NATURAL PRODUCTS

Research Probes Anticancer Mechanisms of Polyphenon E

By Steve Graff

Researchers at the University of Texas M. D. Anderson Cancer Center in Houston are the latest group to show how Polyphenon E (Poly E), a Japanese natural product made up of several green tea catechins, appears to inhibit the growth of cancer cells.

While past studies have suggested how it may prevent bladder, prostate, and lung cancer, this team's in vitro study elucidated how it reduces the proliferation of human Barrett esophagus, the precursor to esophageal cancer, and aerodigestive adenocarcinoma cells.

"We were able to drill down through the mechanisms of how Poly E might work, and how it could potentially affect cyclin D1 expression, as well as pathways that are involved," said Robert Bresalier, M.D., a professor in the Department of Gastroenterology, Hepatology, and Nutrition at M. D. Anderson, who coauthored the study. "We went beyond the descriptive to get at the mechanisms."

Published in a January 2009 issue of *Clinical Cancer Research*, the study is one of the most recent examples of increasing interest in Poly E.

A total of 15 active or recruiting phase I and II clinical trials with the agent are now going on. Seven of those are for prevention; the rest, treatment. The research, most of which is funded by the National Cancer Institute (NCI), is looking at bladder, lung, breast, and prostate cancer, among others.

"In the world of natural substances, that is a lot of activity in the United States," said Jeffery D. White, M.D., director of NCI's Office of Cancer Complementary and Alternative Medicine. The only other natural product receiving as much attention in cancer studies, he said, is curcumin, the principal curcuminoid found in turmeric.

Single-compound green tea extracts, including a compound written as (-)-epigallocatechin gallate (EGCG), have been studied in the lab for decades, but Poly E's well-defined makeup and cheaper cost over nonstandardized compounds help explain why many researchers have focused on it.

"The problem with trying to look at diet or natural products in prevention trials is standardization," said Bresalier. "Here is a good example of where we are trying to take something derived from a natural product that has a basis in observational studies and then apply it in a standardized fashion, in both in vitro and human trials."

"Now, we can study [green tea and cancer] better because we have this well-defined product in order to go through the rigorous

trials," he added. Bresalier is now involved in a phase I clinical trial at M. D. Anderson, studying the side effects and best dose of Poly E in preventing esophageal cancer in patients with Barrett esophagus.

Finding Mechanisms

NCI's Chemopreventive Agent Development Research Group first obtained Poly E back in the early 1990s from Mitsui Norin, a Japanese company that produces a series of polyphenolic extracts from tea and sells them as dietary supplements.

By the time the 1990s ended, many in vitro and animal studies were using the compound. Over the last 8 years, researchers have explored Poly E's ability to increase glutathione *S*-transferase enzymes, which can render cancerous chemicals harmless; its efficacy in preventing bladder cancers; and its effect on growth and activation of the epidermal growth factor signaling pathways in human colon cancer cells.

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A study published in the September 2007 issue of *Carcinogenesis* found that Poly E limits the growth of colorectal tumors in rats treated with a substance that causes the cancer. The total number of tumors per rat, as well as tumor size, was decreased with Poly E, compared with control rats that were not given the extract.

According to the study by Hang Xiao, Ph.D., from Rutgers University, Piscataway, N.J., and colleagues, "Results strongly suggest the colon cancer preventive activity of Polyphenon E and identified possible molecular markers for future colon cancer prevention studies."

The recent M. D. Anderson study answered more questions about the mechanisms that may be responsible for Poly E's anticancer effects. The study was designed to determine the effects of the compound on the growth of human Barrett and aerodigestive adenocarcinoma cells and the mechanisms involved in growth regulation by the agent, using human cells as model systems.

The authors said that Poly E potently inhibited the growth of human aerodigestive adenocarcinoma cells, as well as Barrett cells, by downregulating cyclin D1 expression via both transcriptional and posttranslational mechanisms. The finding provides a rationale for both chemoprevention and therapeutic strategies for esophageal adenocarcinoma and its precursor, according to the authors.

Clinical Trials

"This in vitro study is compelling, but we do want to see what happens in the clinical situation," said Bresalier, referring to M. D. Anderson's phase I Poly E and esophageal cancer trial. "If this is to be used as a clinical agent, the first question is, 'What's the proper dose? Is it safe? And can we show using biopsy from a clinical trial that some of the biological mechanisms that seem to apply in the lab also apply in the human situation?'"

High concentrated doses of green tea supplements have been linked with liver damage in mammals, but Bresalier reports no health issues in the clinical trials, which monitor patients' liver and kidney functions and have controlled doses.

M. D. Anderson Cancer Center is also conducting a randomized, phase IB, double-blinded trial that is studying the side effects and best dose of Poly E in treating women with hormone receptor–negative stage I, II, or III breast cancer. Results for this study and the Barrett esophagus study are expected in late summer.

Other recruiting or active studies include a randomized, phase II trial for preventing cancer in former and current heavy smokers with abnormal sputum at the British Columbia Cancer Agency in Vancouver, as well as a randomized, phase II, double-blinded trial at the Arizona Cancer Center in Tucson, which is comparing a placebo to Poly E in preventing cervical cancer in patients with human papillomavirus infection and low-grade cervical intraepithelial neoplasia.

Polyphenon Pharma, the New York–based pharmaceutical company set up by Mitsui Norin in 2005 to pursue market opportunities for Poly E in the United States, is supporting a cancer treatment study at the Mayo Clinic in Rochester, Minn. Their phase I/II trial is looking at the side effects and best dose of Poly E and its effectiveness in treating patients with stage 0, I, or II chronic lymphocytic leukemia (CLL). Andrew Munro, vice president of legal and regulatory affairs for Polyphenon Pharma, said that his company is sponsoring the CLL study because it has the best market potential.

That support appears to be paying off. In July 2008, the U.S. Food and Drug Administration announced an orphan drug designation for the treatment of CLL with Poly E.

Robert Bressalier, M.D.

"It shows that you have a credible drug," said Munro. It also entitles the company to 7 years of marketing exclusivity for the treatment of CLL upon FDA approval.

In 2006, the FDA also approved a new-drug application—the first such application to the FDA for a botanical drug—for the treatment of genital warts with the company's Poly E.

Cancer prevention researchers, including H.H. "Sherry" Chow, Ph.D., of the Arizona Cancer Center in Tucson, who was one of the first researchers to be involved with Poly E, are looking for a similar outcome within the next 5 years or so. "Right now, there are a number of ongoing, early-phase trials in people at high risk of developing certain types of cancer, and we are tying to move one step further to see where there is any early efficacy to observe in those populations," said Chow, who is part of the cervical cancer trial currently recruiting patients at the Arizona Cancer Center. "We need to finish these studies to see whether we can move this agent further. The ultimate goal is to be able to move it into a large, definitive phase III trial. Hopefully, we will have some positive results to make this happen."

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