Researchers edge closer to delivering personalized medicine to cancer patients

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Dr. Michael Childress (right), Professor of Comparative Oncology at the Purdue University College of Veterinary Medicine, is pictured with Kody (middle) and his owner, Carolyn McGuire. Kodywas in the drug trial which accurately predicted his tumor would be sensitive to chemotherapy, and Childress' team was able to significantly extend Kody's life with chemotherapy. Credit: Purdue University College of Veterinary Medicine / Kevin Doerr

For the first time, Purdue researchers prove that measuring mechanical motions in living cancer tissues is a viable and promising approach for predicting chemoresistance

Chemotherapy can save lives, but often a cancer patient may be resistant to their prescribed chemotherapy, which costs the patient valuable time. Chemoresistance is a topic that researchers need to understand better so that they can match the right type of chemo to the right patient, which is called personalized medicine.

An unusual pairing of veterinary scientists and physicists believe their method of detecting chemoresistance could be the new standard for personalized medicine. Their method is unexpected: Doppler ultrasound. Many people may have heard the term Doppler, either from the weather reports to detect storm activity or expectant parents who see their unborn child for the first time.

Now, a team of physicists and veterinary scientists at Purdue University is using ultrasound to detect how cancer cells respond to chemotherapy. They currently have their method of personalized chemotherapy detection in Phase II clinical trials in humans at the IU School of Medicine and have also been using the method in canine trials.

The concept was born in 2015 by three researchers at Purdue: David Nolte, principal investigator and Edward M. Purcell Distinguished Professor of Physics and Astronomy, John Turek, Professor of Basic Medical Sciences, and Michael Childress, Professor of Comparative Oncology. Nolte is from the Department of Physics and Astronomy at the Purdue College of Science and Turek and Childress are from the Purdue College of Veterinary Medicine.

All three are members of the Purdue University Institute for Cancer Research and have published their findings in *Scientific Reports*.

"The technique developed at Purdue measures motions inside cancer cells and how these motions change when the cells are exposed to anticancer drugs," explains Nolte.

"Because motion is the result of cellular 'machinery,' patients who will respond positively to their chemotherapy show different mechanical responses to the drugs than patients who will not respond. This has the potential to identify patients for whom chemotherapy will not be successful so they can be directed to more effective treatment."

The technique, called biodynamic imaging (BDI), has been under development for cancer treatments for over eight years. The team has published their findings previously, noting that the technique showed potential for identifying chemoresistance, but only under fairly restricted disease conditions. This raised the question of whether BDI might be useful only for special cases.

"The current research shows that BDI is, in fact, a general and robust technique," says Nolte. "It shows similar results across two species (human and canine) and two diseases (lymphoma and esophageal cancer). This provides, for the first time, strong evidence that measuring mechanical motions in living cancer tissues is a viable and promising approach for predicting patient chemoresistance."

The concept of using Doppler in cancer research seems an unlikely scenario. According to Nolte, the concept and process for this technique was born out of basic scientific experimentation. He said the concept was fine-tuned with the benefit of serendipity combined with slow and steady progress.

"We began the work on cancer tissue cultures grown in the lab, so it was natural to eventually move to fresh tumors from patients," he explains. "The Doppler measurements were something that we were led to during

our experiments as we noticed interesting dynamical effects that we had not initially anticipated."

This team formed well over two decades ago. Back in 1999, the Office of the Purdue Executive Vice President for Research hosted a meeting of Purdue faculty interested in various aspects of imaging.

"Dr. Nolte and I met at that meeting, and we started working on using the technology with 3D tumor spheroids (small tumors grown in culture) that I grew in my lab," says Turek.

"We worked with tumor spheroids for a number of years as the technology developed. When it was time to move to patient derived tumors, we approached Dr. Childress and used samples from canine lymphoma patients to track their response to drugs. Working with the canine samples was necessary to determine the feasibility of translating the technology to human samples. From canine samples we moved on to human samples. Our collaboration with Dr. Shadia Jalal of the IU School of Medicine has been an invaluable and critical component to the research."

"The major advantage to using canine tumors as opposed to tumors from laboratory mice is that the former better represent the heterogeneity of human cancers," says Childress.

"Although all the dogs we studied had the same cancer type—lymphoma—each individual dog's cancer was unique, with some more sensitive and others more resistant to chemotherapy. This provided an ideal animal model in which to study a predictive technology like BDI before advancing it to human trials."

Cells in all living creatures have working machinery that is very finely tuned. When outside influences disturb the cellular machinery, the

mechanical motions change. If scientists can see a difference in those changes between patients whose cancers are sensitive to treatment versus those who are not, they can learn those signatures and use them to predict chemoresistance in future patients.

"A deeper question is what the signatures mean," explains Nolte.

"Can signatures of chemoresistance be interpreted in terms of changes in the signaling pathways in cells and tissues and possibly even genetic expression? This is much harder to answer, but we are currently working on this question by comparing our measurements to gene expression profiles. We also use reference compounds that have known behavior in cells and we can cross-reference our measurements with the known changes that occur under those drugs. This part of the research is long-term."

Nolte says that Purdue has strong support for cross-disciplinary research which significantly aids in how this type of research develops. Coupling that with the benefit of the Purdue University Small Animal Hospital at the College of Veterinary Medicine enables the team to arrange for clinical trials with canine patients. Now that they have received these promising results, the team expects their next giant leap in cancer research to include "prospective" Phase II trials.

"The current Phase II was retrospective, where the patient clinical response was cross-validated against the predicted response using BDI. The next step is a Phase II trial that is 'prospective,' meaning that we will predict patient response prior to the beginning of chemotherapy," says Nolte.

More information: Zhen Hua et al, Comparative oncology chemosensitivity assay for personalized medicine using low-coherence digital holography of dynamic light scattering from cancer biopsies,

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