Harvard Medical Labcast
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On Cancer's Case
How family tragedy gave rise to a world-leading cancer biologist

Guest: Joan Brugge
Host: Stephanie Dutchen

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Dutchen: Hello, and welcome to the Harvard Medical Labcast, brought to you by the Harvard Medical School Office of Communications. I'm your host, Stephanie Dutchen.

With us today is Joan Brugge, a cell biologist who has devoted her career to uncovering the fundamental workings of cancer. Her world-renowned discoveries have focused on viruses that drive various cancers, as well as how disruptions in cellular processes lead to tumor formation, metastasis and resistance to cancer treatments. These days she's especially interested in breast and ovarian cancers.

Joan, such a privilege to have you on the podcast.

Brugge: Oh, thank you very much.

Dutchen: So before we get started, let's tackle all of your titles. You are the Louise Foote Pfeiffer Professor of Cell Biology at HMS, and you were the chair of the Cell Biology Department for 10 years. Now you are director of the Ludwig Center at Harvard Medical School, which we will talk about in just a few minutes. All correct?

Brugge: Great.

Dutchen: Okay. So, our unofficial theme this season on the Labcast is journeys, the paths that people have taken to get to where they are now. And I thought maybe we could start with what you originally intended to study when you were in high school and college and what happened to change all of that.

Brugge: Okay. As a high school student, I loved to solve math problems. I could spend hours solving math problems and being very happy. However, in the 1960s, the only career that I considered within the realm of possibility was teaching. So, I went to Northwestern University as a math major, and I had the goal of becoming a high school math teacher. But then in the second year of college, my world was turned upside down when I learned that my sister, who was a year older, had an incurable malignant brain tumor.

So, I then switched from solving math problems to solving the problem of cancer. And I started by asking my sister's neurosurgeon, Dr. Frank Mayfield from Cincinnati, what were his thoughts on the origins of cancer. He replied to me that he thought that viruses might be involved in cancer. So, I went back to Northwestern and did independent studies in order to understand what was known about tumor viruses. I also changed my major to biology and a minor in chemistry in order to be able to pursue a career in cancer research.

Dutchen: Were you able to help your sister?

Brugge: No, unfortunately, my sister passed away.

Dutchen: I'm sorry. But, uh, in a way it was a catalyst to send you down this path of decades of, I mean, research that has made a big difference.

Brugge: Yeah. I think that I would never have been exposed to the world of research had not… had this not happened. Well, who knows, but... and it certainly is highly motivating as well.

Dutchen: Thank you for sharing that story. Could you tell us more about some of the things that you looked into and what you found when you graduated from college?

Brugge: All the reading I did about cancer research got me very interested in actually doing cancer research, and I was lucky enough to get a slot in the summer program at Jackson Lab in Bar Harbor, Maine, and there we basically immersed ourselves in research projects for the summer and also had really great interactions with other students that were interested in the same thing, so it was a really great experience. Basically, I got hooked, and there was no turning back since then.

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Brugge: So, I went on to graduate school, and I went to a department that studied tumor viruses, and then I did my postdoctoral research after getting my PhD in, again, in a lab that was studying a tumor virus.

Dutchen: Now, you made a major discovery when you were a postdoc that people always reference when they describe your contributions to the field, so can we talk about that for a bit?

Brugge: Sure. The virus that I was studying was one of the most well-characterized tumor viruses, called Rous sarcoma virus.

So this virus was known to contain a small piece of genetic information that was required for the virus to be able to cause tumors in experimental animals. And the year before I started my postdoctoral fellowship, the lab of Harold Varmus and Mike Bishop found that this piece of DNA was actually captured by the virus from normal cells. And so what it said was that the genetic information that's responsible for causing this tumor by the virus was actually normal cellular DNA that's in all of our chromosomes. So there was enormous interest in finding the

protein product of this genetic information so we could learn about how this protein was able to cause cancer.

And so lot of people were trying to find this protein, and I was one of them. I basically spent two years trying many different approaches, involving many different types of experimental animals. Then after two years, there was one day when a protein appeared on a gel that had all the characteristics of the protein that we were looking for, and we later found that it was in fact truly the product of this gene that was necessary for cancer formation. That gene was called *SRC*. That was an amazing day, because after looking for so long to find that protein, it was one of those rare "eureka" moments in science.

And I think the excitement of this, together with the opportunities it afforded to dissect the mechanisms involved in cancer, distracted me from many of my concerns about the challenges of balancing work and family, which were very big issues for me at the time. There were very few role models for women in research, and I was seriously concerned about whether I would be able to be a lab director as well as a good mom, basically, and I really wanted to have children. And so that's something that I spent a lot of time thinking about, but then after… after finding this protein and being so excited about following up on it, I basically put aside those concerns and just kept moving forward.

Dutchen: And you've been going steady ever since.

Brugge: Yes, yes, exactly.

One thing interesting is that if Rous sarcoma virus was discovered yesterday and I wanted to identify the gene that was responsible for tumorigenesis, it would take a week or two nowadays, because we can isolate the gene and sequence the DNA within a few days.

Dutchen: As opposed to—

Brugge: —but we had no access to any of that technology.

Dutchen: Whole postdocs were spent on questions like this.

Brugge: Many. [laughing] Many postdoc lives were spent trying to find that protein.

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Dutchen: In the years since that initial breakthrough discovery and now, what have been some of the findings that sort of bridged where you began and where you ended up?

Brugge: Since that time, my… The initial studies that I carried out after getting my own independent lab were focused on understanding how the normal cellular SRC protein works, because I reasoned that if we could figure out what the normal cellular SRC protein does, that we would understand how alterations in this protein associated with cancer would be able to cause cancer and then to develop therapies to block it.

And what we found was very surprising in that we found that the normal cellular protein doesn't specifically regulate cell proliferation or survival but is involved in many different pathways. That really complicated our understanding. Basically, nature's been very conservative in its use of proteins, and a protein like SRC turns out to be activated by most of the receptors in the cell and to regulate many different types of activities in the cell. So we learned a lot, but there were so many different cellular programs that were regulated by this protein. It was really hard to figure out which ones were critical for tumorigenesis.

I kind of had an opportunity to completely refocus our studies after I took a short five-year sojourn in biotech. I was lured into helping to start a biotech company, lured because of my interest in being able to not only do discovery research but also be able to follow up on it to help develop therapies that would be useful to patients. And I did this for five years and then I was interested in returning to academics in order to be able to be more directly involved in the design and interpretation of experiments. I really missed that when I was a high-level scientific director of this biotech company.

Dutchen: It must be really hard to feel tugged between wanting to help develop therapies for people who have cancer currently on the one end, and on the other end to continue to generate the knowledge that's the basis of those future treatments. How do you choose between them?

Brugge: I think initially it wasn't difficult, because we knew so little that we needed the basic answers, but now I think you're right. My lab is really a mix of discovery research to understand more about cancer as well as using the information that we and others have already to try to find the best ways of treating cancer.

I feel like now the field is at a stage where labs that are interested in discovery can still help contribute to using the information and translating, it's called, translating the information that we have from these discoveries into therapies that will help patients.

Dutchen: Well, that could be a good segue into talking about some of the projects you've got going on right now. They fall into a couple of different buckets. One way to think about them is breast cancer, ovarian cancer, other cancers. Another way to think about them is the types of experiments that you're doing to look at these kinds of cancers.

Brugge: So, one of the new approaches that I took after returning to academics and to the position I have now at Harvard was to develop a culture model system in which tumor cells could organize into three-dimensional structures or masses that more closely resemble the organization and architecture of a tumor than what we'd been using before, where we just grew cells, a sheet of cells, on a plastic dish. None of the cells in our body are organized that way, and certainly tumors don't grow that way. Tumors grow as a ball of cells as opposed to a sheet of cells.

We develop culture conditions in which cells, tumor cells, could grow under these conditions. We also used methods whereby normal cells that are targets of mutations that cause cancer could be grown. That turned out to allow us to study behavior of tumor cells in ways that weren't really

feasible before, and we were able to learn about activities of tumor genes that weren't able to be studied in cells that were a sheet.

For instance, when cells grow as a ball, the inner cells actually are under a great deal of stress, and those cells need to adapt programs to allow them to survive, and those programs that are turned on in order for those cells to survive end up being vulnerabilities that can be targeted for cancer therapies. We've identified several different programs that are necessary for that.

We've been able to develop drug combinations that target those vulnerabilities of cells when they're growing as masses as opposed to growing on sheets that now are actually moving towards the clinic, so that's something we're particularly excited about.

Dutchen: By building these models to study cancer that more closely resemble what's going on in a body, you're uncovering new knowledge about things that hadn't been seen in the lab before.

Brugge: Right. Right.

Dutchen: That's awesome.

Brugge: The other thing that we're just starting to do now that we're very excited about because we're getting access to patient samples that weren't really accessible before, and this is only possible because of very close collaborations with surgeons and clinical oncologists within the Dana-Farber/Harvard Cancer Center. We're just developing all the protocols right now for being able to get biopsies from ovarian tumors prior to therapy and then after therapy so that we can directly compare within a single patient what the tumor cells, how they behaved before and how they behave after, what tumor cells are able to survive the chemotherapy and what are the vulnerabilities of those tumor cells that survive therapy.

Ovarian cancer is particularly difficult to treat. Chemotherapy works very well, and the tumors, typically, most of the tumors shrink very dramatically, but they almost always come back. We're trying to figure out, we're trying to learn about those cells, what those cells look like, the ones that survive the therapy, so we can figure out how to prevent them from recurring and relapsing. We're using the most advanced technologies to be able to do that. It's also in collaboration with the Broad Institute, that has really strong technologies in single cell approaches.

Dutchen: You're studying patient samples. Does that mean that the discoveries you make would be in a personalized medicine kind of way for those individuals, or are you synthesizing the information to do something that would be applicable to ovarian cancer broadly?

Brugge: We hope that it will be applicable more broadly, but it's likely that there will be subsets of patients that are more likely to respond to combination therapies that we develop, but what we hope is that we'll identify markers that will predict which patients will respond to which therapies, so it won't be a cure-all for all types, but we hope to be able to know which—

Dutchen: Which type of ovarian cancer do you have?

Brugge: Yes. Right, right, right.

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Dutchen: All right. We talked about 3D tissue modeling, the need to improve treatments for ovarian cancer, and then you've also got some exciting work going on with *BRCA* gene mutations?

Brugge: Right. One of the projects we started more recently was to take advantage of the transformative new technologies that allow you to profile individual cells from normal tissues in order to be able to identify the earliest changes that are taking place in the breast tissues from women who carry mutations in either *BRCA* 1 or 2. Basically, these women have a much higher risk for the development of breast cancer.

Dutchen: These are the ones that you hear about in the news that a celebrity discovered they had this mutation?

Brugge: Yes, Angelina Jolie.

Dutchen: Then they're deciding whether to get a preventative mastectomy or something?

Brugge: The only preventive therapy for these patients is to have a complete double mastectomy. We would love to figure out ways to either prevent cancer before it develops or to at least be able to have a very good way of monitoring the development of cancer so that we can understand when the cancer is starting to develop and then women would have a better idea of when they would need a mastectomy.

Again, through the collaborations with multiple individuals within the Dana-Farber/Harvard Cancer Center, we've been able to get tissues from either women who have no inherited mutations—and these would be women who are having what's called reductive mammoplasties, this is just to reduce the size of their breast—and we can compare those tissues to the tissues from the women who have mutations in *BRCA1* and *BRCA2*.

Basically, we're filtering through hundreds of thousands of cells, looking at each individual cell, to try to find subpopulations of cells that might be altered specifically in the breast from the women who carry these mutations. We've actually found such differences. We find subpopulations of cells that are enriched more specifically in the mutation carriers, and now we're trying to figure out whether these are actually precursors of cancers or whether they're in some way influencing the development of cancer.

We hoped, as I mentioned, to be able to develop strategies to prevent cancer—that would be the best-case scenario—or potentially to develop ways of detecting these cancers much, much earlier, which will have profound impact on the patient.

Dutchen: Yeah. In a way, it's a nice story to think that you were collecting tissues from patients who needed mastectomies in order to prevent future patients from needing mastectomies.

Brugge: Exactly. Exactly. Most women are very anxious to give permission for us to study their tumors, because they know that their children, there's a chance that they may develop cancer, and they want to do whatever they can to be able to find a way to prevent the cancer.

Dutchen: Yeah. Sort of like the familial relationship that got you started on your path too.

Brugge: Yeah, exactly. Exactly.

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Dutchen: You also have a project going on in lung cancer, and it sounds like antioxidants are involved maybe in the opposite way that people would expect. What's happening there?

Brugge: That's a really interesting question. The popular view is that antioxidants prevent cancer, and there's a huge industry associated with dietary antioxidants to prevent cancer, and there is a lot of evidence that suggests that that's the case. But there's also many lines of evidence that indicate that once a cancer is initiated, that antioxidants are actually required to promote cancer development.

The initial alterations that are associated with initiation of cancer cause a lot of stress, as I mentioned, to cells, and one of the stress programs that's activated causes the production of what's called reactive oxygen species. These reactive oxygen species are actually detrimental and prevent cancer development, so tumor cells actually have to adapt programs that neutralize those reactive oxygen species in order to allow the tumor to survive. One of the most common mechanisms that tumors use is to turn on cellular pathways that produce antioxidants.

And so we found that when cells are proliferating outside their normal niches, they develop very high levels of reactive oxygen species, and that in order for those cells to survive, they need to turn on antioxidant pathways. Therefore, antioxidants at that stage of tumor development actually help the tumors to continue growing. Thus, those antioxidant programs are targets for cancer therapy.

This is confusing to people, because—

Dutchen: I'm trying to wrap my mind around it even as you're explaining it right now.

Brugge: Yeah, exactly, because at least people in this dilemma, are antioxidants good or bad, and we don't really know, and lots more research has to be done to understand that. But it, you know, it highlights the complexity of cancer, that there are many different cellular programs which have both a yin and a yang, you know, that in certain contexts they're good for survival, and then in other contexts they're not so good. That's why it's so important to study these pathways. I think that, it was really the studies of three-dimensional cultures that made it possible to identify these programs.

Dutchen: Well, I'm glad that people like you are on the case so we can figure out what's happening.

Brugge: Thank you.

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Dutchen: What else do you have going on that we should talk about?

Brugge: I'd also like to just tell you about the Ludwig Center, because that's something I'm really excited about. Through an endowment gift from Ludwig Cancer Research, we basically have brought together investigators from almost all of the institutions within Harvard Medical School—people from multiple different disciplines and with different expertise in order to be able to either prevent cancer resistance or to prevent recurrence of cancer.

We get together once a week for two hours. And it's pretty exciting, because all of us are learning so much—so cancer immunologists, cancer oncologists, pathologists, surgeons, developmental biologists, cancer geneticists, computational biologists, systems biologists—we're all listening to each other to learn more about their expertise and also to bring this information together. It's been pretty exciting, and there have been a lot of really interesting discoveries made from that.

Most importantly, we're getting access to patient samples in order to either do discovery research or to be able to establish whether discoveries that are made in experimental models are actually relevant to human cancer. So. It's a meeting that I love to go to, and I feel really good about being part of it.

Dutchen: You don't hear that a lot, that people love to go to meetings, so they must be very good.

Brugge: No, they are. In fact, almost every one I walk out saying, "That was awesome," and I don't say it that often.

Dutchen: So I guess cancer takes a village to really figure out what's happening and what to do about it.

Brugge: Definitely. I think that's one of the real advantages of Harvard, that in the cancer community there's just in general very strong interactions. And I think for me, the area in which my knowledge has expanded most significantly is in immunology.

I had no training in immunology whatsoever, but the discoveries that have been made in immunology have led to breakthroughs in cancer. I think it's so important for us to be able to integrate the immunotherapies that are being developed with the more targeted therapies that are directed against genes that are mutated in cancer. And I think, optimally, it's bringing together the immunotherapies and the targeted therapies that will really make a difference.

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Dutchen: I was going to ask you if there are things that you wanted to say to students or researchers or clinicians or just anybody who's interested in cancer biology, things that you wish

they know, hope they know, want them to go into. You started to answer that just now. Are there other things that you would say?

Brugge: Yes.

In fact, I encourage anyone interested in experimental biology now to learn as much computational biology and math and programming as they can, because it's such a critical central part of any kind of biological analysis now. I feel I'm most deficient in that, but the training is available for young scientists, and they really should take advantage of it.

Dutchen: Most efficient or most deficient?

Brugge: I'm most deficient, yes, in computation and analysis, yes.

I think that it's really important to avoid having a really narrow focus, because a tumor is basically like an organ, and the development and progression of a tumor and therapy resistance is totally dependent on this ecosystem within the tumor, and so it's really important to be able to understand the behavior of the many different types of cells that are in the tumor and the consequences of perturbations in any one type of cell or an individual pathway within the cell. It's really important to be as open-minded as possible without completely distracting oneself from gaining an expertise in a particular area.

Dutchen: Yeah, a tumor is—

Brugge: Collaborations are really central to that.

Dutchen: Yeah, and the understanding that a tumor is not just one thing.

Brugge: It's not one type of cell, for sure, yes, exactly. That's what we've learned.

Dutchen: All right. You have found many things that have been influential in the field and of course for patients and their loved ones. Are there particular things that you hope that you will achieve in the next little while?

Brugge: Well, I would… I hope that together with collaborating colleagues, that we will identify the precursors of human breast tumors in women that carry mutations in *BRCA* 1 and 2 and that we can identify strategies to prevent the development of cancer.

I also hope that, again, together with colleagues, that we're able to identify cellular pathways that are required for recurrence of tumors, either breast or ovarian tumors, in order to be able to develop strategies to prevent cancer recurrence.

Something that I'm also very excited about is that studies that we've carried out in the laboratory, again, using the three-dimensional models initially and then moving into experimental animal tumor models, is one in which we found that tumor cells turn on protection mechanisms that prevent the induction of cell death.

Dutchen: So, the cell normally would try and self-destruct, and then that gets kind of co-opted.

Brugge: Yes, exactly. I mean, just like the cells have to find ways of neutralizing reactive oxygen species by turning on antioxidants, they also have to prevent the induction of cell death, which is also called apoptosis. There's a whole family of proteins called anti-apoptotic proteins that get turned on, and they get turned on during cancer development. They also get turned on after treatment with therapies. The tumor cells are so smart, they're able to adapt to treatment with therapies, and they turn on these anti-apoptotic proteins.

So what we've been doing is treating with inhibitors of the anti-apoptotic proteins in combination with inhibitors of the proteins that are mutated in cancer and find that that combination is much more effective than treating with the drugs that target the proteins that are mutated in cancer. We're actually moving towards clinical trials in two different areas for those combinations.

This is the first time that anything we've done has actually gotten to the point where there could be potentially a meaningful outcome for patients, so that is very exciting and satisfying.

Dutchen: Yeah, it sounds amazing. We look forward to hearing about the outcome of that and all of the other things that you and your colleagues have going on. I wish we had more time to cover all of this and more, but this is our time for today, so just thank you so much for giving us a taste of what's happening in your lab and telling us a little about yourself in the process.

Brugge: You're welcome. It's been very enjoyable.

Dutchen: And thanks to all of you out there for listening. This podcast is a production of Harvard Medical School's Office of Communications. To learn more about the research discussed in this episode, to suggest topics for future episodes, or to let us know what you think, visit HMS.harvard.edu/podcasts. You can also follow us on Twitter or Facebook, where our handle is @HarvardMed.