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Cancer treatment shows promise

Therapy strikes afflicted cells, spares rest

By Peggy O'Farrell • **pofarrell@enquirer.com** •
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An experimental cancer treatment developed locally has the potential to revolutionize the way doctors treat the disease.

The compound, called SapC-DOPS, tricks cancer cells into committing suicide without harming healthy tissues - and with no apparent side effects - developers say.

Bexion Pharmaceuticals in Covington, which manufactures the compound, plans to begin the first phase of testing it on humans by mid-2011, said president and CEO Ray Takigiku."There's nothing like this kind of drug in anyone's pipeline," he said

While the compound has only been tested in tumor samples and lab animals, it has the potential to provide a non-toxic treatment that cancer cells can't outsmart, experts say.

A genetics researcher at Cincinnati Children's Hospital Medical Center discovered it in 2002.

In the lab, the compound works against several cancers, but it holds special promise for treating g lioblastoma brain tumors and pancreatic cancer, two deadly cancers with few effective treatments.

"It's one of the most exciting potential therapies I've seen," said neurosurgeon Ronald Warnick, director of the UC Brain Tumor Center. Warnick, who is not affiliated with Bexion, has reviewed the pre-clinical data on the compound.

Cancer occurs when genetic mutations trigger the formation of abnormal cells that invade normal, healthy tissue. Surgery is one treatment option, but not every cancer can be cut out.

Radiation and chemotherapy work by killing cancer cells, but they also kill healthy tissue, and can have debilitating side effects.

New targeted molecular therapies work by blocking the unique genetic signals that create cancer cells.

But scientists haven't identified every signaling mechanism, and cancer is wickedly smart, said Xiaoyang Qi, the human geneticist at Cincinnati Children's who discovered the compound.

Cancer cells mutate rapidly, and they can become resistant to chemotherapy and radiation. I n addition, tumors are remarkably diverse.

"Even the same tumor in the same patient, the genetic profiles are different in different tumor cells," Qi said.

So targeted therapies might work on parts of the tumor, he said, but not the whole mass.

Other defense mechanisms also protect cancer.

Normal cells know when they've reached the end of their life cycle - usually a few days or weeks -

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and die off on schedule, to be replaced by new healthy cells.

Cancer cells don't die natural deaths.

But the new compound can trick them into committing suicide, Qi said.

It takes advantage of the way cancer cells are built. In a nutshell, cancer cells are very acidic because of the way they're constructed.

That unique construction helps them hide from the immune system, which would normally recognize cancer as an invader and "zap" it.

But the new compound likes acid, and grabs on to cancer cells, which then ingest it. Inside the cell, the compound triggers the release of a chemical that, in essence, makes it kill itself.

If cancer cells evolve and change their structure so that they don't attract the new compound, they'll make themselves targets for the immune system, Takigiku said. "I just don't see how they could mutate themselves into becoming unresponsive to this drug," he said.

Nanotechnology for cancer treatment, like the compound developed at Cincinnati Children's, is the wave of the future, said Jeff Bulte, director of the cellular imaging section in Johns Hopkins University's Institute for Cellular Imaging.

The National Institutes of Health has established a new division focusing on developing new nanotech approaches because experts recognize that chemotherapy and radiation have advanced as far as they can.

"At this point, the only way cancer is pretty much cured is surgery," Bulte said. "Chemotherapy and radiation are pretty much stalled. The hope with n anotechnology is that you can do much more aggressive, high-dose treatment. With standard therapies, the problem is, if you really want to kill the tumor, you end up killing the patient."

The compound is made up of two substances found naturally in the body - a protein and a lipid. Qi combined the two substances into what's called a nanovesicle - a tiny, molecule-sized bubble. It's a new way to deliver a treatment, and it's been patented.

The new compound has several advantages over traditional cancer treatments:

It ignores healthy cells; they aren't acidic enough to attract it.

It's not toxic, so super-strong cancer cells can't resist it.

It has exhibited no harmful side effects.

It can travel anywhere in the body to get to cancer cells - including into the brain. Many cancer-killing agents can't get to the brain because they're blocked by a natural defense mechanism designed to protect the brain from poisons, bacteria and viruses and other threats.

Surgery is the standard treatment for most brain tumors, but there are limitations.

Brain tumors aren't easily removed, Warnick said. They usually have tiny tentacles that are impossible to remove surgically.

And, depending on where the tumor is located,

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cutting out sections of the brain could leave a patient paralyzed or unable to speak or see.

The compound can get to the tentacles the scalpel can't reach, at least in lab animals.

Chemotherapy and radiation are also poisonous to delicate brain tissue, and often ineffective against brain tumors in the long run.

In children, especially, standard brain tumor treatments pose a serious risk for long-term developmental damage, said Charles Stevenson, a pediatric neurosurgeon at Cincinnati Children's Hospital Medical Center.

Stevenson and Qi are exploring another potential application. Its ability to attach only to cancer cells also makes it useful for delivering fluorescent dyes to those cells, making it easier for doctors to pinpoint cancers for diagnosis and treatment.

Since the compound is only attracted to cancer cells and can travel anywhere in the body, scientists can attach to it fluorescent dyes that show up on imaging scans.

The addition will light up cancer cells so they're visible anywhere in the body, Stevenson said. That's a great tool to help surgeons cut out as much as possible.

It's also a way to let doctors see if the cancer has spread, as well as how well it's responding to treatment.

The compound shows great potential, Takigiku and Qi said, but so far has only lived up to it in lab animals and cultured human cancer cells.

In lab mice engineered to develop brain tumors, only the mice treated with the compound survived, Takigiku said.

"It was a lethal model," he said. "There wasn't a drug on God's green earth that would save those mice.

"Except ours."

The U.S. Food and Drug Administration will review the compound's effectiveness in mice and cultured tissue, and make the determination as to whether Bexion can test it in humans.

The phase 1 clinical trials, if they get that far, will be used only to determine whether the compound is safe in humans. Its effectiveness against cancer will be determined in later stages - again, if it gets that far.

Getting it to this point has been a long - and expensive - journey.

Takigiku estimates the cost so far is $5 million. He won't speculate on what sales the compound might generate, but globally, cancer drugs generate about $50 billion in sales.

Qi discovered the compound in 2002. He's worked full time on the compound since then.

Cincinnati Children's licensed the technology to Bexion in 2006. Qi continues to study the compound, and indications are it might be useful against other diseases.

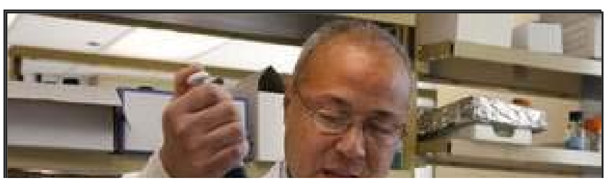
Bexion is a small company, Takigiku said, and so far, they've made the compound "a batch at a time," he said.

They've received several start-up grants from the National Cancer Institute and the National Institutes of Health that have allowed them access to the technology they need to build the compound.

If the compound is as safe and effective as developers hope, Takigiku said, there's no telling what the next step could be.

"There's no roadmap," Takigiku said.

"It's not like someone has done this before. It's not like there's been a drug like this before."



How the compound works

A researcher at Cincinnati Children's Hospital Medical Center and Bexion Pharmaceuticals in Covington have teamed to develop a new way to fight cancer. They've built an experimental compound, SapC-DOPS, that flips the "suicide switch" in cancer cells by taking advantage of the malignant cells' unique construction.

In normal cells, there are structures called lysosomes that contain cellular waste products, bacteria and other structures the cell engulfs.

The lysosome is made up in part of phosphatidylserines. In a normal cell, those chemicals are tucked neatly inside the cell.

In cancer cells, phosphatidylserines migrate to the outside of the cell membrane. The migration prevents cancer cells from triggering inflammation and hides them from the immune system. But it also makes for leaky lysosomes, and that leakage creates an acidic environment in cancer cells. That acidic environment immediately attracts the new compound, which attaches to the cancer cell - and only to the cancer cell.

Once inside the cell, the compound activates an enzyme that produces ceramide.Ceramide is the enzyme that tells cells it's time to die. Once the ceramide is released, the cancer cell kills itself.

The protein is made up of two substances that occur naturally in the body: a protein call saposin C that works in cells' lysosomes, and DOPS, a fat-soluble molecule that helps make up cell membranes. It's often found on the surface of tumor tissues.