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Researchers Hope to Use Cancer's Own Tricks in Novel Strategy to Combat Disease

UNIVERSITY, Miss. – Medical science has made dramatic progress in treating various cancers, but cancer cells remain wily adversaries that employ many genetic and biochemical adaptations to survive. A group of University of Mississippi (UM) researchers hopes to use those same tricks to finally get the upper hand on breast tumors.

The team, led by Dr. Dale G. Nagle, assistant professor of pharmacognosy, is searching for natural products that will either trick cancer cells to transform into nonmalignant cells or cut blood supplies to tumors. The work draws on the latest findings about how cancer cells function and protect themselves against drug and radiation treatments.

“The focus of this work is to find new ways to treat tumors, or cancer, that are not dependant on finding toxic drugs,” Nagle said. “The goal is to get away from the old idea of finding something that can kill tumors a little bit better than it kills people.”

The novel approach of targeting specialized hormone receptors has been rewarded with a Department of Defense Concept Award for Breast Cancer, the first such award ever to a Mississippi institution. The program attracted 1,700 applications, and only about 100 were chosen through peer review for funding.

The \$72,000 award will be used to set up bioassays and determine whether the approach is promising enough to merit continued research. DOD sponsors an extensive program of biomedical research, and the goal of this program is to encourage creative approaches to developing cancer therapies.

Most people know someone who has suffered from nausea, hair loss and other side-effects of conventional chemotherapies. New treatments under development should spare patients much of that misery, leaving them healthier and better able to recover.

The UM project targets hormone receptors called peroxisome proliferator-activated receptor-gamma. In normal human cells, PPARs are involved in controlling blood sugar levels and fat metabolism. They can stimulate cells into becoming more like normal fat cells and to import and use blood glucose. Some drug companies are using these findings to develop new anti-diabetes drugs.

If a way can be found to activate PPARs in breast tumor cells, the cells might be tricked into becoming non-malignant fat cells, Nagle said. And because they would not be in the right place for fat cells, they would simply die off.

Working with Nagle on the project are Dr. Dennis Feller, chair of the pharmacology department, and Dr. Yu-Dong Zhou, a molecular biologist at the National Center for Natural Products Research. Feller has worked with PPARs in studies of blood sugar and fat regulation, and Zhou is helping set up bioassays to screen potential drug candidates.

This multidisciplinary team is particularly interested in whether compounds produced by some marine algae and soft corals could be used to activate PPARs and suppress tumors.

“Marine algae produce a lot of fatty acid-derived chemicals that are very close to the same chemicals in our bodies that regulate these receptors,” said Nagle, who has worked with other UM pharmacognosists to examine the medicinal potential of many marine organisms. “There’s a good hypothetical reasoning to say that these molecules may stimulate or suppress some of these receptors, based on their structure.”

Dr. William Gerwick, who has studied marine algae at Oregon State University for many years, also is helping examine fatty acids produced by the organisms to identify candidates for further study.

The team also is investigating other possibilities to combat tumors, including a way to starve off cancer cells by depriving them of blood flow.

As tumors grow, they secrete a type of protein called vascular endothelial growth factor (VEGF) that stimulates the body to build new blood vessels, Nagle explained. The process, called angiogenesis, ensures that tumor cells get plenty of nutrients and oxygen.

The group is searching for natural products that will suppress VEGF secretion and keep tumors from growing.

“During our normal everyday functioning as an adult, we don’t make many new blood vessels,” he said. “By suppressing blood vessel formation, you can starve out tumors without adversely affecting people, so this might be an alternative to toxic drugs.”

The team recently was awarded another similar DOD-sponsored research grant for a study exploring the possibility of using hypoxic gene regulation to make tumors more susceptible to drug or radiation treatments.

When exposed to chemotherapy drugs or radiation, cells deep inside tumors – where oxygen levels typically are low – activate genes that help them survive. The UM team is looking for compounds that will switch off these so-called hypoxia-inducible factors.

“If we can suppress the cancer cells’ ability to activate these cell survival pathways, then when we use conventional types of therapy – chemotherapy or radiation – these cells would be much more likely to just undergo cell death like the other cells.”

All three projects build on recent discoveries in molecular biology and tumor cell biology.

“The science is so much more advanced than it was 10 or 15 years ago, so there’s no reason we should be using the same approaches people used in the ’60s and ’70s to look for anti-tumor drugs,” Nagle said. “These new approaches look very promising not only in finding ways to kill tumors, but also in keeping the patients healthier.”

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