“Chipping” away at prostate cancers

Treatments for prostate cancer have been moving towards a personalized medicine approach, which attempts to match a patient with the best treatment option available for their specific type of prostate cancer.

David Jarrard, MD, Associate Director for Translational Research at the UW Carbone Cancer Center, in collaboration with UW Carbone member John Denu, PhD, at the Wisconsin Institute for Discovery, have developed a method to screen advanced prostate cancer samples to find out if multiple patients would benefit from a new type of treatment that uses drugs to stop proteins that regulate how tightly DNA is wrapped around histones. Histones are proteins that act much like a spool around which a DNA strand is wrapped

Jarrard and Denu looked at histones in prostate cancer cells by taking a sample from a patient’s prostate tumor and putting it on a small chip, about the size of a microscope slide, called a microarray, which was created in Denu’s lab.

“The microarray allows you to look at histone modifications at a number of different sites all on one little chip,” Denu said.

These modifications are the result of acetylation, a chemical modification that causes different genes encoded in the DNA to be turned on or off. After a patient sample has been applied to the microarray, the spots where proteins have altered the histones will light up, allowing them to identify which patients have these modifications.

During their research, Jarrard and Denu discovered that these histone alterations in advanced cancer were regulated by a protein called SIRT2, which could also be a target for drug therapy.

“There are a lot of acetylation inhibitors that drug companies have developed, and seeing this specific alteration in SIRT2 would help you identify those patients that may benefit from those drugs,” Jarrard said.

There is still more work to do, however. The investigators plan to downsize the chip to allow for smaller tumor samples to be used.

“We’ve also begun exploring other strategies to look at these histone changes in order to better understand why these tumors develop resistance to other types of treatment,” Jarrard said.

All of this information should help doctors quickly find the best treatment for specific patients that will shrink their prostate tumors with the fewest side effects possible.

“All the goal here is to come up with a patient-specific chip that will allow us to provide a personalized medicine approach using newer classes of drugs,” Jarrard said.
With more advances in personalized medicine, it makes sense that people want to take charge of their health by learning about their personal disease risks. Many direct-to-consumer (DTC) genetic tests exist on the market today offer a personalized risk analysis. UW Carbone Cancer Center genetic counselor Kelcy Smith, MMSc, tells us what information DTC tests can offer – and what they cannot.

Q: What are DTC ("at home") genetic tests and what information do they provide?
A: DTC tests can be purchased at your local pharmacy and do not require a physician order. They provide a range of information, from your ancestry, to physical traits, to your risk for cancer and other diseases. However, it is important to know how these tests differ from clinical genetic tests. DTC companies use a wealth of data from research done on large groups of people, comparing the genetics of people who had a specific disease to the genetics those who did not. It is then assumed that these genetic factors are increasing, or decreasing, risk for cancer or disease. Unlike clinical genetic tests, there is no evidence that these genetic differences have any effect on cancer development. Put another way: neither your health insurance nor your healthcare provider will approve or prescribe treatment plans based on your DTC genetic test results.

Q: How do I decide which genetic test is right for me?
A: I think the most important question to ask before you undergo any genetic test is: What’s your goal? Are you trying to gather information on your family history or ancestry for fun? If yes, then DTC tests are fine! But if you are concerned about your cancer risk based on your family’s history, you would be a good candidate to talk with your primary care provider or oncologist about a referral to see a genetic counselor.

Q: How does a genetic test ordered by my doctor or genetic counselor differ from a DTC one?
A: Clinical genetic tests look for gene mutations that are proven by research to significantly increase one’s risk for developing cancer regardless of other factors. These tests are diagnostic and the results from a clinical genetic test are often used to make screening and treatment decisions moving forward.
One woman finds many ways to give back

Like everyone, Andrea Mace and her family are all too affected by cancer. “We’ve lost a lot of family members to cancer,” Mace said. “What really kicked us into gear was when my uncle was diagnosed with pancreatic cancer ten years ago, and the whole family was like, ‘ugh, another one.’ We wanted to channel our energy back into something positive.”

At first, Mace and her family’s energy went into forming an informal family foundation, for which they hold bowling and golf tournaments amongst other events, to raise money for cancer research. For Mace, that was just the start. In the years since her uncle’s diagnosis, she has been throwing herself into many different cancer fundraising and awareness organizations and events. 2017 marked her final year of service in UW Carbone’s young professionals group, the Emerging Leadership Board. She also served on UW Carbone’s Pancreas Cancer Task Force for several years.

One of her favorite charitable ventures she spearheaded? The Ribbon Room at the Hilton Madison Monona Terrace. For each night the room is booked, The Hilton donates $25 to UW Carbone – the guest pays nothing additional.

“The idea was to transform the whole room, so we got custom-made furniture, new lighting, new room accents, and the artwork was done by a survivor who had been treated at Carbone,” Mace said. “We also included survivor books, and a photo book with blank pages where guests can share their story. I just think the Ribbon Room is such a cool idea of a different way to give back.”

Renovating a hotel room may be more than most people can take on, but Mace has advice for anyone who wants to help raise money for a cause. “It doesn’t have to be millions of dollars, because every little bit helps,” Mace said. “And you can do small, creative things that will catch attention and make a huge difference.”
Attacking cancer cells with anti-cancer drugs is one of the best tools in the fight against cancer. However, many promising anti-cancer treatments – from chemotherapy to gene therapy – have not been pursued clinically due to their low treatment efficacy and high systemic toxicity.

Engineering professor and UW Carbone Cancer Center member Shaoqin Sarah Gong, PhD, has thus focused her research on the field of nanomedicine, in which she is working to more safely deliver a variety of drugs to treat cancer, heart disease and even blindness.

“We engineer nanoparticles to deliver all sorts of payloads for medical purposes, including small molecular drugs, proteins, DNAs, RNAs, and CRISPR-based genome editing agents, and so on,” Gong says. “They allow the delivery of drugs more specifically to the target organ or cells while enhancing their stability during circulation in the bloodstream.”

The nanoparticles Gong and her research group engineer are effectively tiny cages that house the various payloads. The nanoparticles can be designed with different structures and chemical features. These differences allow the nanoparticles to be tailor-made for the type of payload and the type of disease being targeted. For example, much like oil does not mix with water, some nanoparticles are specially designed to house oil-like payloads, and others are designed to house water-like ones.

“Also, we’ve designed the surface of the nanoparticles such that they can be functionalized by incorporating various moieties such as cancer-cell targeting molecules,” Gong says. “Because most cancer cells overexpress certain types of proteins on their surfaces, the targeting molecules attached on the surface of the nanoparticle can interact specifically with the protein overexpressed by the cancer cells, leading to cancer-targeted drug delivery.”

Imaging probes can also be incorporated, so that researchers, and eventually clinicians, can monitor if the nanoparticles are reaching the tumor while avoiding healthy tissues.

Most nanoparticle research currently being conducted uses particles made up of multiple molecules, but a concern is that they do not have adequate stability in the bloodstream and can lead to premature release of the payloads and loss of their targeting specificity. Instead, the Gong lab is focusing on engineering “unimolecular” nanoparticles.

“Our nanoparticles are unique because they are formed by one single molecule, and thus are much less likely to fall apart during circulation in the bloodstream,” Gong says.

Gong collaborates with researchers throughout UW Carbone and campus to tailor the nanoparticles for different uses. To read about one collaboration, please visit: uwhealth.org/nano
Cancer patients need to plan ahead when traveling

Whether for vacation, work or to spend time with distant friends and relatives, any travel requires planning. For cancer patients, it often requires extra planning.

**Consider the following when traveling:**

- Notify your provider in advance.
- Plan ahead for your destination.
- Make sure you have enough medical supplies.
- If you are flying, contact your airline to let them know if you are on oxygen or if you have any other special needs.
- Reduce your risk of infection with diligent handwashing.
- Have a letter from your physician about your condition, your medications and any implanted devices, such as ports.
- Check immunization needs for your destination, and ask if you are able to receive these immunizations.
- If you experience symptoms like high fevers, increased pain, nausea, or vomiting, you should seek medical attention right away.
- Protect yourself from the sun and stay hydrated.
- Get plenty of rest and go at your own pace.

**PLEASE VISIT UWHEALTH.ORG/CANCEREVENTS FOR DETAILS ON ALL EVENTS**
Unlocking the mystery of triple negative breast cancer

Unlike the majority of breast cancers that are receptor positive, and therefore have druggable targets (known as ER+, PR+ and/or HER2+ breast cancers), nearly one in five breast cancer cases is “triple negative” (TNBC), with no targeted markers. In addition to relying on chemotherapy as the primary treatment, TNBC patients have higher rates of relapse and a worse overall prognosis compared to receptor-positive patients.

Medical oncologist Kari Wisinski, MD, specializes in treating patients with TNBC. Her work includes conducting clinical research to improve patient outcomes, but she rarely steps into a research lab.

Basic scientist Deric Wheeler, PhD, can churn out lab research questions a mile a minute, but he jokes he does not know the first thing about well-designed clinical research. So how did these two UW Carbone Cancer Center members end up collaborating on lab research that has led to a clinical research trial for TNBC patients?

It starts with a perplexing observation about a protein, EGFR, which sits on the surface of cells and signals them to divide and survive. Wheeler’s research group studies EGFR in the lab. A majority of TNBC cases express excess EGFR, meaning anti-EGFR targeted therapies such as cetuximab should have at least initially benefitted TNBC patients, even if they developed resistance later.

“But clinical trials with cetuximab in TNBC patients didn’t work. To a clinician’s eye, EGFR is not a viable option for TNBC, and I’d agree,” Wheeler says. “In the lab, however, we would grow TNBC cells or tumors in mice, we’d pluck EGFR out of those cells genetically, and the tumors would crash. So EGFR must matter.”

Wheeler’s group had previously studied resistance to cetuximab in lung cancer patients, where they found that the main way cancer cells grew resistant was by moving EGFR inside the cell; cetuximab...
only inhibits EGFR on the surface of cells. Other researchers had already shown that another group of proteins, the SFKs, are responsible for bringing EGFR into cells. An SFK inhibitor, dasatinib, was already FDA approved. Wheeler grew lung cancer cells in the lab and treated them with cetuximab until resistance developed. Then he treated the cells with dasatinib. He found that EGFR was no longer inside the cells, and the cells could once again be killed by cetuximab.

Lung cancer physician and clinical research faculty leader Anne Traynor, MD, learned of Wheeler’s research, and suggested he and Wisinski talk about how it may apply to TNBC. “Maybe the TNBC trials with cetuximab didn’t work because it was about where EGFR lives,” Wheeler says. But he needed patient tumor samples to be able to know for sure.

Fortuitously, Wisinski was already acquiring breast cancer tissue. “When I came to UW Carbone, there was an effort to increase communication between clinicians and basic scientists, and one of the things we kept hearing was that there was not well-annotated patient tissue available,” Wisinski says. “The Cancer Center then supported a project where we collected tissue from 380 early-stage breast cancers, with information about grade, receptor status and clinical outcomes.”

Together, Wheeler and Wisinski, along with UW Carbone pathologist David Yang, MD, first identified which of the 380 tissue samples were from TNBC patients, then they asked how many of that subset contained EGFR inside the cancer cells. Around 15 to 20 percent did. Wheeler also grew TNBC cells in the lab and repeated similar experiments that he did with the lung cancer cells. The results in TNBC were the same as in lung cancer: dasatinib treatment kept EGFR out of the cells. This data led to a clinical trial currently available to non-metastatic TNBC patients at UW Carbone.

“Based on biopsy results, if a patient has triple negative breast cancer and we find EGFR inside the cells, they may be able to enroll in this trial where they take dasatinib for 7-10 days and then they either have their tumor removed surgically or they receive another biopsy,” Wisinski said. “Then we look at if the EGFR has gone back to the cell surface.”

This type of trial is called a “window” study, with the goal to learn about the effect of dasatinib on EGFR during this short time while patients would normally be waiting for the next step in their therapy—usually surgery or chemotherapy.

The trial is just in its early stages, but Wisinski and Wheeler say the initial results look promising. Wheeler adds, “I was pleasantly surprised and excited to see the change in EGFR location, but I was also like, ‘Ok, it should work based on the lab data.’”

If the trial continues with this same trend, the ultimate goal is to initiate a second trial to administer dasatinib plus cetuximab to TNBC patients, with the expectation that these patients will see a benefit from the anti-EGFR therapy that they were not before.

“I think sometimes the work that is done in the lab is so far from the clinic,” Wisinski says. “I like working on it, but it’s hard for me to say, ‘How is this going to get to my patients?’ I like that this work gave the scientific evidence which drove the design of a clinical trial.”

15-20% of all breast cancers are TNBC

Triple negative breast cancers are so-named for lacking three receptors common in breast cancer:

- ER
- PR
- Her2

TNBC patients have a higher rate of relapse and worse overall prognosis compared to receptor-positive breast cancers
The UW Carbone Cancer Center is on social media! Connect with us to learn more about our groundbreaking research, prevention information and remarkable patient stories:

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BIG TEN CANCER CENTERS UNITE

Just ask Sam Lubner, MD about the value of collaboration. He and several other UW Carbone physicians are members of the Big Ten Cancer Research Consortium (Big Ten CRC). Formed in 2013, Big Ten CRC encourages clinical researchers from Big Ten schools to work together to develop new clinical trials and open them to patients at participating Big Ten cancer centers.

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