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Tim Lightfoot. Hello and welcome to the weekly edition of the Huffines Institute For Sports Medicine and Human Performance Podcast. We're so glad that you took the time to download us and you're taking time to listen. Every week we bring you interesting people from the world of sports medicine and general health. And this week is no exception. We are so pleased to have Miss Jessica Wapner who is the author of a new book named "The Philadelphia Chromosome" and we will give you the full title here in a few minutes. But we're so pleased that she's with us. Welcome to the Podcast, Jessica

Jessica Wapner. Thanks so much. Good to be here.

Tim Lightfoot. Let me tell the folks a little bit about you and why we're so excited to have you here. Jessica's a freelance writer who focuses on science and health. She's had her work in The New York Times, Scientific America, Slate, Science…that's a big one, Nature Medicine and elsewhere. She really concentrated her writing on cancer research and treatment and writes a blog called Work In Progress about drug development and the ethics and economics of drug development. She has quite a history in science publishing, having been the founding managerial editor at two science journals. One wasn't enough, you had two, huh? And we're going to put links or a website, which is jessicawapner.com and her blog and the show notes so everybody can find her and read about her and the stuff she's got going on. But as I mentioned, she's here today because her first book came out last month and it's called "The Philadelphia Chromosome, A Mutant Gene In The Quest To Cure Cancer At The Genetic Level," and I will say I got it last night and I've read about 100 pages of it so far and it's a fascinating read about the battle to actually cure a specific form of cancer. And she is so nice because she gave a talk last night at the Bush Presidential Library here in College Station and she agreed last night that she would come by and do a Podcast with us before she flies back to New York. So thank you for that.

Jessica Wapner. Yeah, great.

Tim Lightfoot. Yeah. So, again welcome to the Podcast and let's just start off with an easy question.

Jessica Wapner. Sure.

TL What is the Philadelphia Chromosome?

Jessica Wapner. Is that an easy question? It is a great question. So the Philadelphia Chromosome is a genetic mutation that is associated with chronic myeloid leukemia which is a cancer of the white blood cells. The mutation involves a translocation which is when two chromosomes have a swap of genetic information. So in this case, a little bit of Chromosome 9 and a little bit of Chromosome 22 swap places and that small change brings together two genes

that lead to a mutant protein that triggers the production of white blood cells. That is the hallmark of CML.

Tim Lightfoot. Okay. Let's do a 30,000 foot question here before people tune us out and go, oh gosh, I didn't want to tune into a genetics like, for the day. Why is this important for everybody, the public? Why is it important…why is your book important for everyone to read?

Jessica Wapner. Well there's a couple of things I would say about that. First, this story is the origin story of the current moment in cancer research so whenever we hear about target therapy, finding the genetic underpinnings of cancer, this story is why we kind of think that's a good idea. Because it proved the principle behind targeting cancer at its root cause, so it's really…on the current mountain that cancer researchers are climbing, this is a story that is the foothills of that mountain. But at the same time, there's a bigger picture, in that, one thing that I was trying to do with this book was to really pull the curtain back on how drug development happens. How does a new medication go from being an idea to being a reality and all of the difficulties therein? And I wanted to…I love the knowledge of that. I love knowing these things and what that then causes in us just to have the information and allow…that allows us to speak intelligently about healthcare, about the pharmaceutical industry and also gives us understanding about ourselves, about how belief plays into it, how persistence and determination and also the kind of emotional story of the patients who really rescued this drug and saved their own lives in the process.

[00:05:05]

Tim Lightfoot. Well [??? 00:05:06] this is a fascinating story. From hearing you talk and what little I've read so far, the book, you've done a great job of putting this in a story form and as scientists many of us don't think of what we do as a story and you've done a great job of going back to what, almost 60 years?

Jessica Wapner. Well it was…the Philadelphia Chromosome was discovered in 1959. Some of the science, like some of what I spoke about last night at the talk with Payton Rous and his virus that caused cancer in chickens, that was from 1910. But we really date the story from 1959 and to then, through the approval of the drug that I write about, called [Gleevak? 00:05:48] which was approved in 2001.

Tim Lightfoot. Okay. So you mentioned the chicken and I have that on my list of questions, so let's talk about the chicken and how a chicken actually plays a role in this.

Jessica Wapner. A chicken plays a very important role and it was one specific chicken which was brought to a man named Payton Rous who was a scientist at Rockefeller University. This chicken had a tumor and the farmer showed up carrying her chicken to this man's laboratory and asked him to operate.

Tim Lightfoot. And this was in 1910?

Jessica Wapner. Uh-huh.

Tim Lightfoot. Wow.

Jessica Wapner. Yeah. So it was her Plymouth Barred Rock hen. She was a farmer and she didn't want to lose her valuable hen to cancer. So when Payton Rous removed the tumor the chicken died. Remnants of the cancer had remained in its body but the…he was able to take the tumor and grind it up and create a, kind of an extract from it and discovered that within that extract there was a virus because when he injected that into another chicken the next chicken got the same cancer. It was years of research…and I really describe those years of research in some depth in the book to find that there was a gene within the viral G-Gnome. And I won't get into the specifics of RNA viruses and DNA viruses. I'm speaking very generally here. There was a gene called sarc, that was named sarc because it caused this Sarcoma in chickens that was responsible for causing the cancer in the chicken, right? Because they could figure out that the virus could still replicate without this gene but when that gene was removed it didn't cause cancer.

Tim Lightfoot. Cancer.

Jessica Wapner. And all of the…it sounds so kind of neat and tidy but it took a lot of experiments to figure that out…

Tim Lightfoot. Sure.

Jessica Wapner. …to find out how to remove that gene in the era before recombinant DNA. So they found out that this gene was triggering the cancer and then they found out that the gene had come from the chicken. That the virus had kind of scooped up this gene from the chicken G-Gnome into its own G-Gnome. And when it got scooped it up it mutated, which led to eventually the terms "proto-oncogene and oncogene", right? We know that oncogenes are genes that can trigger cancer and we also know that we have…that they can exist as proto-oncogenes. They don't always cause cancer but they can mutate and that's when they start triggering cancer in our bodies. So the notion that cancer can be triggered by our own DNA all started with this farmer and her chicken back in 1910.

Tim Lightfoot. Yeah. The role that luck plays in this is amazing.

Jessica Wapner. Yeah.

Tim Lightfoot. Of all the people that, as I think you mentioned last night, if someone walked into my office now with a chicken and said it has a tumor, I would say a) you're in the wrong place. The vet school's down the road…

Jessica Wapner. Right.

Tim Lightfoot. …and you probably wouldn't even get in the front door nowadays.

Jessica Wapner. That's right. It just would never happen. I mean there'd be feathers flying and nobody wants that.

Tim Lightfoot. No.

Jessica Wapner. So.

Tim Lightfoot. In your experience how often does luck play a role in science?

Jessica Wapner. Well I think it plays a pretty significant role in this story. There's many moments of serendipity where with Peter Knoll and one of the co-discovers of this genetic mutation back in 1959 he talked about the role that luck played in his life early on in his career with rinsing cells under tap water instead of distilled water and what that caused in the cells. There's other times of other technical moments in the story where somebody just doing something a little different because they felt lazy or because they didn't think to check or because there had been a similar discovery a week before and lightning doesn't strike twice, so they looked elsewhere, all of these things that we do, right, ways that we think. But at the same time, it's not just luck, right?

[00:09:59]

It's definitely not just luck because another major theme in this book or in the story for me was seeing that when there is good science, it will lead somewhere. It won't always lead to where you think but there are so many instances of people asking the right question at the right time and answering it in the right way, that it just…there's no good science that's ever wasted but you never know where it's going to lead to.

Tim Lightfoot. You never know. It's right, right. So to that point, no good science is every wasted, what also impresses me about is…about this story is the length of time from the 1959 kind of discoveries to when we had enough knowledge to kind of put it all in context. And that really runs counter to our society's expectation now that any research is done we should know immediately how it works and why it works and the context in which to use it. And yet some of these things don't pay off for years and years and years.

Jessica Wapner. Yeah, that's right. That's right. I often think of publically funded research as we are funding curiosity, right? That's what we want. We give research grants to people who are curious and want to use science to test out a hypothesis. It's not the same as saying we want to know what causes breast cancer and trying to create a program or a drug development program, let's say, to answer that question. That can work too, it has worked, but there are so many instances that where we can find that…where we got…you know getting from point A to point b was not a direct route. So I think the basic research is its own world and you can't always place demands on it for a specific result although it's not hard to because it's a whole lot of money that

we invest in scientific research and I think it can be difficult to do that without the expectation of a result. But it just doesn't…life just doesn't work like that.

Tim Lightfoot. Yeah. I wish you could go speak to some of the review committees I've had experience with. Well, we have another guest in the studio right now. There's scientist Penny Riggs and she's here shaking…nodding her head vigorously on that one. We've mauled [??? 00:12:28] I think. Let's talk a little bit about your story is a drug development story as well. It's not just about cancer. Talk a little bit about the drug that is kind of a main player in this.

Jessica Wapner. Right. So this is the first ever so called kinase inhibitor, right? Because this protein that I talked about being haywire is a kinase which is a kind of enzyme and this particular kinase triggers the production of white blood cells. The drug that was created to block that activity is called gleevec, the brand name is Imatinib. It was approved, as I said, by the FDA in 2001. Made by a drug company called Novartis which, when Novartis was founded, it was the biggest pharmaceutical company in the world. But the creation of the drug took 18 years.

Tim Lightfoot. Wow.

Jessica Wapner. So, I mean it's interesting because if you go to the…if you go listen to the press release conference, the press conference when the drug was approved in 2001, there's people from the FDA and the chairman of Novartis at the time, Daniel Vasella, saying that it was two-and-a-half years from the time that the clinical trials started to the time that the FDA approved the drug, which is absolutely true, right? And once the drug company got onboard with making this drug they did the right thing but it was 18 years from the time that the program first started at the company till the time it was approved. And part of why it took so long was because it was very difficult to get the company to fully commit to this drug even when all of the signs were pointing towards its promise.

Tim Lightfoot. Yeah and that was what I was going to ask you is not like they didn't have some indication that this would work.

Jessica Wapner. That's right. I mean there were cell studies, of course, the pre-clinical studies in the lab that were showing that the drug was working or working as you would expect it to in a laboratory setting…

Tim Lightfoot. Sure.

Jessica Wapner. …right? You can't infer much about what it will do in people. The drug was safe in animals, there were toxicities but it was not the kind of thing where you would stop the drug although some people wanted to.

[00:14:52]

And then in human trials, which began in 1998, there were very early signs of response, even in a time where you wouldn't be looking for response, right? Because then a Phase I clinical study you're just testing for safety, you're not testing for efficacy at that point.

Tim Lightfoot. So it was working pretty early.

Jessica Wapner. It was. Yeah, it was quite amazing. Actually after all of the kind of blood, sweat and tears that had gone into convincing the company to start a clinical trial by the third month they were starting to see patients responding, blood counts going down. Yeah.

Tim Lightfoot. Wow. So we'll talk about the implications of that. Before we get too far away though, you did extensive interviews for this book. I mean you talked to all the major players in this and the drug companies and the physicians and the…many of the early subjects that used the drug. Any of the people that you talked to that were initially opposed to the drug being made? Some of the accountants or some of the other folks that you talked about, what's their, what's their thought now? The fact that they were against the drug being made, are they…as they said wow, I was really wrong and…or?

Jessica Wapner. Uh-huh. Well I didn't talk to those so many people who were absolutely opposed to the drug. I don't know that anybody was opposed to the drug. There was this one toxicologist who had said not over my dead body will this drug go into men. I didn't talk with him.

Tim Lightfoot. I was going to say I hope he didn't die or anything…

Jessica Wapner. No.

Tim Lightfoot. …as part of this.

Jessica Wapner. No, no. I did not speak with him but I did speak with people who offered a balanced view. I interviewed Daniel Vasella who, as I said, was the chairman of Novartis at the time and his story was that this drug was not going to be shelved as people thought. I learned a new term when I was doing interviews was File 13, which means in the trash, right?

Tim Lightfoot. Oh, okay.

Jessica Wapner. One of the patients had said to me I was told this drug was File 13. He said…he explained that no. What happened was that there was a big demand for the drug. Once the Phase I study was looking good, people wanted it fast, they wanted the trial to be expanded fast, and they couldn't make the drug quickly enough.

Tim Lightfoot. Oh really. Oh so it was a production issue, huh?

Jessica Wapner. He talks about it being a production issue because you never have enough drug to go from. with 30 patients to 1,000 patients. So they had to take over a facility in Ireland and get them to work only on this drug 24/7.

Tim Lightfoot. Wow.

Jessica Wapner. And it requires special equipment, they have to have kind of Hasmet suits to make it. So it was a big deal. So there's another side to this story. And there's also not wanting to be too risky if the drug was going to be harmful to people, because you just don't know. That you can do as many animal studies as you want you will never know what the drug will do once it goes into people.

Tim Lightfoot. Until you start doing humans.

Jessica Wapner. Yeah. Which was part of the argument against continuing the animal studies. There was one moment where somebody said to Brian Druker who…Brian Druker is one of the heroes of this story. Patients with CML really credit him for saving their lives. He fought for this drug to get into clinical trials for years. And there was one point where…I spoke with Juerg Zimmerman who was the chemist who created the drug who explained that you had to be very careful taking a risk, right? So you can say, well it should have gone to patients faster. But you can also say if it had hurt someone why did you take the risk? So there's more than one side to this story and I really tried to tell it as fairly as possible to show that there were delays. That it was never certain that this drug was going to be made. But there's also another side to this story and it's not to kind of jump on it as bad, a big pharma.

Tim Lightfoot. Yeah. One of the…I think the exciting…and to come back to the implications of this drug…one of the exciting things about this story is that, the realization that, here finally is a way to treat a form of cancer without chemotherapy, without radiation and a variety of other blunt instruments that have been used. That's exciting news isn't it?

Jessica Wapner. Absolutely, yes. A lot of people don't know about it. When I tell people there's a type of cancer that used to be fatal and now there is a pill that you take once a day that many…with many people experiencing no side effects and you can live a normal, healthy life, I mean, a lot of people say what?

[00:20:05]

Tim Lightfoot. You're right. Right. Would you say that's a cure for this cancer?

Jessica Wapner. No I wouldn't call it a cure because if a person stops taking the drug the cancer returns most of the time. There have been some studies now, kind of, where people have been taking the drug for 10 years and they wanted to see if you stop taking it, will the cancer return? What happens is this drug keeps at bay the white blood cells housing the Philadelphia chromosome mutation so those cells disappear when a person takes this drug. But if you stop

taking it, they return because you're no longer blocking it, right? You're no longer throwing that wrench into the clockwork. You're removing it so it all starts back up again. Technically speaking doctors don't like to speak of it as a cure because it's not gone, right? And the only real cure for CML is bone marrow transplantation but, then again, a bone marrow transplantation will leave you damaged for the rest of your life. I met someone while I've been doing author talks, who said I've been through a bone marrow transplantation and I wanted to know how are you doing now? Does it really…are you really cured? And he said, well yes, but I have neuropathy, I have this, I have that. He's not better, 100 percent.

Tim Lightfoot. Right, right.

Jessica Wapner. When I did a talk with Brian Druker in Portland somebody asked him the same question and he said we really don't like to use this word cure because it gets us in trouble, right? But you're taking this drug. There's been people who have been taking it for 15 years and are fine. What other word do you want to use for that?

Tim Lightfoot. Right. It's 100 percent effective in these patients?

Jessica Wapner. It can be. There are…

Tim Lightfoot. Okay.

Jessica Wapner. …some people that don't respond to gleevec in particular and there are second and third generation versions of the drug. There's about six kinase inhibitors just for CML right now and there are some people who might become resistant or relapse and then it's untreatable at that point because of other mutations that arise as the cancer progresses. So it's not 100 percent but I've seen 10 year survival statistics that are around 95 percent.

Tim Lightfoot. Wow.

Jessica Wapner. Yeah.

Tim Lightfoot. Wow. So is this…does this pretend a new approach to treating other kind of cancers as well?

Jessica Wapner. Absolutely. There are other kinase inhibitors. There's about 15 on the market now and it also provides evidence for finding the genetic underpinnings of cancer. I mean this drug treats the protein not the gene, right? But it's the root cause. So it shows that if you can find the root cause you could create a drug, it's treated. It's not always that easy and people often refer to this as kind of a one off. Is this a one off? Because of the nature of CML, because it's one gene and one disease maybe it will work in CML and not so much in other cancers. That really remains to be seen. The other kinase inhibitors do extend survival time. It's not this kind of home run, indisputable home run that we see with CML, but it does improve it for sure. And it also is this bigger picture of it shows that if you can find the root cause that you could create

compounds and a lot of people are researching combinations of drugs. So that it might not be one drug, it might be multiple drugs that attack multiple root causes.

Tim Lightfoot. Interesting. So we have a new era of cancer treatment in front of us.

Jessica Wapner. Absolutely. I mean that's the hope for sure and we don't know, nobody wants to give false promises and I don't think any of us are walking around sort of naïve and starry eyed about what's possible with cancer research because of so many disappointments. But at the same time, I find this notion that we are at the beginning of a new era very compelling. I kind of like to think well we were there then and who knows what could be the case in 20 or 30 years.

[00:24:49]

Tim Lightfoot. Yeah. And you got to be the historian of the moment.

Jessica Wapner. Or one of.

Tim Lightfoot. Or one of.

Jessica Wapner. A privilege, yeah.

Tim Lightfoot. I tell you before we conclude, one of the things that we talk about on this Podcast quite a bit, because we have younger audience as well, it's how you got interested in doing, as I call it, science translation? Because you're not a scientist yourself on a daily basis but you have written about science, you try to translate that to the lay public so they can understand it. How did you get into that? What interested you about that?

Jessica Wapner. Well I always loved science. I mean definitely back in high school I dreamed of being an ethnobotanist and running off into some rainforest and finding cures for cancer and everything else. But I was interested in science. I studied biology in college, not anything microscopic. I mostly studied mockingbirds for four years. But I love it. I mean…which is why I want to be around it as a first thing. The idea of translating these complicated ideas into a potentially compelling read is…I mean it's fun and it's challenging and [??? 00:26:01] always fun. It is always challenging. It is sometimes fun. The end result is fun. So…but it's so…it's such interesting work. I get to learn new things every day and the challenge of finding a way to convey some technical idea in a way that somebody, anybody can understand, I love that. I mean if it's…I always feel if it's something real, right, if this life, the stuff of life that we're learning about, there has to be a way to convey the information. It can't be that it's just going to be behind the laboratory door that people understand this.

Tim Lightfoot. Right. Well that's a great talent and thank you because…

Jessica Wapner. Well I'll try.

Tim Lightfoot. Well the thing is, my concern as a scientist is that the more that goes on behind the lab doors that the public doesn't understand it's more, it's magic to the public. And so that's…I'm grateful that we have folks like you out…you out there doing this kind of thing.

Jessica Wapner. Well thank you.

Tim Lightfoot. We're coming close to the end of our time here and we always ask our guests to give us a take home message.

Jessica Wapner. Right. My take home message is read the book.

Tim Lightfoot. There you go. That's all right. We'll put another plug in for the book. "The Philadelphia Chromosome."

Jessica Wapner. No, I'm joking. No my take home message for real.

Tim Lightfoot. Sure.

Jessica Wapner. My take home message for me about this story I would say, I don't know what anybody else's take home message would be but I think my big take home message has been that when people are working together great things can happen. This is a partnership between the industry, between academia, between patients, between the FDA and the National Cancer Institute. It is everybody. There was no one hero behind this story. There are people credited as being the hero. The truth is that everybody who played a part in getting this drug made was doing a heroic act and it was only from everybody playing their part that it got a shot in the world.

Tim Lightfoot. Super, super take home message. Thank you for that.

Jessica Wapner. Yeah.

Tim Lightfoot. Thank you for being with us today

Jessica Wapner. Thank you so much. Thanks for having me here.

Tim Lightfoot. And I want to thank all of you that have been listening for taking the time to download us and if you're a regular listener you know that every week we do a Podcast question of the week and here with our Podcast question of the week is our producer Kelly.

Kelly. What is the name of the drug that inhibits the protein activity that causes CML?

Tim Lightfoot. Great question. Be the first one to e-mail us the response, the correct response at Huffinespodcast@hlkn.tamu.edu and you'll win one of those nifty Podcast tee shirts.

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