Science Will Win Podcast
Season 2
Episode 1 Script

Martha:
I was diagnosed, uh, with metastatic breast cancer at the beginning of January 2015. I did not know what the word metastatic meant. I didn't know what it meant initially when I saw the word palliative for my treatment plan. It was definitely a big shock actually, you know, I mean, I remember crying… nobody cries in the cancer center publicly… at least at mine. It's like, it's like, everybody's got on their stoic faces.

So I was standing in the middle of this like big section with everyone sitting, waiting for their appointments. And I was like crying so hard on the phone with my husband because, um, I had just learned, they thought that there was probably cancer in my ovaries as well. They already knew it was, you know, very likely in my lungs. One of the nurses came up to me, well, two people came up to me, the nurse, my oncologist nurse came up to me and said, you look like you've been hit by a truck. And I'm like, I think, you know, I have been hit by a truck. That's why I looked like this. And then someone else came up and asked me if I needed a hug, an employee. And I was, you know, it was very nice of her to do that, but I was like, I don't need a hug, you know, I need to not be hearing this news.

[MUSICAL TRANSITION]

ADAM: That is Martha Carlson. She's a volunteer breast cancer advocate, a writer for Cure Magazine…and she lives with metastatic breast cancer.

When Martha was diagnosed with breast cancer – so, metastatic meaning that it's spread to other parts of the body – she had to quickly get on board with new medical terms, and a new reality.

And she dove in. She went from being a writer and editor to using her talents to give patients a voice. She now volunteers as a patient advocate. Her story isn't rare: Each year in the U.S. more than 250,000 people are diagnosed with breast cancer.

That's why the innovation in science and treatment must keep pace with this disease. New technologies, novel science, and collaboration are expanding our knowledge of breast cancer, and hopefully helping us find new, effective ways to treat it.

This is season two of Science Will Win. I'm your host, Adam Rutherford. I'm a geneticist, writer, broadcaster and a lecturer at University College London in the UK.

[MUSICAL TRANSITION]

ADAM: In the last season of Science Will Win, we talked about innovation and advances in gene therapy. This season, we'll be looking at breakthroughs in another area: oncology - that's the study and treatment of cancer.

We'll hear from scientists tasked with developing new treatments, oncologists who lead clinical trials and treat patients, and the patients and patient advocates themselves. The truth is, we have more effective means to treat cancer than we ever have before. But the challenges, well they still remain.

We'll be honing in on *breast cancer* research and treatment. Why? Well, breast cancer is now *the* most commonly diagnosed cancer, globally. But despite how common it is, it's often misunderstood. It is a surprisingly varied and complicated disease.

Yet, there are many innovations arising from the hard work of oncologists, researchers, advocates, and patients themselves. That's why breast cancer is the disease that we can best use to illustrate the incredible process that gives rise to new cancer treatments.

These innovations pose many potential benefits for patients.

> Edith:
> And that's what it's all about. Working with patients, taking care of patients and thereby offering therapeutic interventions for patients with cancer that might allow for benefit, by number one, decreasing the side effects that patients experience from cancer and two, whether or not there is a shrinkage of tumor and therefore, benefit to the patients.

ADAM: That's Dr. Edith Mitchell. She's a medical oncologist in the department of medicine and medical oncology at Thomas Jefferson university in Philadelphia.

> Edith:
> I have been working in oncology for more than 45 years.
> When I was a fellow in training, I had completed my residency and part of my research work was to analyze the patients in the center, and their tumors. And at that time, the procedure was that the fellow had to go to the operating room, pick up the specimen from, the surgeon or the nurse in the operating room and take it directly to the laboratory. And that was because, the process, at that time, involved immediate determination of the procedures for, managing the specimen.

ADAM: Cancer testing and treatment has come a long way in those 45 years. And a lot of that is thanks to the work of scientists and researchers, like Pfizer's Jeff Settleman.

> Jeff:
> I'm Jeff Settleman. I'm the chief scientific officer for Pfizer oncology and I'm based at Pfizer's research site in La Jolla, California.

ADAM: At the La Jolla site, Jeff oversees the research and development of potential cancer treatments – from the early discovery of potential therapies, through clinical testing that can result in a proof of concept. At the site, about a thousand researchers across a variety of disciplines work together to help bring breakthrough therapies to people living with cancer.

This is important work, and Jeff keeps a physical reminder of that close at hand.

Years ago, he came to know one of his students whose mother was undergoing treatment for breast cancer. As part of her treatment management, she took up painting.

> Jeff:
> I have one of his mom's paintings hanging in my office. It's an abstract painting that reflects what she imagined the drug that saved her life might look like. it was her way of feeling more connected to her treatment. And that painting's been hanging in my office for about 12 years. And it reminds me that for most cancer patients, the science behind their treatment is very mysterious and abstract, but it's also very personal and of course, very important.

ADAM: For many patients, cancer treatment *is* very mysterious and abstract. So let's start with the basics:

Cancer, in its most basic sense, is when some of the body's cells become abnormal or damaged, and they multiply free of normal checks and balances. So they can spread into other parts of the body.

There are a variety of treatment options available to stop and slow that spread of cancer.

So there's surgery, where cancerous tissue or other contributing factors are removed. There's radiation therapy, where ionizing radiation is targeted at cancer cells to kill them and shrink tumors. There's chemotherapy, where powerful medicine is used to kill fast-growing cells. There's a newer type of treatment called immunotherapy, which works with the patient's own immune system to fight back against the cancerous cells.

Additionally, there's targeted therapy, a rapidly developing treatment method that uses medication targeted at a specific contributor to a patient's specific *type* of cancer.

These treatments have become incredibly important tools for oncologists. But, there's still more to be done. Some of these treatments involve essentially the same process for every patient – like surgery, or cytotoxic chemotherapy, which can result in non-cancerous cells getting damaged in the process.

Over the past few decades, breast cancer research has made astonishing advancements, particularly developing those last two types of treatment – immunotherapy and targeted therapy. Jeff has also watched, and taken part in this change during the 35 years he's worked in the industry.

Jeff:
You know, around the time that I was doing my postdoctoral training and, and in the early years of my academic career, and we started sequencing cancer genomes, which really came into fashion in a substantial way in the early 2000s. And I think that really paved the way for rational drug treatments that were informed by a fundamental understanding of what is going wrong in a cancer cell. What are the changes at the genetic level, which we know lie at the heart of the development of this disease and to translate that into a strategy for rational drug design is something that's really evolved and taken off in an exponential way. I would say over the past, say 20 years.

ADAM: When Jeff talks about rational drug design, he's referring to a way of developing medications with a specific target molecule in mind. It's a more targeted methodological way of researching, focusing on a specific receptor or enzyme.

[MUSICAL TRANSITION]

ADAM: This need for specificity gets at the heart of why cancer is such a difficult disease to treat. Cancer is heterogeneous – what that means is that it's actually not just one disease at all.

Jeff:
Cancer is, you know, hundreds, if not thousands of different diseases. And so there's a lot of heterogeneity among cancer patients and tumors of these diverse types respond to treatment in very different ways. Understanding how to attack these distinct diseases by exploiting their specific vulnerabilities is really critical to our ability to, to find novel treatments that can deliver some robust clinical benefit for patients.

ADAM: To make it more complicated, even more specific types of cancer you've heard of – like breast cancer – are also heterogeneous. There are many types of breast cancer, which are classified based on the type of protein, or hormone receptor, they have. I'll let Dr. Mitchell explain:

Edith:
we usually divide the tumor types into three. One is the hormone receptors and that's estrogen and progesterone. The next is the erb-b2 receptor. And that determines whether the tumor is HER2+ or HER2- . And then the third type would be the patients whose tumor had none of the three receptors that I've mentioned. And if there is no estrogen progesterone erb-B2 or HER2 then we call the type of breast cancer, triple negative.

ADAM: HER2 stands for human epidermal growth factor receptor 2. It's a protein that contributes to the growth of cancer cells.

Now, understanding the different types of breast cancer is important when it comes to developing potential treatments. Increasingly, treatments like targeted therapy, or precision oncology, help doctors get at the specific cause of a patient's particular type of breast cancer.

Martha Carlson – the patient advocate we heard at the beginning of the episode – she has HER2+ metastatic breast cancer. Martha's oncologist started her on a treatment that involves two different targeted drugs, aimed at the HER2 protein.

> Martha:
> I have remained on those same treatments this entire time. I was diagnosed with cancer in the end of 2014 after all the tests and everything with metastatic breast cancer at the beginning of January 2015, and then started treatment in January 2015. And I've been on those same treatments ever since.

ADAM: The average life expectancy for people with Martha's type of breast cancer is about four years. Martha has been living with metastatic breast cancer now for *eight* years, with the help of this medicine.

Targeted treatments are also available for another breast cancer subtype: hormone receptor positive breast cancers. These treatments target and reduce the hormones responsible for driving that cancer, whether it be estrogen or progesterone.

The third type of breast cancer, triple negative, remains a particularly challenging type to treat. Because it's negative for all the usual cancer receptors, it doesn't have easily identifiable drivers that can become targets for therapy.

[MUSICAL TRANSITION]

ADAM: The fact of the matter is, sometimes even treatments that initially produce benefits for the patient won't work indefinitely. That's because of drug resistance. Here's Jeff again:

> Jeff:
> Drug resistance is one of the major limitations to achieving a sustained treatment benefit for cancer patients, including breast cancer patients. We know that when cancer patients receive drug treatments that produce some measurable clinical improvement over time, they often face the prospect of the emergence of drug resistance as tumor cells mutate and find ways to evade the assault from cancer killing medicines. So despite remarkable progress in the treatment of cancer with these new therapeutics, the nearly inevitable development of drug resistance remains a major limitation to the utility of most cancer medicines

ADAM: There's a snag: Similar to antibiotic resistance, cancer cells can also mutate and avoid the effects of drugs. And if that wasn't enough, there's another major hurdle researchers like Jeff are up against when trying to develop new breast cancer treatments.

Jeff:
One of the challenges that we face when designing new immunotherapies, just broadly speaking, is that the immune system is, is remarkably complex. And the ability to effectively leverage a patient's own immune system to battle their cancer is conceptually very powerful. But because of the complexity of the immune system, we don't really understand how to do that optimally and without kind of dialing up the immune system so much so that it's actually toxic to the patient, uh, and achieving that balance is, is something that we work hard to better understand.

ADAM: Heterogeneity, drug resistance, and the complexity of the immune system. These are barriers to the effective treatment of all cancers, breast cancer included. The good news is, researchers have been working to address these challenges with new innovations. But, it does take time.

Jeff:
Finding new cancer treatments invariably involves a long process.
And it starts with a deep understanding of the disease biology associated with a particular type of cancer and determining the right target to go after in that disease. And we wanna understand what the vulnerability might be in that specific type of cancer.
Then we need to discover a candidate therapeutic molecule that we believe can effectively disable the target of interest in a way that selectively stops the tumor cells from growing, but without causing too many side effects through its actions on non-cancerous cells. One of our biggest challenges is that tumor cells often look a lot like normal cells. And so it can be difficult to discover therapeutics that specifically impact cancer cells while sparing normal, healthy cells. But once we have a promising molecule, even at that point, it then takes many more years of clinical trials to establish its safety and efficacy before it can be approved for use. So it's a very long timeline, again, spanning typically 10 years or, or more in some cases.

[MUSICAL TRANSITION]

ADAM: So let’s dive into some of the research that’s currently in progress. Many exciting new therapeutic options fall under the category known as small molecule treatments.

Jeff:
Small molecules are essentially chemicals. So we know about other chemicals that are commonly used. So for example, table salt is sodium chloride. It's a chemical, it's a small chemical, it's a small molecule now in, in the world of drug discovery, small molecules are a little bigger than that, but they are designed to be both effective in specifically targeting a protein that we believe is playing an important role in cancer, but without affecting other proteins in the cell.
We look at the shape of the protein, and then we design small molecules that match the shape of that protein and that allow that small molecule to find its target in a cell where there are thousands of proteins. We just wanted to find the one we wanna target and nothing else ideally find that pocket on the protein where it needs to grab onto and block

its function. So that's quite a process. But I think we've, we've become pretty good at it over time.

ADAM: In other words, these treatments are *not* a one-size-fits-all approach.

Jeff:
Kind of like an assassin, yeah. An assassin kind of hiding out, waiting to pounce and knowing exactly who the target is and going after it specifically and making a clean getaway. Ideally.

ADAM: These assassin-like small molecule treatments attach to a cancer's specific type of protein. Because of that, they can also result in a medication with fewer side effects, and better quality of life for individual patients.

Within this category of small molecule treatments, Pfizer is working on medicines called cell cycle inhibitors.

Remember, cancer is simply made of up cells, just like everything else in your body. As cells grow and divide – like when a fertilized egg begins to grow into a mature organism – they go through a process called the cell cycle. It's a series of steps where the cell copies its DNA, and then splits and divides into two cells. The cell cycle also kicks in when cells naturally grow old and die, and new cells replace them.

This process requires the cooperation of proteins and enzymes that read signals and ensure there are no mistakes in the copied DNA, and that everything happens at the right time.

Cancerous cells also follow this cycle, but things don't happen the way they should. Cancer cells can grow when there are no signals telling them to grow. They can accumulate mistakes in the DNA of new cells.

Cell cycle inhibitors that are currently available to patients target the proteins that signal whether that process should stop or continue. Pfizer is working to develop next generation Cyclin Dependent Kinase inhibitors. "CDKs" are the family of protein kinases first discovered for their role in regulating the cell cycle.

If these new CDK inhibitors succeed, it could also help oncologists combat drug resistance.

Jeff:
So what we've learned about through the development of our CDK inhibitor that's already approved for use in the clinic is, comes from, you know, the, the experience of so many patients where we get to see not only the, the benefit, the duration of benefit, but also mechanisms of resistance. Patients will often develop resistance to therapeutics that specifically target proteins that are known to drive self proliferation. It's through that experience, we've learned about the the limitations of the currently available therapeutics, both in terms of their efficacy, how long do they deliver benefit before this

resistance emerges? And also what is their safety profile and are there ways we can make the drug more safe so that patients will be able to stay on it and tolerate it longer? And so we've learned about those, those elements of safety and efficacy and that has helped us to come up with novel designs for molecules, small molecule drugs that have distinct profiles that we predict based on preclinical science will have advantages when it comes to their efficacy.

ADAM: Pfizer is also working on a cutting edge set of therapies known as epigenetic modulatory agents. They're medicines that target the epigenome.

You're probably familiar with the genome: the DNA that codes proteins in our cells to do what they're supposed to do. Basically, it's a set of instructions for all our cellular functions.

The *epigenome* sits on top of our DNA. It turns certain genes on and off, and determines which genetic instructions actually get through to the cells.

Jeff:
This epigenome is very important in cancer because we now understand that it's, that the epigenome of cancer cells looks quite different than the epigenome of normal cells. And so that tells us that there is something going on with the epigenome, that's likely to be contributing to cancers and it also yields a therapeutic opportunity. And so there are now a few approved epigenetic regulatory drugs. We actually don't really understand fully their mechanism of action, but we're developing a better understanding of the epigenome and how it drives cancer to the extent that we now have more rational targets in mind.

ADAM: When it comes to cancer, the epigenome is abnormal. In some cases, the cancer epigenome even *helps* the tumor *evade* the immune system's defenses, and treatments like chemotherapy. So, scientists are now looking to use the cancer epigenome to their advantage.

Jeff:
We're pursuing targeting a protein called Kat6a, which is a regulator of the epigenome that we think is especially relevant in hormone receptor positive breast cancer. And so we have, we discovered a small molecule inhibitor of Kat6a and that's in phase one clinical development currently. And so we're excited about the prospects for targeting breast cancer with an epigenetic regulatory, small molecule.

ADAM: There are *plenty* of exciting developments currently underway. The research continues to build on itself, creating new combinations of treatments that better target the root cause of the cancer. But don't forget, immunotherapy is another tool in the oncologist's arsenal. And scientists have been working on improving the effectiveness of immunotherapy in breast cancer treatment.

Jeff:

I think in addition to that there have been developments in the immunotherapy space that have also really changed fundamentally the, the paradigm for how we treat cancer the ability to engage the immune system of a patient to attack the tumor in that individual is something that has really taken hold, I would say, in a substantial way over the last decade.
We do have a phase one program going now using what's called a bispecific antibody. This is an antibody that is designed to promote the interaction of a type of immune cell called a T-cell, which has the ability to kill cancer cells to promote the interaction of that T-cell with, uh, a breast cancer cell that expresses another protein called B7- H4.

ADAM: This form of immunotherapy has shown promising early signs of helping to eradicate tumors. Next, researchers will need to see how those promising signs play out in the clinic.

There are so many new innovations on the horizon. More than ever, researchers and doctors have the technology to create meaningful change in patients' quality of life.

Edith:
So patients are living longer. The mortality rate from breast cancer has decreased significantly over the last decades. And with research, continuing both research supported by the national cancer Institute and research supported by pharmaceutical companies, by radiation companies all of these have allowed for a decrease in the death rate from breast cancer and therefore so important. So for diagnosis, we've got better, x-rays better mammograms, better ultrasounds. All of these are very important and the technology for evaluating tumors that allow us to choose the right therapy for the right patient at the right time.

Jeff:
Looking forward, you know, when I think about what, what lies ahead and what's exciting in the context of breast cancer, as we discussed, there are certainly some limitations to the benefit of our currently available therapeutics. And we're always aiming to extend the duration of benefit to produce long term remissions, durable, remissions, and even potentially curative outcomes.

[MUSICAL TRANSITION]

ADAM: In part two of this story, we're gonna dive into an essential key to the treatment development process: clinical trials.
Remember Martha, the patient advocate? When she was *first* diagnosed with breast cancer, her doctor suggested she try a clinical trial.

Martha:
I was really lucky. My oncologist is somebody who is active in research. And when I walked in … I remember on her cabinet door, it says clinical trials are not the last option. It's just, you know, a printout on a piece of paper taped to her cabinet door. And so that, first of all, just seeing that made me think, be aware like the word clinical trial was in my

mind. They were saying you can… would you be interested in this, it's X clinical trial, but in order to do that, you need to have these scans, like, we need to confirm that you do not have metastatic breast cancer. So it was brought up. I feel like it was at the very first, my very first appointment with her. She said, you know, based on the information, you might be interested in this.

Martha:
We were working on the assumption that I was, was early stage based on the information that we had. And I agreed to be on the clinical trial. And because of that, I had scans that showed that I had metastatic breast cancer. And then further biopsies to confirm that.

ADAM: Now, this is not the purpose of clinical trials – to provide a more thorough diagnosis. But, that's how it worked out for Martha.

Unfortunately, the new diagnosis meant that she wasn't eligible for that particular clinical trial. But she stayed involved in the trial process: A lot of her work revolves around working with researchers and patients and making sure they are aware and have access to this important part of the treatment development process.

In episode two, we'll do a deep dive into how breast cancer clinical trials actually work. And we'll get a look at how cutting-edge design and technology are helping reach more potential participants.

END CREDITS
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