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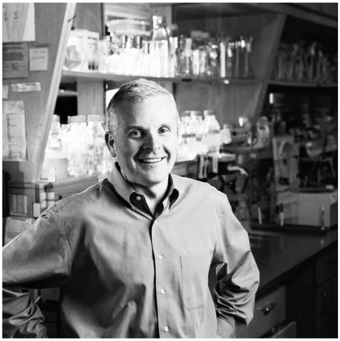
“Luck Favors the Prepared Mind”

November 4, 2022
By: Julie Poucher Harbin, Senior Writer, DCI

Two MBC Drug Discoveries Emerge from the McDonnell Lab into the Clinic



Donald McDonnell, PhD

More than 1.5 million women in the U.S. are currently on endocrine therapies (hormone therapies) for breast cancer — either as monotherapies or in combination with other drugs.

These drugs and drug combinations have been found to work well, in some cases for many years until they don’t. Recently it has been demonstrated that mutations can develop in genes within breast cancer cells that render even the best endocrine therapies ineffective. While more and more women are living with stage 4 breast cancer (upward of 150,000), 42,000 die of metastatic breast cancer each year. Metastasis, cancer that has spread to distant organs, is the major cause of breast cancer death.

The majority of breast tumors (~75%) have receptors for estrogens within cancer cells and such cancers are classified as ER+. When estrogens bind to these receptors, they can drive processes responsible for tumor growth and metastasis.

One type of anti-estrogen hormone therapy (endocrine therapy) — a **s**elective **e**strogen **r**eceptor **m**odulator (SERM) — works by binding to the estrogen receptors present in cancer cells and in the body’s immune cells. This stops the estrogens from binding and driving cancer cell growth. Another type of endocrine therapy, aromatase inhibitors, suppresses estrogen synthesis.

SERMs (such as tamoxifen), aromatase inhibitors (such as anastrozole, letrozole, or exemestane), and **c**yclin-**d**ependent **k**inase 4/6 inhibitors (therapies that target the CDK4 and CDK6 enzymes important to cell division, such as abemaciclib, ribociclib, and palbociclib) — taken alone or in combinations thereof — are currently used as first- and second-line treatments for ER+ breast cancer. (CDK 4/6 inhibitors are targeted therapies, not endocrine therapies)

Unfortunately, the majority of patients with metastatic ER+ breast cancer will eventually develop resistance to these drugs.

When this happens, oncologists may try a different type of endocrine therapy, a **s**elective **e**strogen **r**eceptor **d**ownregulator (SERD), which, like a SERM works by targeting the estrogen receptor in cancer cells and the body’s immune cells, but instead of blocking estrogen by *binding* to the estrogen receptor like a SERM, it blocks estrogen by *degrading* the estrogen receptor.

The only drug of this class (SERD) approved for clinical use in ER+ breast cancer is fulvestrant (first FDA-approved in 2002), which has been shown to have only modest efficacy. Additionally, as an injectable drug, the administration of fulvestrant can be very uncomfortable for patients.

A few years ago, mutated estrogen receptors (ESR1 mutations acquired through the course of the disease) were discovered to be responsible for endocrine therapy resistance in up to 40% of patients with ER+ breast cancer, especially those who'd been extensively pre-treated with aromatase inhibitors. Since ESR1-mutated ER+ breast cancer is only somewhat receptive to tamoxifen and fulvestrant, the development of new approaches that would inhibit the activity of these rogue receptors and stop breast cancer from advancing emerged as a priority in the field.

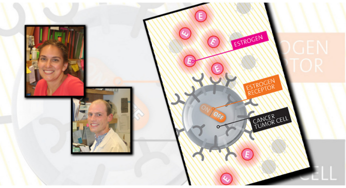
Particularly over the past decade, Donald P. McDonnell, PhD — Glaxo-Wellcome Professor of Molecular Cancer Biology and associate director of Translational Research at Duke Cancer Institute — and his lab teams have been focused on identifying and developing new endocrine therapies to treat advanced ER+ breast cancer. This has included revisiting and researching, in the lab, older hormone therapies originally designed to treat hot flashes and osteoporosis; one of which McDonnell first worked on in the early 1990s.

Leveraging the work and insights of the McDonnell Lab — with regard to mechanisms of action of various SERDs, SERMs, and SERD/SERM hybrids — various pharmaceutical companies now have several new drugs in clinical development. The lab has been involved directly or indirectly with most of these development programs.

The two most promising drugs are elacestrant and lasofoxifene.

A Q & A with Donald McDonnell, PhD, about the long evolution of and research behind these two Duke drug discoveries & what's next

ELACESTRANT



Working in the McDonnell Lab, Suzanne Wardell, PhD, and Erik Nelson, PhD, elucidated RAD1901/elacestrant's mechanism of action.

There's a lot of buzz right now around elacestrant following successful Phase 3 trials and the NDA (New Drug Application) filing with the FDA for marketing approval. I understand that this drug (originally called RAD1901) was designed to treat hot flashes brought on by menopause but failed. Instead, members of your lab discovered a new utility — that it could work to treat ER+ breast cancer.

Yes. That's right. We love drugs that don't work the way they're supposed to and/or demonstrate peculiar pharmacology. You can learn a lot by defining the mechanism of action of such drugs. Suzanne Wardell, PhD (an assistant professor working in my lab), and Erik Nelson, PhD (now at the University of Illinois and a former post-doctoral trainee), elucidated the drug's mechanism of action with their eureka moment coming just two weeks after starting work on the project in 2012.

They found in their studies of human breast cell lines that RAD1901 was effective at blocking estrogen from binding to the receptor, thus stopping cell growth — a SERM property. Quite unexpectedly they also found that the drug had SERD properties and downregulated the expression of the receptor in breast

LASOFOXIFENE

Donald McDonnell, PhD, Kaitlyn Andreano, PhD, Stephanie Gaillard, MD, PhD, and Ching-Yi Chang, PhD, MSPH, are the inventors listed on the utility patent for "the use of lasofoxifene to treat ER+ breast cancer.

There's also interest right now around lasofoxifene. The utility of *this* endocrine therapy — an old osteoporosis drug — in ER+ breast cancer was also discovered in your lab. Your lab filed "an invention disclosure" on May 25, 2016. Sermonix Pharmaceuticals came to an agreement with Duke's Office of Licensing and Ventures (now called Duke OTC, the Office for Translation & Commercialization) that same year to acquire exclusive rights to further develop what was Duke's intellectual property. Duke University was issued a utility patent in April 2019 covering the use of this drug in breast cancer and an international multi-site Phase 2 clinical trial, the ELAINE Study, was launched in September 2019.

On May 31 this year, Sermonix released the results of two Phase 2 clinical trials. ELAINE 1 (just lasofoxifene) and ELAINE 2 — lasofoxifene in combination with the targeted therapy abemaciclib (a CDK 4/6 inhibitor). These trials evaluated efficacy in patients with locally advanced or metastatic ER+ breast cancer with an ESR1 mutation who had already progressed through first-line therapies. Any updates?

Yes. The results in both trials were exceptionally promising and it was announced that the company is moving forward with Phase 3 trials in the very near future. Duke participated in Phase 2 clinical trials.

cancer cells. They further demonstrated that the drug effectively inhibited the growth of ER-positive tumors in mouse models of breast cancer. We published these findings in Endocrine-Related Cancer on July 10, 2015.

Positive results of the Phase 3 EMERALD trials evaluating RAD1901/elacestrant in metastatic breast cancer were recently published, and the FDA (US) and EMA (Europe) are currently reviewing the data. We hope that this drug, a SERM/SERD hybrid, will be approved soon and available to patients as early as spring 2023. We believe that it has the potential to become the endocrine therapy of choice in late-stage breast cancer and that it will replace fulvestrant.

Why did your lab choose to study RAD1901 as a possible therapy to treat ER+/HER2- breast cancer in the first place?

RAD1901 was initially in development for the treatment of hot flashes in post-menopausal women, although it was never approved for this use. However, the results of the clinical trials (for hot flashes) intrigued us as they revealed that at low concentrations the drug was effective at reducing the number and severity of hot flashes. Paradoxically, at higher doses, it actually increased hot flashes. We would have expected that if “a little was good more would be better” but that was not the case. We were intrigued by this unusual pharmacology and began to figure out the mechanistic basis for this unexpected finding. It turns out that the reason for its failure as a treatment for hot flashes was actually a useful property for a breast cancer drug.

After the 2015 paper was published, what happened next? Did your lab team apply for a patent on this discovery?

The path to the development of RAD1901 as a breast cancer therapeutic was not straightforward. My colleagues and I filed several patents covering the use of RAD1901 in breast cancer and they were granted. The drug was a relatively old one and was running out of patent life. We were concerned that if we did not give it new life in the form of these patents it would be forgotten. But that was not enough. We then had to go into “persuasion” mode to convince Radius Health, Inc., the owners of the drug, to develop it for breast cancer. They were not a “cancer company.” It took nearly three years but finally, everyone bought into the concept, we licensed our enabling patents to them (Dec. 2017), and the drug’s clinical development as a breast cancer drug began.

Is Radius Health the drug developer?

Yes, together with the Menari Group.

I understand that your lab had discovered the first oral SERD, etacstil, — a major breakthrough in the field for its ability to overcome tamoxifen-resistance — back in the 1990s after you joined Duke.

The scientists in our group were early adopters/promoters of the idea that drugs that degraded the estrogen receptor would have utility (might work) in the treatment of advanced metastatic breast cancer that had failed standard-of-care endocrine therapies.

In 1996, John Norris and Caroline Connor (at that time graduate students in the laboratory) embarked on a search for ER-drugs that would downregulate/degrade ER. John was also working on another project in collaboration with scientists at GlaxoWellcome examining the molecular mechanism of action of novel anti-

How is lasofoxifene different than elacestrant?

Lasofoxifene, like tamoxifen, is a selective estrogen receptor modulator (SERM) whereas elacestrant is a SERM/SERD hybrid.

Lasofoxifene, like other SERMS, targets the estrogen receptors in breast cancer cells and blocks estrogens from driving tumor growth and metastasis. However, in advanced or metastatic cancer, the estrogen receptors can mutate, rendering them insensitive to existing endocrine therapies. While doing her doctoral studies in our laboratory, graduate student Kaitlyn Andreano discovered that lasofoxifene effectively inhibited (blocked) the rogue activity of *all* the commonly occurring ER mutations.

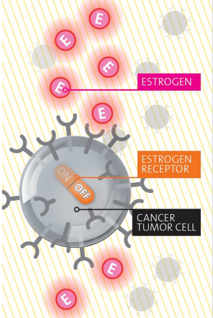
HOW LASOFOXIFENE STOPS CANCERS

Out of all breast cancers, 70 to 80 percent have receptors for the hormone estrogen (estrogen-receptor positive). Estrogens can fit into the receptor and promote tumor growth and metastasis.

To reduce tumor growth, patients are prescribed drugs that inhibit the activity of the estrogen receptor.

Unfortunately, in advanced disease the estrogen receptor in the cancer cell can mutate, making these drugs ineffective (an ESR1 mutation).

In tests in the lab, even when those other drugs won’t work, lasofoxifene “turns off” or inactivates the estrogen receptor in breast cancer cells. Thus, in animal models, the drug reduces tumors and metastasis.



Lasofoxifene was initially developed for the treatment of osteoporosis and vaginal atrophy.

What is it about lasofoxifene that makes it different than other SERMs?

Two things (a) it binds to the receptor in a different way than other SERMs and as such the mutations don’t affect its activity and (b) upon binding it “messes up” the overall shape of the estrogen receptor and renders it unable to modulate growth promoting pathways in cancer cells.

I should note that you have an interesting past with lasofoxifene; having been part of the team that developed the drug to treat osteoporosis in women stemming from estrogen loss in menopause. It was 1992 and you were a young researcher with Ligand Pharmaceuticals, which developed the drug in collaboration with Pfizer.

Yes, I figured out how to manipulate the estrogen receptor to identify drugs that inhibited the negative actions of estrogen in breast cancer cells, but which were bone protective. Building on this discovery, and upon arriving at Duke in 1994, I set out to identify estrogen receptor-targeting drugs that worked better than those available and that would be particularly effective in the treatment of metastatic breast cancer.

I would be remiss if I didn’t mention that lasofoxifene was never marketed for osteoporosis. Following clinical trials and FDA approval, Pfizer received European Union authorization in 2009 but chose not to market it after acquiring Wyeth and a competing drug — a similar SERM designed to treat osteoporosis called bazedoxifene (brand: Conbriza). In 2012, Pfizer’s three-year

osteoporotic drugs. During the course of this work, he and Caroline identified a drug called GW5638, which for reasons we determined later, ended up being a spectacular inhibitor of the growth of tamoxifen-resistant tumors in animal models. So dramatic was the activity that we tried to get Glaxo interested in developing it for breast cancer, but they were not actively working in this area at the time and were not interested.

Then Linda Abruzinni (then with Duke OTC) proposed the "out of the box" idea that Duke should out-license the drug from Glaxo and move it along the development path. Indeed, in what was a "first of its kind" agreement, Duke acquired the rights to the drug and further explored its activities. The data package kept getting stronger and stronger and another graduate student (Ashini Wijayaratne) determined that the drug very effectively degraded ER. With this data in hand, we were able to out-license the drug to Dupont (name changed from GW5638 to DPC974).

In a small study of patients with advanced heavily pretreated breast cancer, the drug also demonstrated efficacy, but clinical trials were suspended in 2001 after Bristol Myers-Squibb (BMS) acquired Dupont. For non-scientific reasons, BMS closed the trial and chose not to continue its development.

Although the cessation of the development of DPC974 was very disappointing, the program was in some ways very successful as (a) it confirmed the utility of degrading ER as a therapeutic approach in cancer and (b) encouraged many companies to "get back into the game."

marketing authorization lapsed and the rights to lasofoxifene reverted to Ligand, but again, the drug was not brought to market. It wasn't until Kaitlyn Andreano, as you have described, "collected or synthesized nearly every endocrine drug that had ever been made," that she discovered that lasofoxifene, unlike the other SERMs, worked against ESR1-mutated ER+ breast cancer. It seems that what goes around, comes around … 20 years later and in the best possible sense. (READ MORE about this discovery)

I once heard a seasoned pharma veteran say that "every good drug fails three times." In the case of lasofoxifene, this definitely seems to be the case!

Treating breast cancer that's spread to the brain has traditionally been a big challenge due to the limited therapies available that can cross the blood-brain barrier (BBB). Can elacestrant penetrate the central nervous system? Can lasofoxifene?

Based on studies in animals we and others believe that elacestrant does cross the BBB, but this must be confirmed in humans. Regardless, there is an ongoing study, in which Duke is participating, that is exploring the utility of elacestrant, together with the CDK4/6 inhibitor abemaciclib, in patients with breast cancer brain metastasis. We are currently doing studies to examine if other SERMs and SERDs cross the BBB and if and how this activity contributes to drug efficacy.

What's next?

Are elacestrant and lasofoxifene being tested/trialed in other settings and/or in other cancers?

It has recently been found that SERDs and SERMS can favorably regulate the immune system and this activity also contributes to their anti-tumor efficacy. The preliminary data in this regard are extremely promising.

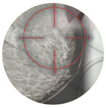
We are very interested in SERMs *and* SERDs as modulators of tumor immunity and hope that their use will enable us to unleash the power of the immune system to treat breast cancers.

Our preliminary studies in this regard are very encouraging and if all goes well we expect that the clinical use of elacestrant and lasofoxifene can be expanded to other cancers in the near future.

We recently published a study (Oct. 2021) highlighting a role for such drugs in increasing the efficacy of immunotherapies in melanoma. More to follow on this story in the near future.

How did your lab happen upon these two different "new utilities" discoveries in such a relatively short period of time? Are there other hormone therapies (endocrine therapies) that your lab is currently looking at as well for the treatment of breast cancer?

I have been told that we have been "lucky," but I promise there is more to it than that. Indeed, there is an old golf story that I like that about sums it up. Apparently, after a particularly good shot at a tournament, a reporter remarked to Arnold Palmer, "You were really lucky with that shot," whereupon Palmer replied, "You know I have noticed that the more I practice, the luckier I get." My outstanding team has been working in this field for a long time and has "blood-hound" instincts for new drug discovery. We are not finished and recently have identified some new approaches for breast and prostate cancer that we hope to evaluate in the clinic in the very near future. To those who say we are lucky I would reply, "Luck favors the prepared mind."



A Bench-to-Bedside Story

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