

Prevention before cure

DR DORIS MANGIARACINA BENBROOK

Dr Doris Mangiaracina Benbrook tells us about her latest research: pioneering preventative medicines in the fight against cancer that could have far-reaching potential



What is the primary concern of this research and what prompted it?

Cancer is currently treated with surgery, drugs and radiation that cause serious harm to patients. While some low-toxicity agents have been shown to prolong disease-free survival, most patients eventually succumb to cancer recurrence. While our plan is to initially test the cancer prevention activity of our pill in humans by determining if it can prolong disease-free survival after primary surgery and therapy, our long-term goal is to prevent cancer in the first place.

Why are you focusing on the cancer chemoprevention application?

When people are treated for cancer, they experience significant side effects, and often severe suffering and eventual cancer induced death. Preventing cancer with a non-toxic pill would prevent this suffering and death, and there would no longer be a need for enduring the hardships and expense of surgery, radiation and toxic drugs currently used to treat cancer.

Can you explain why your drug, SHetA2, reduced development of both cancer and polycystic kidney disease (PKD) in animal models?

Our current knowledge of how SHetA2 functions indicates that it targets key molecules inside cells that control a natural programme of cell death, present in every cell, called apoptosis. This programme uses molecular detectors to monitor the health of a cell, if the cell is damaged beyond repair, the programme causes it to die through a process that causes the cell to break up into pieces that can be engulfed and recycled by

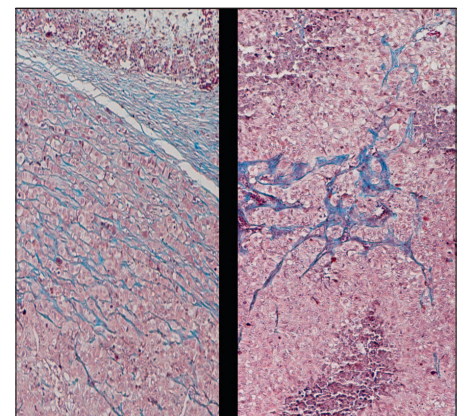


FIGURE 1. Inhibition of Angiogenesis by SHetA2. Comparison of untreated control and SHetA2-treated tumours shows that SHetA2 blocks their blood vessels (blue) and prevents them nourishing the tumour (light purple) resulting in necrosis (dark purple) and death of the cancer cells.

This picture was adapted from: Myers, T, Chengedza, S, Lightfoot, S, Pan, Y, Dedmond, D, Cole, L, Tang, Y, Benbrook, DM (2008). Flexible Heteroarotinoid (Flex-Het) SHetA2 inhibits angiogenesis *in vitro* and *in vivo*. *Investigational New Drugs*, 27 (304–318).

other cells. This prevents the cell contents from spilling out and causing an immune reaction or damage to nearby cells, and also provides an efficient re-utilisation of the cell contents. If the cell can be repaired, this programme slows down cell growth until the repairs are made. Once the programme detects there is no more damage, the cell is released from the growth arrest and normal cell function is restored. Cancer and PKD cells are diseased because they have found a way to bypass this natural programme. SHetA2 gets around this problem by directly activating this programme. We've found that there are multiple additional diseases that bypass this programme, and have the potential to be treated with SHetA2.

With breast cancer being predominant in developed countries, could this drug potentially be used to treat aggressive diseases like this?

SHetA2 is only weakly active against cancer that has already spread and is aggressively growing. Our plan to increase the potency of Flex-Het drugs, by improving their binding to the apoptosis-regulating molecules, is anticipated to produce new drugs that can fight already existing cancer. Prevention of breast cancer is important in both developed and developing countries. I was particularly moved on a recent trip to India by the high rates of breast cancer incidence and death there. A low-cost prevention pill could have a tremendous impact in areas where the economy cannot support cancer screening and treatment. If SHetA2 proves effective, it would greatly reduce the need to invest in development of the infrastructure required to institute prevention and high-cost treatment plans for the citizens. The precious resources could be focused on the other needs of the country.

In terms of passing U.S. Food and Drug Administration (FDA) requirements, how has the lead Flex-Het, SHetA2, fared? How does it differ from pre-existing drugs?

So far no toxicities have been identified and the IND application is set to be submitted in 2011. Depending on the complete set of results and the RAPID programme priorities this year, they will support the Phase I clinical testing. RAPID support can continue through Phase I trial, as long as it is warranted by the data and based on their available resources and the prioritisation according to the overall goals of their division. Assuming no unexpected toxicity is revealed in the evaluations of SHetA2, an IND filing to the FDA can occur shortly after completion of the preclinical studies. It is presently estimated that preclinical studies may be completed within the first eight months of 2011. A Phase I trial can start soon after the acceptance of the IND. This trial will determine a safely tolerated dose in humans, as well as pharmacokinetics of SHetA2 at these doses.



A pill for prevention

In the search for a preventative pill for cancer, one leading study has focused on the mechanism of SHetA2 action in ovarian cancer and other diseases

WHEN ONE THINKS of modern day cancer treatments, words that spring to mind probably include 'chemotherapy' and 'radiotherapy'. While these treatments have proved effective in the fight against various cancers, they remain very intrusive, often harmful and patients are faced with the possibility that the disease may return. In recent years, scientists have begun to look to natural products that have the inherent power to fight disease in humans, seeking not only cures for terminal illnesses, but also methods and drugs that prevent their onset. One such study, headed by Dr Doris Mangiaracina Benbrook, with the support of K Darrell Berlin PhD and Stan Lightfoot, MD, is underway, with the ultimate goal of developing a non-toxic pill that prevents cancer and other diseases such as colorectal cancer, breast cancer and polycystic kidney disease (PKD).

CREATING COMPOUNDS

Retinoic acid, the major metabolite of vitamin A, is one such natural molecule that can treat many diseases, including cancer, through its binding to retinoic acid receptors inside the nucleus of cells. Retinoic acid is used to treat some cancers, but is limited by toxicity to the patient and eventual ability of cancers to develop resistance to this treatment. In efforts to improve the pharmacological properties of retinoic acid, the numerous synthetic analogues, called retinoids, were synthesised and tested. Through their work, the team succeeded in advancing retinoid research, by developing a series of compounds, called heteroarotinoids (Hets), which exhibited the medicinal properties of retinoids, but were less toxic. Through Hets, a first step to achieving their goal had been accomplished, Dr Benbrook explains: "Our goal to improve the therapeutic ratio (ability to treat cancer in comparison to the side effects induced) was promising, but we still needed to increase the potency of the compounds against cancer cells".

Through a series of structural modifications to increase the disease-fighting properties while retaining the reduced toxicity, they developed another group of compounds called Flexible heteroarotinoids (Flex-Hets), named with their intended flexibility – when compared to conventional heteroarotinoids – in mind. While some of the beneficial properties of retinoids were retained in Flex-Hets, they represent a novel class of drugs, because they possess additional disease-fighting properties and work independently of the retinoic acid receptors. In multiple animal models, Flex-Hets did not exhibit any of the classical retinoid toxicities or teratogenicity. The Flex-Het, SHetA2, was chosen as the lead because it exhibited the most potent activity against cancer cells, while not harming normal cells and, to date, has passed all of the U.S. Food and Drug Administration (FDA)-required preclinical testing conducted by the US National Cancer Institute (NCI) with flying colours.

DEVELOPING NEW DRUGS

In order to appropriately design the future clinical trials, however, Dr Benbrook was faced with a challenge: to understand how Flex-Hets worked, since they do not work through the retinoic acid receptors. She elaborates further the complexity of Flex-Hets' action within the cell: "Further refinement of the structure could not be accomplished without understanding which of the tens of thousands of molecules in the cell mediate the ability of Flex-Hets to selectively kill cancer cells over normal cells". Dr Benbrook was, therefore, forced to go back to an earlier step in the drug development scenario to identify and validate the molecular target of SHetA2 within the cell, before appropriate analogs could be designed and synthesised. Through continued studies, Dr Benbrook demonstrated that the medicinal properties of SHetA2 were exerted through differential effects on specific organelles within

INTELLIGENCE

MECHANISM OF SHE2 ACTION IN OVARIAN CANCER MIVAC

OBJECTIVES

The goal is to develop a non-toxic pill that prevents cancer and other diseases. Inhibition of colorectal cancer, breast cancer and polycystic kidney disease (PKD), and lack of toxicity of our drug was demonstrated in animal models. Clinical trials and development of improved drugs are planned for 2011.

Dr Benbrook is currently focused on deciphering how the drug works at the molecular level. She is following up on her recent discovery that the drug directly binds to three related proteins. If her validation studies determine that these proteins are the primary mediators of SHetA2 action, she plans to develop a pipeline of drugs with improved ability to manipulate these proteins in ways that can prevent development of cancer and other diseases.

FUNDING

NIH – NCI (Cancer)

KEY COLLABORATORS

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Stan Lightfoot, MD, Professor, Department of Pathology, University of Oklahoma (Pathologist)

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DORIS MANGIARACINA BENBROOK earned a PhD in Biochemistry from Loyola University, did fellowships at the La Jolla Cancer Research Foundation in the U.S. and the Imperial Cancer Research Fund in the UK. Now a Professor at the University of Oklahoma, her career is focused on developing prevention drugs and mentoring other scientists.

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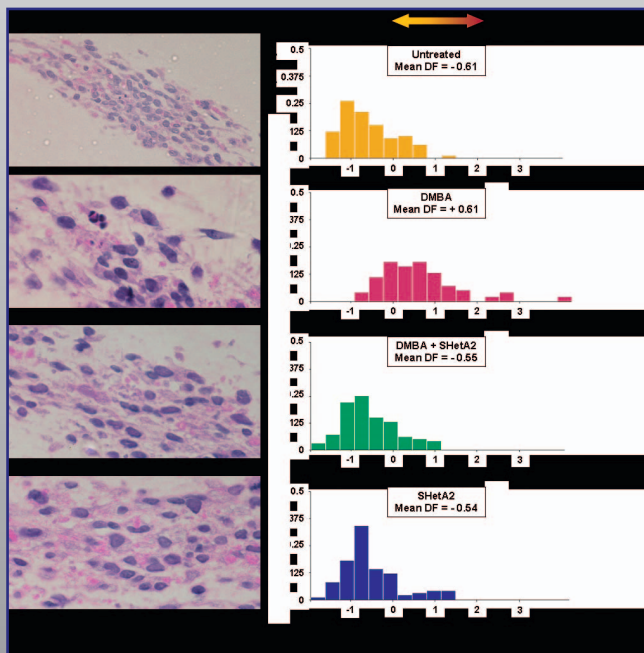


FIGURE 2. Organotypic culture model demonstrating SHetA2 cancer prevention activity. The left panel shows abnormal nuclear morphology is present only in cells treated with the DMBA carcinogen and prevented by subsequent treatment with SHetA2. The right panel represents a measure of the carcinogenic phenotype (discriminant function score) by karyometric analysis.

This picture was adapted from an open access journal: Benbrook, DM, Lightfoot, S, Ranger-Moore, J, Liu, T, Berry, W, Dozmorov, I (2008). Karyometric and Gene Expression Analysis in an Organotypic Model of Endometrial Carcinogenesis and Chemoprevention. *Gene Regulation and Systems Biology*, 2 (21-42) (http://la-press.com/article.php?article_id=549).

diseased cells causing a natural form of cell suicide, called apoptosis, in the diseased cells, while leaving normal healthy cells unharmed. These organelles, called mitochondria and endoplasmic reticulum (ER), which control energy and protein metabolism within the cell, are characteristically overactive and dysfunctional in cancer.

In normal and pre-cancerous cells, SHetA2 works through these organelles to slow down metabolism and cell-duplication, while any damage present is repaired and normal cell function restored. However, the destabilised condition of these organelles in cancer cells is often beyond repair, so that when SHetA2 binds its target proteins within these organelles, the resulting effect is apoptosis. In addition to the proteins directly bound by SHetA2, Dr Benbrook's research identified other key down-stream molecules that mediate the medicinal effects of this drug on diseased cells. These molecules, known to be altered in cancer and other diseases, can be used as targets for developing improved drugs and for developing biomarkers of drug sensitivity and response. Dr Benbrook is confident with the positive outcomes of the study so far: "We are very excited about this recent finding and plan to develop a new class of drugs specifically targeted at them".

ONGOING SUPPORT

To date, the project has been funded through grants from the U.S. National Cancer Institute (NCI). The laboratory research has been supported by Research Project Grant (R01) funding, while the preclinical testing was supported by the Rapid Access to Intervention Development (RAID) and Rapid Access to Preventive Intervention Development (RAPID) programmes. At present, Dr Benbrook believes the preclinical trials will be completed shortly after the first half of 2011, after which Phase I clinical testing may begin. As long as the

Our project is on track to produce a cancer prevention pill and develop a pipeline of drugs effective against cancer, polycystic kidney disease (PKD) and other diseases

potential drug continues to prove a lack of toxicity and depending on their own identified priorities, RAPID support will continue through this Phase I period. The objective of the Phase I clinical trials will be to assess whether pills containing SHetA2 can prevent cancer. In contrast to drugs that treat already existing cancer, there is little tolerance for any potential toxicity or side effect in drugs that are used for prevention of cancers that have not yet occurred. Thus, the preventive activity and lack of SHetA2 toxicity in preclinical testing is very promising.

Upon completion of the Phase I clinical trial, Dr Benbrook's goals are to perform Phase II clinical testing to determine if SHetA2 pills can prolong disease-free survival in cancer patients after primary therapy is completed. If SHetA2 is proven effective and exhibits acceptable toxicity given the cancer risk, the next test will be to discover whether it can prevent cancer in individuals at high risk. If the drug still proves effective in this setting without exhibiting any toxicity, then Dr Benbrook will test if SHetA2 pills can prevent cancer in the general population. Thus far, Dr Benbrook is very positive about the potential her project has for fulfilling its objectives: "To date, our project is on track to produce a cancer prevention pill and to develop a pipeline of drugs that will be effective against cancer, polycystic kidney disease (PKD) and other diseases," she closes.