

WE ARE ETH – Episode 45

With Stefanie Flückiger, ETH Alumna, CEO of Tolremo Therapeutics

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[00:00:00] Stefanie Flückiger: It was the first time when we really had a drug that could really help melanoma patients. So a disease that was so notoriously resistant to anything we would throw at it, all of a sudden within weeks these tumors would literally melt away.

[00:00:23] Susan Kish: In this episode, I'm talking with Stephanie Flückiger, ETH alumna and co-founder and CEO of the ETH spinoff and biotech company, Tolremo Therapeutics, focused on non-genetic cancer drug resistance. This is the We Are ETH podcast, and I'm Susan Kish, your host.

Stephanie, good afternoon. How are you?

[00:00:51] Stefanie Flückiger: Good afternoon. Doing very well. Thank you. How are you?

[00:00:54] Susan Kish: Very well. Thank you. It's morning here. I'm in Washington DC and it's hot and extremely humid. So I'm feeling a bit jealous. We're so pleased to have you here today. And everything I read about you, it seems like you get nominated or win an award every other week.

[00:01:16] Stefanie Flückiger: I hope you also get the impression that we're doing really great work.

[00:01:22] **Susan Kish:** Well, one does, but why do you think that is? Other than the fact of course, that you're a fabulous CEO and your company's amazing, but talk about awards. What role do they play? Are they? Do you think they help your company and help you raise money and help on all those things?

[00:01:37] **Stefanie Flückiger:** I'm personally, I wouldn't say a big fan of awards, but we don't try to focus too much on them, especially now that we're a much more mature company, I think a lot of it of course has to do with, especially in Switzerland, you don't have a lot of female CEOs, female founders, female led businesses. So there's a lot of focus on that.

People rightfully trying to promote female entrepreneurship, but it's a little bit of a double edged sword, isn't it? You don't want to get all the attention that you get just because. You're a woman. We're grateful when we do get nominated or when we are awarded a, an award, but it's not the core of our business.

[00:02:26] **Susan Kish:** Do you have an all-female leadership team?

Did I see that correctly?

[00:02:33] **Stefanie Flückiger:** It's not by design.

[00:02:34] **Susan Kish:** I just had to do a reality check.

[00:02:37] **Stefanie Flückiger:** It's not by design. No, we just, you know, we hire for qualification and it was very difficult to find well qualified men for these positions. We did end up with an all female leadership position.

That's correct.

[00:02:51] **Susan Kish:** I have to say, given that you raised close to 40 million last fall with an all-female Leadership team that makes it, I have to say, unfortunately, even more impressive. Did you find it a challenge to walk into some of these VCs and investors, especially the new ones you added in this round?

[00:03:13] **Stefanie Flückiger:** It's certainly something that people notice, especially usually we're in a room full of men. And then you have an executive team of women. It lightens the mood. Usually people notice we talk about it. You can joke about it. I don't think it was an advantage or disadvantage. I think it's becoming more normal also seeing women in these positions.

Um, so it was, it's been a good experience so far as with the team that we have. We also do employ men though, just at lower positions.

[00:03:44] **Susan Kish:** Okay. Well, that's good to know. You have a diversity policy, I see.

[00:03:49] **Stefanie Flückiger:** That's right.

[00:03:52] **Susan Kish:** Which actually is an interesting question. You had a wonderful quote about diversity being a, not a male or female issue or results issue. How did you come to that conclusion?

[00:04:04] **Stefanie Flückiger:** This goes a little bit back to those awards, right? Like being, Yeah. Put in a spotlight mostly because you're a woman and I think what we need to do moving forward is really celebrating people's accomplishments, right? No matter what their gender is. And speaking of diversity, that's also what we have in our leadership team. Of course, we're not a very diverse team because we're all women, but we are diverse in terms of our backgrounds, right? We have a medic, we have a business development person who doesn't have a scientific background. A very strong chief operating officer with a financial background. And I think moving forward, that's what we have to focus on in our teams.

It's not to please anybody. It's not to do women a favor. Focusing on diversity because we know it promotes better results. And that's what we want to achieve as businesses and societies. Right.

[00:05:02] **Susan Kish:** And I have to say innovation tends to come more easily with diversity.

[00:05:11] **Stefanie Flückiger:** Because you do need those different viewpoints. And I have to say diverse teams, because you have so many different people. Yeah. It doesn't necessarily make it easier work as a team, right? Because it does create friction, but it's that friction that actually makes us better as a team. In our company, especially, I'm We do talk about that, you know, us being diverse doesn't make it easier, but it makes us better.

How do you find being the leader in that context? To what extent do you embrace that occasional abrasion of perspectives?

I really try to Utilize it to, to spearhead that innovation that is at the core of what we do. And I think especially when you talk about it openly, this is the cost that we have to pay for being innovative, for living diversity, then it becomes much easier for people to accept and to celebrate.

[00:06:14] **Susan Kish:** Really interesting. And I, I would completely agree. I agree with that. So talk to us about Tolremo. What was the catalyst that made you go, Oh gosh, I should start a company because that's not always the thing one wakes up one morning and decides to do.

[00:06:30] **Stefanie Flückiger:** And it actually wasn't for me. Um, my catalyst was my prof at ETH, Professor Willy Krek.

He was relatively hands off when it came to his PhD students. But towards the end of,

[00:06:43] **Susan Kish:** you were a PhD, you were an master's, PhD and a postdoc?

[00:06:46] **Stefanie Flückiger:** Correct. Yeah. I, so I spent quite a few years in his lab. And towards the end of your PhD, he will sit you down. And he would say, okay, what is it that you want to do with your life?

And of course, as a PhD student, you have no idea. So I don't know. I'll probably just become a scientist at Roche. I don't know. And then he was the one who first asked, well, have you ever thought about actually, you know, using your science to, to help people? And my first response was, I think very disappointing to him.

I said, no, because I had just worked in his lab because I love science and I love pipetting and I love being creative in the lab, but I did it for the science really in a very isolated context. And, but his question, exactly. Yeah. Which was the beauty of it almost, right? You don't have to worry about the applicability of your work.

It's just about the beauty of science. But then it was his question that kind of triggered these thoughts. If, and how could we, and how would that even work? And for me, that was really the start of our entrepreneurial journey.

[00:07:57] **Susan Kish:** Did you take the research? Was there something you had been working on that all of a sudden went click and you said it might have applications in. It might solve a problem in, or did you go through a huge number of papers and say, here's the problem I want to solve. And there's a solution. How did you connect the dots? Was it the same research you had done as a master's PhD and postdoc that you... Really? It's all the same. That's cool.

[00:08:25] **Stefanie Flückiger:** It's the only thing

[00:08:25] **Susan Kish:** you know the topic well.

[00:08:27] **Stefanie Flückiger:** It's the only thing I know, but yeah, it started as a master thesis. I don't know if they still have it, but back then they a fast track PhD, where a certain percentage of top master students, they could apply with a pro... with a project to become a PhD student, even before you're awarded your master's. And

[00:08:50] **Susan Kish:** that sounds very efficient.

[00:08:52] **Stefanie Flückiger:** It was very efficient. And I did that in Willy's lab. And I just approached him with, look, I read about this program. That's what I want to do. And I was like, all right, fine. If that's what you want to do, go figure it out then. With him being relatively hands off, initially he would just give you his crazy ideas and you just had to make out of it whatever you could.

And We were a lab that studied how cells respond to environmental stimuli, both in terms of

[00:09:22] **Susan Kish:** Generic cells or particular cells, or...

[00:09:25] **Stefanie Flückiger:** it was, we had one subgroup, one subgroup that worked with the myocard heart cells. And there we studied how does the heart respond to a lack of oxygen. Okay. And then we had another subgroup that dealt more with cancer cells.

They're also hypoxia, the lack of oxygen is important. And more generally, we start at how cancer cells would respond to the external stimulus of being exposed to a cancer drug. And what does that do to a cancer cell?

[00:09:58] **Susan Kish:** So you take a cancer cell, you expose it to a cancer drug and what does a cancer cell do?

[00:10:05] **Stefanie Flückiger:** I see. That was the question. We didn't know. Because when people think about it, it's like, okay, you have a cancer, you treat it with a cancer drug. The cancer goes away and that's it, right? And then...

[00:10:18] **Susan Kish:** It goes in a remission or whatever they call it.

[00:10:20] **Stefanie Flückiger:** It goes into remission. And then usually after a while, the cancer starts growing again.

When it becomes drug resistant.

[00:10:28] **Susan Kish:** Oh, that's not good.

[00:10:29] **Stefanie Flückiger:** That's not good. And I started my research when BRAF, so called BRAF inhibitors first got on the market. So these are, BRAF is a gene that can be mutated, and it's mutated in about half of all black skin cancers, and it drives cancer. So what people did is at first they found out, okay, half of melanoma is black skin cancer. They have this oncogene BRAF. So developed small molecules, cancer drugs that would inhibit BRAF. That sounds good. And it was the first time when we really had a drug that could really help melanoma patients, so a disease that was so notoriously resistant to anything we would throw at it, all of a sudden within weeks, these tumors would literally melt away and melanoma being a cutaneous disease. It's very visual. You just see tumors that are gone.

[00:11:32] **Susan Kish:** When you say cutaneous, cutaneous is your, your skin?

[00:11:36] **Stefanie Flückiger:** Exactly. On the skin. So you would just

[00:11:38] **Susan Kish:** It would be on your arm and it would just disappear.

[00:11:40] **Stefanie Flückiger:** Pretty much. Yeah.

[00:11:42] **Susan Kish:** That sounds like magic.

[00:11:43] **Stefanie Flückiger:** Which was like magic until then people realized that these clinical responses were very short lived. So tumors would disappear very quickly, but they also come back very quickly.

[00:11:56] **Susan Kish:** That's yeah. Which is really. upsetting.

[00:11:59] **Stefanie Flückiger:** And so that's when people started studying, okay, why do these tumors come back? Why did it become drug resistant? And they would compare a tumor at baseline before it would receive therapy.

And then once it had come back and they would study the DNA and they would find that these tumors over time changed to acquire new mutations that would make them resistant to therapy.

[00:12:24] **Susan Kish:** Cancer is so smart.

[00:12:26] **Stefanie Flückiger:** It's very, and it doesn't mean to be smart. It just happens to be any cell, not only cancer, but any cell in the body.

All they do is they sense their environment and they run certain programs to respond to their environment. If they sense that they don't have enough oxygen, they start expressing genes that help them switch their metabolism so that they're not dependent on oxygen anymore. Or they sense that they don't have nutrients, so maybe they can start losing less nutrients or different nutrients or crawl away and find a source where there is more nutrients.

It's all about responding to your, to your environment.

[00:13:09] **Susan Kish:** Okay.

[00:13:09] **Stefanie Flückiger:** And cancer is the same. If a cancer cell is so dependent on a certain oncogene and you take that away with a cancer drug, the effect of the oncogene. A cancer cell senses that, and it doesn't just die, it is programmed to fight back, because that's what cells do.

[00:13:30] **Susan Kish:** So it adapts.

[00:13:32] **Stefanie Flückiger:** It adapts. And that's what we started studying in the lab. Why don't they just die? You inhibit that oncogene, and then they die. that the cancer cell is so dependent on for its survival. Why doesn't it just die?

[00:13:46] **Susan Kish:** And what did you find?

[00:13:47] **Stefanie Flückiger:** What we found is that very quickly within hours, really a cancer cell would express gene programs that would be almost like early stress responses.

You see a certain de differentiation in cancer cells, for instance. So they would start activating genes that are normally only active in the developing embryo. And so usually in the adult organism, these genes aren't needed anymore, so they're turned off.

[00:14:22] **Susan Kish:** When you say embryo, do you mean a human embryo or you mean like a cancer embryo? What's an embryo in this context?

[00:14:27] **Stefanie Flückiger:** A human embryo.

[00:14:29] **Susan Kish:** Okay.

[00:14:29] **Stefanie Flückiger:** So usually.

[00:14:31] **Susan Kish:** They create genes that are in human embryos as a way to respond?

[00:14:36] **Stefanie Flückiger:** They always have the genes. So on our DNA, we always have the same genes, but what makes us different

[00:14:43] **Susan Kish:** Oh, you just go down to that level and say, I want those genes.

[00:14:46] **Stefanie Flückiger:** Exactly. Which ones do we actually turn on and which ones do we turn off? And what we found was when you treat cancer cells with these targeted therapies, for instance, with BRAF inhibitors, they have two responses. On the one hand, of course you can measure that the oncogenic signal goes away. That's the intended effect.

But at the same time, you have this unintended effect, which is for instance, turning on genes that are usually just needed in the developing organism.

[00:15:18] **Susan Kish:** Okay wapproach due to that, because I read something about you. It happens like within hours of administering,

[00:15:27] **Stefanie Flückiger:** Yes, it does. And so when I, by the time I finished my PhD, at ETH, that's basically what we had, we had done all these experiments and we found, okay, These cancer cells, they reboot, they fight back. And that was that.

[00:15:42] **Susan Kish:** Right.

[00:15:43] **Stefanie Flückiger:** And at that point, I had this conversation with my prof. He was asking, what do you want to do with your life? And when I said, I don't know. And he asked, why don't we help people with the science? My question was, but how? We're just scientists. These are just data in my lab books. It's not like we can just make a cancer drug out of this.

I said, why not? Because we're just scientists. He was like, just go and figure it out! And. That's when for me, the challenge was, okay, how do you take basic science that was never intended to help anybody and turn that into something that is really value creating and you use that to spur a new development of cancer. And in our case, how we try to capture that scientific value is we use our science to develop a, a screening technology that would allow us to find small molecules, synthetic drugs that would prevent this rebooting that cancer cells do when they're exposed to cancer drugs.

[00:16:50] **Susan Kish:** Oh, that's cool. So you found like little ninjas that would invade and say, no,

[00:16:58] **Stefanie Flückiger:** No, no, no! :)

[00:17:00] **Susan Kish:** Okay.

[00:17:01] **Stefanie Flückiger:** A little bit. Yeah. Because in academia we found, okay, this is a bad thing that happens in cancer cells. How do we stop it from happening?

[00:17:10] **Susan Kish:** What's actually super smart of the cancer, we don't want it.

[00:17:14] **Stefanie Flückiger:** But we don't want that. Exactly. We don't want that. To translate this basic academic research into a more biotech setting, we developed the screening technology that would allow us to help small molecules that can prevent cancerous bad behavior. And that was the start of Tolremo because it takes a lot of money and a lot of time and a lot of expertise to actually take a small molecule that you pulled out of a screen and actually develop it into a potential cancer drug.

[00:17:46] **Susan Kish:** Got it. Very interesting. You started the company with yourself and what sounds like an all-star crew. You have five founders, which is a lot, but it sounded also like in the first years, it was basically you, yourself, and you. What was the trigger to move on for that structure?

[00:18:04] **Stefanie Flückiger:** It's always, they all serve different purposes, founders, I think. In our case, it was a little special because A, we were five co-founders, which is a lot. And B, it was four elderly men and myself. And C, I was the only one, as you said, that was actually operationally involved in the company.

[00:18:26] **Susan Kish:** The others would sort of walk into the lab, say, Oh, it looks good.

[00:18:29] **Stefanie Flückiger:** Good job.

[00:18:34] **Susan Kish:** What can I do to help?

[00:18:36] **Stefanie Flückiger:** And they did help by validating really what we did. We founded a company back in 2017, and I think about six months later, we closed our seed financing of two and a half million Swiss francs.

Now, nobody would have ever given, would have ever given Stephanie the postdoc, who might be small, but what has she really ever done in her life?

So nobody would give me two and a half million. However, if you throw in a couple of very accomplished ETH professor in the mix, somebody who's done very successful clinical development, somebody who actually knows how to deal with finances, then you have a group of people. That can raise two and a half million Swiss francs.

[00:19:28] **Susan Kish:** Very smart. And Very smart.

[00:19:31] **Stefanie Flückiger:** But early on, the first hire, she's still with us. I hired to help me out in the lab, so that it would be not a one woman show anymore, but at least a two woman show. You see, the women have always been well represented at Tolremo.

[00:19:46] **Susan Kish:** I understand. You did your undergrad work at the University of Freiburg, and then you switched over to the ETH. Tell us about why you chose ETH, right? Because you're a smart woman in STEM. The world's your oyster. Why would you pick the ETH?

[00:20:04] **Stefanie Flückiger:** What I was really interested in was... so at Fribourg, I did biomedical sciences. It was basically half medicine, half biochemistry. You learn all about the human body and how it works and what can go wrong with it.

I was not interested, not necessarily interested in what you can do about it. So I never wanted to do medicine. And then for my master's then I wanted to go deeper into, but how does this really work and why and how did these proteins interact with each other? I just wanted to go deeper. And for me in Switzerland, ETH is the best place to do this.

You have the greatest science, you have amazing labs. I imagine it to be this very creative scientific place where you could just love science.

[00:20:55] **Susan Kish:** Castle on the hill?

[00:20:56] **Stefanie Flückiger:** That's right. And that's what I found.

[00:21:00] **Susan Kish:** That's a lovely image. How did you find your particular professor that you whose lab you joined?

[00:21:06] **Stefanie Flückiger:** The first work that I actually did as a master's student was in the lab where we studied the ends of DNA. They're called telomeres. And back then, back in Fribourg, I had read a book about Elizabeth Blackburn, who was later on awarded, um, the Nobel prize in medicine for the discovery of telomerase, an enzyme that protects the ends of the DNA. And I thought it was so fascinating and she was so cool and so brave.

So I wanted to study telomerase too. And there was this one lab at ETH where they would do that in yeast. So I contacted a professor and said, I think it's really cool what you guys do. I like to work for you and I'm going to be here in the summer and I have nothing else to do. So I'd really like to work in your lab for free just to experience this.

And he said, sure, free lab, free work, come and join us. And I think I stayed with him for about nine months or so. And it was the first real molecular biology experience that I had. And then later it came to picking a lab for My master's project. And I knew I wanted to do the fast track PhD. So I just looked around and I found Willie's lab and I thought their work was really interesting about how these cells will respond to stimuli.

And so I thought that was really cool. And that's when I reached out to him.

[00:22:34] **Susan Kish:** Stephanie, thank you so much. This has been a great conversation. And now I understand about ninjas and rebooting and cancer drug resistant and how to attack it. We'd love to close with some questions that we often ask our regularly ask our guests, if I may.

So building on the theme of what we talked about, when you were a little girl, like eight or nine, what did you want to be when you grew up?

[00:23:03] **Stefanie Flückiger:** I wanted to be either a German teacher or a midwife.

[00:23:07] **Susan Kish:** That is an incredibly cool diversity of things. Why a midwife?

[00:23:12] **Stefanie Flückiger:** I don't know. I just thought it was a cool job.

[00:23:18] **Susan Kish:** Okay, cool. And what are you curious about now? What are you learning about?

[00:23:24] **Stefanie Flückiger:** I'm in the very fortunate position to learn something new almost every day, really, as I I got to, in those seven years of Torimo, I got to

learn everything starting from drug screening and development and building chemistry and preclinical models.

And now I get to learn about clinical development. Amazing.

[00:23:48] **Susan Kish:** Okay. What are the books on your bedside table or on your Kindle or your phone or your AirPods?

[00:23:57] **Stefanie Flückiger:** Currently on my Audible. Ah, it is a, uh, the book called "[Why We Sleep](#)" by say Andrew Walker. I think Walker is the author about just the biological reasons, uh, why we sleep and what happens to you when you don't sleep enough and the different, just latest updates on sleep research.

[00:24:24] **Susan Kish:** Very cool.

[00:24:25] **Stefanie Flückiger:** And it has prompted me.

[00:24:26] **Susan Kish:** You don't play in the chance of small children, do you? Cause that's when the question of sleep often comes up.

[00:24:31] **Stefanie Flückiger:** Three and a half and one.

[00:24:32] **Susan Kish:** Okay. So this is a relevant question then.

[00:24:39] **Stefanie Flückiger:** It has prompted me to prioritize sleep a little bit more.

[00:24:44] **Susan Kish:** Yeah. You'll do that when they're older.

How about podcasts? Any podcasts that you listen to?

[00:24:51] **Stefanie Flückiger:** I like the [Huberman Lab](#). Huberman. By Andrew Huberman. Very interesting, also very sciency, uh, podcast.

[00:25:00] **Susan Kish:** Excellent. And in Zurich, what is your favorite place in the city or at ETH? Where is it you'd like to go to?

[00:25:08] **Stefanie Flückiger:** I really love the, now we live in Basel, so I do miss Zurich a little bit.

I do...

[00:25:13] **Susan Kish:** You get to float down the Rhine. How great is that?

[00:25:15] **Stefanie Flückiger:** Which is a lot of fun. But I think to me, The ETH campus up on Höggerberg has been and I think always will be a very magical place. People sitting out in the sun under a tree, reading a paper. Perfect.

[00:25:32] **Susan Kish:** Stephanie. Thank you very much. I really enjoyed our conversation.

[00:25:36] **Stefanie Flückiger:** Likewise. Thank you so much, Susan.

[00:25:39] **Susan Kish:** I'm Susan Kish, host of the We Are ETH series, telling the story, the alumni and friends of the ETH Zurich, the Swiss Federal Institute of Technology. ETH regularly ranks amongst the top institutions and universities of the world with cutting edge research, science, and people.

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