

New Drug Development

A Marathon, Not a Sprint

Bringing a new drug from concept to the market takes about 20 years and \$900 million. Not to mention the dead ends, delays and disappointments inherent in the process of developing a drug, even one as promising as SHetA2. Fortunately, the drug's developer, Doris Mangiaracina Benbrook, Ph.D., has plenty of patience.

Benbrook also has the conviction that a current National Cancer Institute testing process will show SHetA2 to be every bit the cancer-preventer she believes it will be. Half-way through tests for breast cancer only, she was told the drug appeared to be effective. Critical Phase I trials in humans could be just a year or two away.

Through a similar NCI testing process, the drug – one in a class of compounds called flexible heteroarotinoids, or Flex-Hets, has already proven itself to be effective in reducing growth of kidney tumors.

Perhaps further tweaking can boost its power to kill cancer in other organs from the 40 percent shown to beyond the 60 percent level required to demonstrate efficacy. Benbrook is hopeful the NCI will approve a new round of testing on a revised version of the drug.

Taking a drug from bench to bedside takes time, lots of time, time that many people with cancer – and those at high risk for the disease – simply don't have. In recent

years, hyped news accounts of SHetA2's success in shrinking a wide range of tumors in test tubes and mouse models reached the international press and resulted in a torrent of phone calls and letters from desperate cancer patients and their frantic loved ones. Each of them begged Benbrook for doses of her experimental drug, regardless that it is still not approved for humans and might be of little or no use to these particular patients.

"Look at this," Benbrook said as she removed the contents of an envelope from Scotland that had arrived on her desk just that morning. "I get so many of these." Inside was a photo of a middle-aged woman named Vivian, a small landscape painting, a handmade chart detailing medical aspects of Vivian's losing battle with ovarian cancer and, finally, a plea for Benbrook's drug.

Within days came another plea, this time from a distraught husband in France: "Doris, I ask you so much to save Daniela's life. Please send the medicine! I will pay what you want for it. I am so much desperated! If Daniela has to die I will also finish my life."



Doris M. Benbrook, Ph.D., professor and director of research, Department of Obstetrics and Gynecology

"It's heartbreaking," says Benbrook, who has temporarily ceased speaking to the news media about her research. "Many of the callers are men who want the drug for their wives. I have to tell them that I can't give it to them. It might be years away."

The years for Benbrook and her drug now total 17. It was in 1993 that she and K. Darrell Berlin, Ph.D., Oklahoma State University Regents Professor of Chemistry, began working to develop a cancer drug involving retinoic acid.

They started with a standard approach of developing a drug that would target a particular molecule and inhibit its contribution to cancer. In this case, the target was retinoic acid receptors. Two problems with this strategy became obvious fairly early: making the compounds (by Berlin) and testing each of them (by Benbrook) was too expensive, and targeting just one molecule would be ineffective against cancer's ability to mutate and use other signaling pathways to grow.

So instead of focusing on a molecule she thought would cure cancer, Benbrook looked to the cell itself and used a cell-based assay to see which modified versions of the drug had better killing power against cancer. Modifications continued until Benbrook and Berlin found the one they felt was the most potent against cancer, but did not harm normal cells. Ironically, the winner didn't work through the pathway it was designed for. Structural modifications made to eliminate toxicity meant it was no longer a retinoid.

Eight years had passed, and the Benbrook-Berlin team was ready to publish their findings in *The Journal of the National Cancer Institute*. However, publication required showing the structure of their drug, and that couldn't happen until the drug was patented. Another delay ensued until a patent was applied for and received as a 50/50 partnership between OU and OSU.

Efforts to show not only that the compound worked, but also why it worked, revealed that within 15 minutes of treatment, the mitochondria in a cancer cells were swollen and releasing molecules that prompted cell death. Nothing similar happened in normal cells, "so we were able to define that the drug induced an intrinsic apoptosis pathway to kill cancer cells," Benbrook said.

"It was very exciting, but I have a realistic point of view. It's easy to find evidence you have anti-cancer activity in a test tube. And it's easy to kill cancer in mice. I will not have that 'Oh, my God!' moment until I see a clinical trial where the drug is actually working in a human."

Her hope that this will happen lies with the NCI's Rapid Access to Prevention Intervention Development program, or

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William Hildebrand, Ph.D.,
Robert Glenn Rapp Presidential
Professor of Microbiology
and Immunology.

T-Cell Vaccine for Breast Cancer Possible

Perched on the surface of our cells are molecules that give T-cells a sampling of what's going on inside, from bits of normal proteins to viral ones, if the cell is infected.

This key piece of the complex immunological interaction between T- and other cells is the focus of OU research that seems likely to produce the first-ever vaccines for several viral infections, including HIV, plus tuberculosis and even cancer.

Already, a vaccine that triggers a T-cell assault against West Nile virus has been created from this research, and breast cancer cells have been killed in animal models.

At the center of this study is that cell sampler, the human leukocyte antigen molecule. HLA has been the focus of study by microbiology and immunology professor William Hildebrand, Ph.D., for much of his career.

In 2000, Hildebrand developed a precise DNA test

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RAPID, which can actually be quite slow. Nothing at all happened in the first year after Benbrook got word in 2006 that her drug was accepted for testing as a breast cancer preventer.

RAPID began living up to its name in 2007, although the process of proving prevention takes much more time than the process for determining whether a drug can shrink existing tumors. This preclinical testing involves using a mouse model that develops breast cancer. Half are treated with Benbrook's drug. At a certain point, the numbers of tumors that developed in the treated and untreated groups are compared.

If the drug is statistically successful in repeated tests and is not harmful, a request will go to the FDA for approval of a Phase I toxicity study in three women per dose level to determine the maximum tolerated dose. Later Phase II trials would evaluate efficacy. Eventually,

a randomized Phase III trial would compare the results with thousands of women receiving SHetA2 or the current standard of care.

"(The prevention-testing process) is expensive because you have to treat for a longer period of time and more patients are needed. In prevention, you're treating someone who doesn't have cancer, so you can't cause any toxicity."

Meanwhile, Benbrook plans to return to the NCI with a new proposal, this one to define the effectiveness of combining SHetA2 with a drug that activates cell death receptors in ovarian cancer.

Drug development is not a sprint but a marathon, Benbrook says. "It's frustrating that it takes so long, but in the process, I've trained a lot of people and there's a lot of talent coming out of my lab. If I fail, I'll have a lot of progeny." ❧



Students at Edmond Memorial High School participated in dozens of crazy stunts and wound up smashing all fundraising records during its annual Swine Week activities by raising more than \$500,000 for the Jimmy Everest Center for Cancer and Blood Disorders in Children. Accepting the check is Jimmy Everest, front row center, father of the late Jimmy Everest. On the back row are OU Health Science Center Provost Joseph J. Ferretti, Ph.D., left; Terrence Stull, M.D., chair of the Department of Pediatrics, center; and William H. Meyer, M.D., director of the Everest Center.