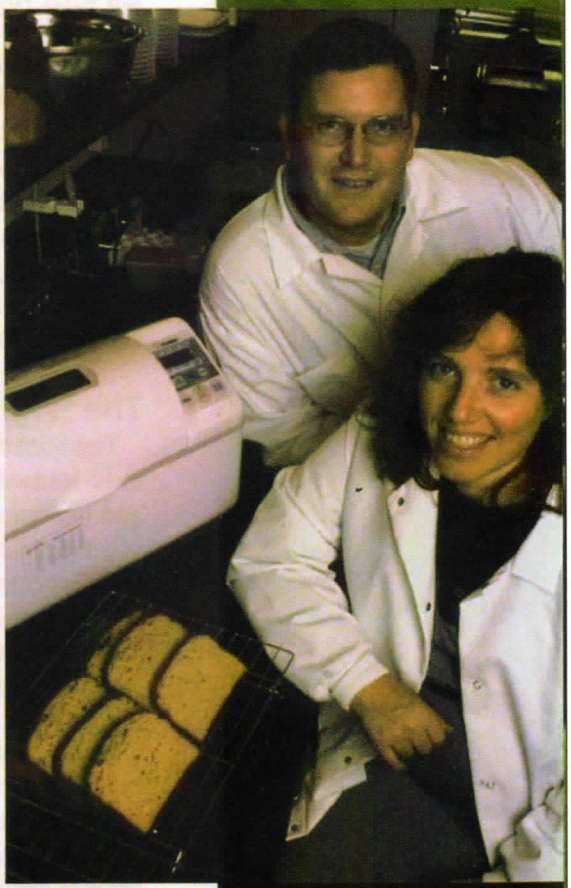
Soy contains isoflavones, or chemicals with the ability to block cell proliferation and stimulate apoptosis (natural cell death) – important weapons against the unregulated and destructive spread of malignant cells that characterizes cancer. Soy isoflavones known as "genistein" and "daidzein" are structurally similar to naturally occurring estrogens, which suggests that these compounds may protect against hormone-dependent cancers such as prostate and breast cancer by disrupting estrogen activity.

Tomatoes contain carotenoids (pigments found in plants and animals). Of particular interest is the carotenoid called lycopene, which gives tomatoes their red color and also may serve as a potent antioxidant that helps prevent cancer by reducing oxidative stress that leads to oxidative damage to DNA in cells.

"Among the byproducts of the oxygen we breathe are oxygen radicals that can form in our bodies and are very reactive," explains Joshua Bomser, PhD, an assistant professor in the College of Food, Agricultural and Environmental Sciences, who studies the cellular and molecular mechanisms by which phytochemicals act to prevent chronic disease and cancer. "These radicals damage DNA, proteins and lipids within cells. A lifetime of exposure to these oxidants contributes to the development of cancer. Our focus is learning how phytochemicals can inhibit mechanisms that lead to cancer – an area that needs further exploration."

Dr. Bomser and colleague Yael Vodovotz, PhD, also an assistant professor in the College of Food, Agricultural and Environmental Sciences, played major roles in writing the tomato/soy grant application, which noted the overall lack of knowledge about phytochemical interactions.

"At present, the potential health benefits of soy and tomato products are undergoing extensive investigation as individual foods; however, the impact of combining these two foods, developing new products and characterizing



Student Cory Ballard (top) and Yael Vodovotz, PhD, display their new soy bread, which they describe as both healthful and tasty.

Steven Schwartz, PhD, and colleagues are devising a model system for studying functional foods. The OSU tandem mass spectrometer is shown behind Dr. Schwartz.

their functional characteristics and benefits has not been investigated," the grant proposal stated. "The combination of soy and tomato products is particularly relevant since each component is associated with a lower risk of cardiovascular disease and prostate cancer."

What new foods might come from this combination? The grant proposal describes them as "soy-based tomato soup and juice products." But Dr. Schwartz, who holds the Haas Endowed Chair in the Food Industries and is a member of the OSU Comprehensive Cancer Center, says the investigators aren't yet entirely sure. "It will likely be a tomato-base containing soy, or perhaps a tomato juice or soup with soy; we just don't know yet."

Whatever it is, it will be designed with optimized nutritional impact, which in terms of cancer means containing the level and mixture of phytochemicals needed to inhibit the transformation of cells from normal to malignant. Once the novel food exists, the scientists will assess the bioavailability of its constituent phytochemicals in human clinical trials. Trial data will then be used to educate consumers, health professionals and industry stakeholders about the health benefit of tomato-based products containing soy and to evaluate the marketing environment for such products.

"It's important to remember that this tomato-soy combination is just one example of developing new functional foods," Dr. Schwartz says. "On a larger scale, we are working in this project to establish a model approach that can be applied to other combinations as well."

Soy Bread Rising

If the project does yield an acceptable product, it won't be the first novel soy food produced at OSU. A tasty and healthful soy bread recently unveiled by Dr. Yael Vodovotz and colleagues is making a favorable impression among all who have tried it.

Dr. Vodovotz, who formerly worked on creating foods for astronauts at the NASA Johnson Space Center and now researches physical properties of food on a molecular level at OSU, worked for months on a secret soy bread recipe with one of her students, Cory Ballard, a food scientist with a culinary arts degree who is also an accomplished baker. They wanted to develop an affordable and healthful product that could be consumed daily, last a long time and also taste good.

"The problem with many soy products is that they just don't taste good to a lot of Americans," says Dr. Vodovotz. "We've adjusted our formulation to overcome this problem. People actually like our bread."

> "Our bread is the first soy-containing baked good that can legitimately carry the FDA claim that consuming it is associated with a lower risk of heart disease."

Not only that, she adds, but this bread is "the first soy-containing baked good that can legitimately carry the FDA claim that consuming it is associated with a lower risk of heart disease." According to the FDA, consumers must eat at least 25 grams of soy protein daily in order to gain its heart-healthy benefits. For a product to meet this standard, each serving must provide 6.25 grams of soy protein and also be

low in fat, saturated fat and cholesterol. Dr. Vodovotz says their bread makes the grade. And because soy has also been implicated in preventing some forms of cancer, nearly everyone who hears of this product wants to obtain it.

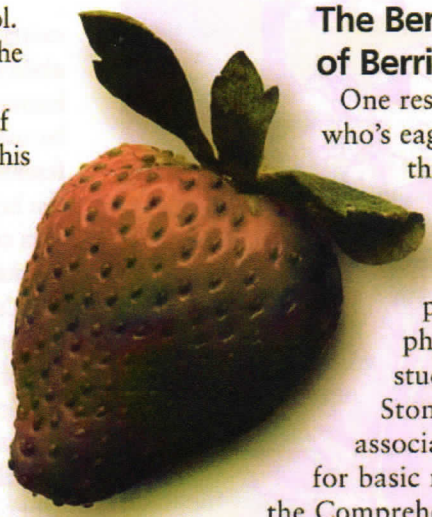
She notes that they have field tested the bread at local grocery stores with good results and are negotiating an agreement to license it to a Cleveland, Ohio bakery that markets to grocers in four states.

Dr. Schwartz says soy bread and the forthcoming tomato-soy products are prime examples of functional foods that go above and beyond normal nutrition requirements for consumers. Others may be in the offing thanks to continuing phytochemical research that will soon be boosted at Ohio State by a newly acquired and highly sophisticated technology called tandem mass spectrometry.

Purchased last year with funding from the Ohio Agriculture Research Development Center (OARDC), the Comprehensive Cancer Center and collaborators on the OSU campus, the tandem mass spectrometer is superior to conventional phytochemical analysis systems in three ways: positive identification capability, optimum detection selectivity and ultra-high sensitivity.

"This is a powerful analytical tool for phytochemical research, providing molecular and fragmentation data that is indispensable for identifying and quantifying bioactive compounds and their metabolites," Dr. Schwartz says. "Hard-to-analyze compounds, or components of unknown identity or mass, can be detected with unprecedented sensitivity of parts-per-trillion."

He says the spectrometer is in place but has seen limited use. "We're learning how to use it by analyzing compounds we already know – carotenoid compounds such as lycopene in tomatoes, and lutein found in green leafy vegetables such as spinach. We are trying to recruit a post-doctoral research associate to conduct some more advanced studies with this technology."



The Benefits of Berries

One researcher who's eager to apply the spectrometer to his lab team's widely publicized phytochemical studies is Gary Stoner, PhD, associate director for basic research at the Comprehensive Cancer Center and holder of the Lucius A. Wing Chair in Cancer Research and Therapy.

Years ago when he spent boyhood summers scarfing raspberries and strawberries fresh from his back yard in Montana, he neither knew nor cared what the berries were made of. "We picked and ate tons of berries in the summer, and Mom would make jellies and jams out of them," recalls Dr. Stoner. "All that mattered then was taste, not chemical composition."

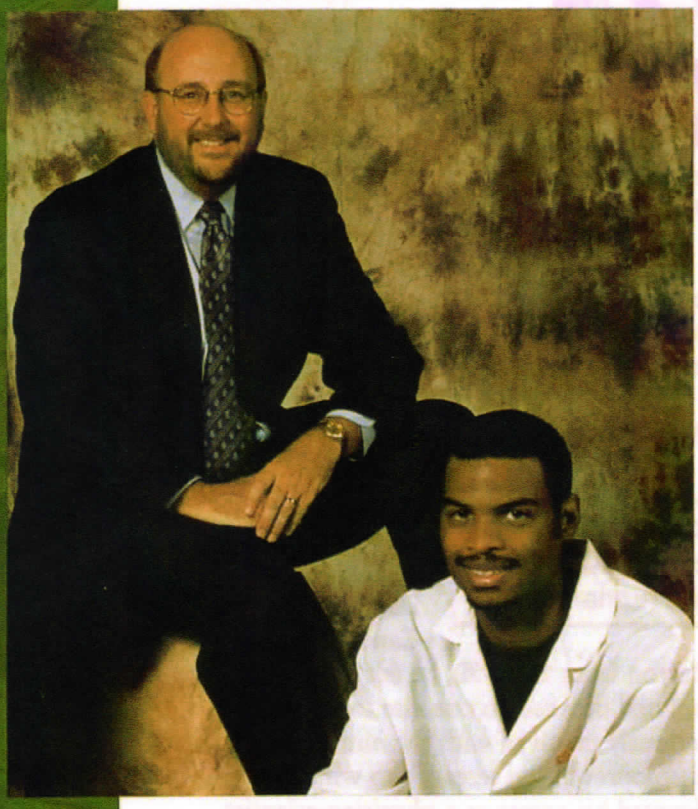
But over the past 15 years, he and his colleagues have taken a close look at what's inside those berries and discovered that they are crammed with chemopreventive compounds.

Dr. Stoner started his chemoprevention studies in the mid-1980s when his research team at the Medical College of Ohio, where he worked before coming to Ohio State in 1992, decided to seek natural sources of ellagic acid, a polyphenolic compound that had been found to inhibit carcinogen-induced cancer in animals. They examined 50 to 60 fruits and found that ellagic acid is most abundant in berries.

Shown here are black raspberries in various stages of development. The black ones are ripe; the red ones will soon turn black.

"That led us to take a food-based approach to cancer prevention, and we began testing the berries' ability to inhibit chemically induced esophageal and colon cancer," he says, explaining that ellagic acid is most locally absorbed in those organs as food passes through the digestive tract (he notes that it is not well absorbed in the blood and therefore is not readily transported to other organs, such as the lungs).

In collaborative studies between the OSUCCC and the College of Food, Agricultural and Environmental Sciences, Dr. Stoner, Dr. Schwartz and colleagues found that freeze-dried strawberries and black raspberries, when added to the diet of rodents, prevented carcinogen-induced esophageal cancer by 50 to 70 percent compared with rodents that had no berries added to their diet.



Steven Clinton, MD, PhD, (top) and graduate student Corey Scott have extensively studied cruciferous vegetables in addition to soy and tomatoes.

They also found that freeze-dried black raspberries inhibited colon cancer by 45 percent when added to the diet of rodents chemically treated with carcinogens.

At first, Dr. Stoner says, researchers thought ellagic acid was principally responsible, but they have come to realize that the inhibitory activity of berries cannot be attributed to just one substance.

> "The National Cancer Institute recommends four to six servings of fruits and vegetables per day," he says. "We're suggesting that one of those servings involve berries."

"We naively thought this single substance might be responsible for thwarting cell transformation, but now we know better," he says. "The berries in our dietary studies with rodents contain only one-sixth to one-tenth the amount of ellagic acid we used years ago when first experimenting with it, yet the berries are more effective in cancer prevention than ellagic acid itself. So we know there are other components – vitamins, carotenoids, anthocyanins, other polyphenols, folic acid – that are responsible for inhibiting cell transformation. Ellagic acid is a factor, but we no longer think it's a key factor."

The goal now, Dr. Stoner says, is to determine which berry compounds are the most effective cancer fighters. He emphasizes that, at present, this research is strictly aimed at cancer prevention, not treatment. However, he thinks some of the compounds could one day be utilized as effective chemotherapeutic agents when administered in high enough amounts.

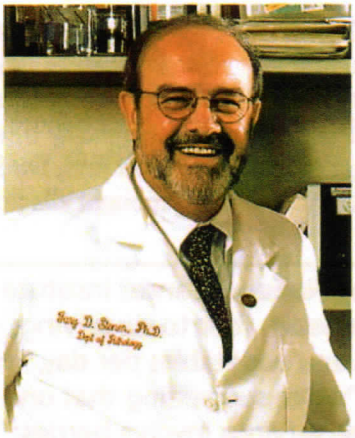
He admits that scientists may never sort out all of the compounds, "but we're going to try. We've made organic extracts of the berries and found that some of the extracts do inhibit cell transformation, either by quenching free radicals that damage DNA and lead to cancer, or by reducing oxidative DNA damage that can also lead to cancer."

The tandem mass spectrometer will be invaluable for identifying and analyzing the myriad compounds in berries, he says, noting that researchers plan to study blackberries and cherries as well.

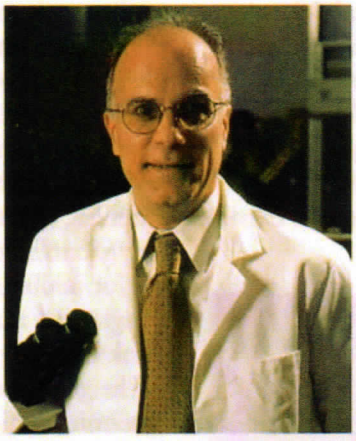
They also hope to examine the chemo-

preventive effects of berries in human clinical trials involving subjects with pre-cancerous polyps of the colon or with pre-cancerous lesions called Barrett's esophagus. Will adding berries to the diet reduce the level of expression of these biomarkers? "That's what we'd like to find out," he says. "We're trying to raise the money for these studies. We hope to get started on at least one clinical trial within the next year."

For now, he says, consumers can be advised to add berries to their diet whenever possible. "The National Cancer Institute recommends four to six servings of fruits and vegetables per day," he says. "We're suggesting that one of those servings involve berries."



Gary Stoner, PhD, has been studying the cancer preventive properties of foods for many years.



Mark Failla, PhD, is studying absorption of phytochemicals in the body.

Anticancer Collaboration

A serving of berries per day is simple advice born of sophisticated research – just the type of collaborative academic outcome that pleases a scientist like Dr. Failla, who came to Ohio State in September 2000 from the University of North Carolina, where he chaired the Department of Nutrition.

"Here we have the opportunity to attack complex problems by using a team approach," says Dr. Failla, whose research interests include bioavailability and absorption of microconstituents and phytochemicals. "I continue to learn so much from my colleagues at OSU and hope that I bring a little something to the mix."

So far he has, collaborating on the tomato-soy project with Drs. Schwartz and Clinton, the soy bread project with Dr. Vodovotz (simulating digestion and absorption of isoflavones in the bread), and on a recently funded project with Dr. Schwartz on assessing degradation and intestinal cell uptake of chlorophyll derivatives from spinach puree using an *in vitro* human cell model. He sees it all as important work.

"According to scientific estimates, there are 20,000 chemicals and 50 to 60 essential nutrients in the human diet," he says. "We know that many of these compounds are biologically active, but understand little about what happens to them after being ingested – which are absorbed, which have beneficial properties, and how they all interact with one another. That's the basis for attempting to develop a novel, broad-based approach to the problem, and it's a challenging but rewarding adventure. This may be the most exciting project of my career."

Dr. Steven Clinton knows the feeling. Although surrounded by brilliant basic scientists and clinicians while at Harvard Medical School and the Dana-Farber Cancer Institute in Boston from 1988-98, he felt somewhat isolated because no one else there was seriously involved with the nutrition and chemoprevention research to which he has devoted his career as a physician-scientist.

"I decided to seek a position that provides more opportunity to develop this

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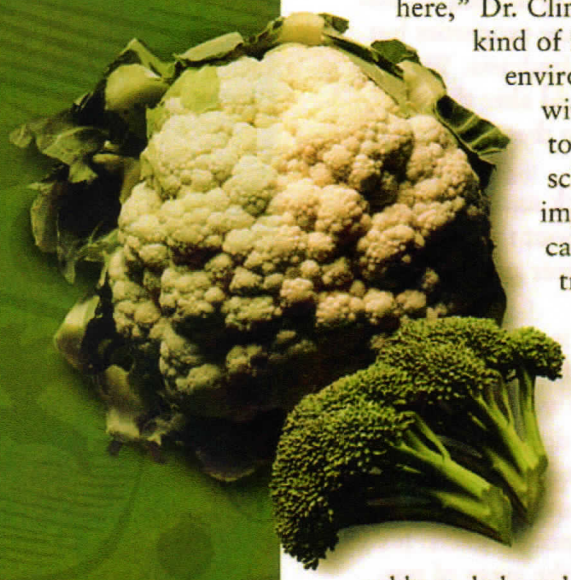

area of study and to do the kind of translational research necessary to move the field forward. That's how I got here," Dr. Clinton says. "With the kind of interactive academic environment we have, and with leadership that wants to raise the status of the scientific enterprise and impact the future of cancer prevention and treatment, a lot of good things are happening."

Among them are some of his own lab's collaborative phytochemical studies with soy, tomatoes and cruciferous vegetables such as broccoli, cauliflower, cabbage, kale and brussels sprouts.

Long before the USDA tomato-soy grant came along, Dr. Clinton and collaborators were studying the anticancer properties of soy isoflavones and other substances produced by the plant. "Soybeans are a major crop in Ohio and other midwestern states, but most of the soy is used for animal feed or processed into vegetable oils," Dr. Clinton says. "In Asian nations where soy products are consumed more frequently by humans, the risk for prostate and other cancers is much lower than in the Western Hemisphere."

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Their studies showed that prostate cancer was suppressed in laboratory animals fed soy extracts and soy proteins, due in part to direct effects of isoflavones on tumor cells. "Soy products appear to reduce production of certain hormones that stimulate prostate tumor growth," Dr. Clinton says. "In addition, diets rich in soy also appear to inhibit tumor angiogenesis, or blood vessel formation. Growing prostate tumors require blood vessels to deliver oxygen and remove metabolic waste in order to expand. So we have strong evidence that soy products contain substances that can reduce cancer risk."

Drs. Clinton, Schwartz and graduate student Craig Hadley have also conducted studies on the chemopreventive power of lycopene in tomatoes. Specifically, they sought to determine changes in plasma lycopene and oxidative stress biomarkers among healthy adults who consumed one of three processed tomato products (condensed tomato soup, "ready-to-eat" tomato soup and vegetable juice) providing approximately 30 mg of lycopene per day. They found that consuming processed tomato products rapidly increases lycopene concentrations in the blood and reduces susceptibility to oxidation, suggesting a protective effect against oxidative stress.

They are now moving into research involving patients with prostate cancer, first to examine how consumption of tomato products will influence blood levels of phytochemicals, and then to determine whether tomato products can influence the course of this disease. "Prostate cancer is a unique disease in that some men can live for several years with it regardless of their course of therapy," Dr. Clinton says. "If we can alter their diet and lifestyle in ways that further slow the progression of this disease, we can add years to their lives. The question is, will proper diet, nutrition and exercise slow the growth of these tumors and enhance the efficacy of our treatments?"

It's probably safe to say that many people prefer tomatoes and tomato products to cruciferous vegetables, but broccoli, cauliflower and the like may be among the most potent of cancer-fighting foods.

After a case-control study showed a lower risk of prostate cancer among younger men who consumed at least three servings of cruciferous vegetables per week, OSU researchers led by Dr. Clinton, Dr. Schwartz and graduate student Corey Scott added extracts of these vegetables to

prostate cancer cells in culture flasks and discovered that broccoli, particularly in sprout form, profoundly inhibits proliferation and stimulates apoptosis. Next, they characterized the extracts and identified chemical components that are active against the prostate cancer cell lines; these analyses yielded unique profiles for each vegetable. The team then isolated bioactive components from the broccoli sprout extract and observed that four components inhibited proliferation in each of the malignant cell lines by at least 70 percent, while three other components caused at least a 50-percent inhibition.

"We now know that these substances can disrupt the spread of prostate cancer cells but seem to have little effect on normal prostate cells, which is good," Dr. Clinton says. "During the next year, we'll be further evaluating these compounds in laboratory models and subsequently in human studies.

"We'll also look at the effects of cooking and food preservation processes on these anticancer compounds. For example, we know that cooking cruciferous vegetables at high temperatures will degrade these compounds, so we're examining novel processing and sterilization techniques that will enhance the anticancer properties but preserve the qualities of freshness. We think these processes could alter the amount of compounds in these vegetables by a thousandfold."

Dr. Clinton has a quick answer for anyone who inquires about the importance of food-based cancer research in modern medicine.

"My view," he says, "is that the cancer problem will ultimately be solved by three approaches that have to work simultaneously: prevention, early detection and treatment. Over the past 30 years, the vast majority of funds have been invested in treatment with only modest gains. It's obvious, therefore, that the areas of prevention and early diagnosis have the potential to enormously impact the cancer burden for the next generation." ■

Glossary

antioxidants – agents that help prevent cancer by reducing oxidative stress and damage to DNA caused by oxygen radicals in the body

apoptosis – the process of natural cell death that eliminates injured or genetically damaged cells

bioactive – affecting a living organism

carotenoids – various red or yellow pigments found in plants and animals

functional foods – foods providing health benefits beyond their contributions to nutrition requirements

isoflavones – chemicals found in soy

lutein – a chemical found in green leafy plants

lycopene – a carotenoid found in tomatoes that gives them their red color

phytochemicals – natural chemicals in plants

polyphenols – chemicals found in certain berries and other plants

tandem mass spectrometry – a sophisticated technology useful for phytochemical research

For More Information:

www.jamesline.com (Web site for the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, with links to the OSU Comprehensive Cancer Center)