DR. VALTER LONGO INTERVIEW
Fasting Mimicking Diet Studies

By Chris Wark

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Hey everybody. It's Chris. Welcome to another interview. I've got Dr. Valter Longo back. It's been two and a half years – which I can't believe – since I interviewed Dr. Longo last. He's the author of the book, *The Longevity Diet*, which is an absolutely fantastic book. He's one of the foremost researchers in the world on fasting, immune system regeneration, longevity. And we talked about a ton of amazing stuff in our previous interview. I'll link to that in the show notes. I hope you'll go watch or listen to that. And I don't want to redo that interview. We'll touch on some of those things that we covered last time. But there are two really, really exciting studies that have come out that Dr. Valter Longo has been involved with. And I can't wait to share them with you. I can't wait to have him share them with you.

Chris: Here's just a quick bio. Dr. Longo was born and raised in Genoa, Italy. He received his PhD in biochemistry from UCLA in '97. He did his postdoctoral training in the neurobiology of aging and Alzheimer's disease at USC. He's currently a professor of gerontology and biological sciences, and director of the Longevity Institute at the University of Southern California. His most recent studies are on dietary interventions that can affect stem cell-based regeneration to promote longevity and reverse the course of many diseases. Like I said, he is a global leader in aging and nutrition, with over a hundred peer reviewed publications in top tier journals – including *Science*, *Nature*, *Cell*, *JAMA*, *Cancer Cell*, *Journal of Translational Medicine*, and more. He also developed the ProLon Fasting Mimicking Diet. And a lot of the new research we're going to talk about today is centered around fasting and cancer therapy, and the effects that a fasting mimicking diet can have on chemotherapy treatment and patient outcomes and hormone therapy. So, thank you, Dr. Longo, for taking the time. I know you're a busy guy.

Dr. Longo: Well, thanks. Thanks for having me. And by the way, you mentioned ProLon, and I just want to make sure people know that I don't benefit from it. All my part, whether it's consulting or shares, go to charity. So, yeah, just to make sure that we make the clarification.

Chris: Sure. Noted. So, before we talk about these new studies, can you give a brief overview on why fasting is good for us?

Dr. Longo: Yeah. So, I assume you're asking independently of cancer.

Chris: Yes. Independently. Just generally speaking, what does fasting do for the body?

Dr. Longo: First of all, I always say that fasting doesn't mean anything. It's like saying "eating." And so, we need to move away from… We wouldn't use the word "eating" – like why is eating good for you? Right? And the same is true for fasting. I mean, there are ways to fast that are beneficial, and ways to fast that are detrimental. So, for example, if somebody just went home and fasted for 15 days, water only, it would probably be pretty detrimental overall. Right? So, now we've spent many, many years working on the genetics of nutrition and fasting to come up with ways that sort of keep the good of fasting and eliminate the bad. And it's not as straight forward as you'd think.

Why? Well, if you do water only fasting, your blood pressure can get very low. You're much more likely to develop gallstones. Depending on how you do it, you may actually have a reduced lifespan and more cardiovascular disease. But if you do it right, everything points to really remarkable benefits. And I think that, in our first trial, we showed that people that were at risk for cardiovascular disease, that had high risk factors for cardiovascular disease… So, the cholesterol, the blood pressure, the triglycerides, the IGF-1, fasting glucose… You could tell that almost everybody that started to have a problem came back to normal. And so, then I think the fasting mimicking diet is food that tricks the cells in the body into responding as if it was only water. This seems to be very beneficial if done, let's say, once a month or less for five days. That's what we've established. And that's what we know.

And then, there are other forms of fasting, for example, alternate day fasting. That seems to be beneficial. But then, again, what are the long-term consequences? Well, lots of data will suggest that if you do that, first of all, it's going to be very difficult for you to eat one day and not the other. So, maybe like 1% or 2% of the population will ever be able to do this long-term. And then, you start getting the side effects – the gallstones, etc. So, that's just to point to some of the negatives. And then, another positive I think is the 12/12, something that Satchin Panda and others and ourselves have we've been preaching about, which is eat for 12 hours, fast for 12 hours. Water only is fine. That seems to be very healthy. I know of not a single study showing that to be negative. So, yeah, I think that that's a good way to do fasting. And then, the periodic fasting diet, to me, is not a very healthy way of fasting. And trying to do it whenever you need to do it.

Chris: Now, the Fasting Mimicking Diet that you developed is a plant-based, five-day program that is calorie restricted. I've done it. My wife's done it multiple times. It's not difficult (I've done a lot of difficult things in my life that I would not call difficult). And the food actually tastes good. So, it's pretty easy to follow. But it's interesting to me that there's a certain level of calorie restriction that triggers your body into this regeneration and protection mode. Can you talk a little bit about that?

Dr. Longo: Yeah. So, it's not just the calorie restriction. The body… I mean, if you think about the past, it was either summer or a plentiful season, let's say that there's a lot of food. And so, what we did was eat a lot and store everything. And then, eventually, you know, we got to the opposite. There was nothing available. So, you used what you stored. So, the body has this response. So, basically, the fasting mimicking diet is consistent with a starvation period. So, the cells are detecting fats, but not sugars and proteins and not certain amino acids. So, to the body, to most of the organs, you've entered a true fasting mode. But at the same time, it's keeping you active enough, and it's keeping enough food coming in and enough ingredients of all kinds coming in, where we can, in a sort of gentle way, prevent problems.

For example, the gallstone. We have fats that are introduced. And so, this is expected to cause the bowel release from the gallbladder and reduce, if not minimize, the chance of developing gallstones. We have salts in there. Well, we don't want people to get hypertense. So, you might have low blood pressure, or you may even have normal blood pressure. And if it's hard enough, you're going to drop. And now, after days and days of fasting or water only fasting, you could have problems. So, the fasting mimicking diet has all kinds of things in it. I mean, these are just a couple. But we are respectful of where fasting comes from, because we understand the idea of water only fasting, of course. But at the same time, it's trying to protect people from all kinds of potential problems by having all these ingredients in there. And so, that's we call nutri-technology, and the ability to combine not only technology, but also tradition.

Chris: One of the things that I got really excited about, years ago, was when I stumbled across the study you published on how fasting helps regenerate your immune system. And that, to me, was… At that time, were you the first person, or was your team really the first people to illuminate that idea?

Dr. Longo: Yeah, I think we were the first. Not just that idea. The possibility of fasting to get rid of damaged components, and then figure out a way during the refeeding (not during the fasting, by the way) to rebuild has always been there. So, the fasting serves as sort of like a clean-up. "Let's look around. What's damaged? You're a normal cell, you're a bad cell. Let me just leave you alone. You respond, I kill you." Right? And to be very clear for cancer cells, for immune cells, for insulin resistance cells. So, we started showing paper after paper after paper, that it's very good at getting rid of damaged cells. And it's very good at then turning our stem cells. And then after the animal refeed, to generate new cells that are no longer showing those problems of the original cell.

So, say if you kill a cancer cell, it's not like now you turn on and multiply the stem cell and you make a new one. You make a good white blood cell. And the same thing for the immune system that you were asking me

about. So, that was one of the first examples, because we saw this big drop in white blood cell numbers. It's not excessive, meaning they're still pretty high. They're still able to function, allow the immune system to function. But you see a clear drop and you see it in people as well. Not a big drop, but a drop. And then, during the refeeding, we saw it going back to normal.

And in the original cancer treatment, we were using something called cyclophosphamide, like a chemotherapy drug. And when you combine the chemotherapy drug with the fasting mimicking diet, you do not see a protection of the white blood cells. That was very surprising. So, we thought, these white blood cells are going to be protected from chemo. But we saw the drop. But then we saw that after five or six cycles of this, the population that received chemo plus the fasting mimicking diet, went back to normal. The normal range. And the population from the mice that were on the normal diet, stayed very low. And that's when then we were directed towards the hematopoietic stem cells and figured out the chemo, plus the fasting mimicking diet, was giving the message to the bone marrow to prepare to regenerate new white blood cells. And that's exactly what happened.

Chris: So, basically, when a person is fasting, the old and damaged immune cells are going to die off, but then it triggers this stem cell activation. And as soon as the person starts eating again, then the body just ramps up production of young, new, healthy immune cells. Is that the best way to summarize it?

Dr. Longo: Yeah. And that was our understanding. But we were also working on something, then we got beat by three different groups at the same time last year. And they published three papers in Cell, showing that it's not just about that and regeneration, but it's also about redistribution. So, they show very elegant studies showing that the white blood cells that are moving from secondary lymphoid organs to the bone marrow, and they extend the bone marrow, they get reprogrammed, and then go back out. So, it's really a remarkable set of changes that occur. Very coordinated. Probably with the job of resetting some of the problems that accumulated in the immune system and making sure they are ready for the next fight. You can imagine how important that would be throughout the history of any organisms.

Chris: So, reorganization is also this really important benefit?

Dr. Longo: Yeah. Probably an opportunity to determine what you're missing, what's damaged, what you need. And so, things get reorganized and get maybe reset, and they're ready to go back out and do the fighting again. You know, of course the immune system is playing such an important role in fighting almost anything – bacteria, fungi, cancer cells, viruses. So, yeah, you can imagine right now with COVID-19, we see how central the immune system is. But also, with immunotherapy dominating and being

very important in cancer therapy, we see that. Again, the most powerful medicine is the medicine from within. I say it's 3 billion years of research and development. So, it's a very sophisticated system in 3 billion years that has moved from very rudimental immunity to very sophisticated immunity. And so, if you could turn it against all kinds of problems, then you can have a powerful effect, like immunotherapy is having.

Chris: So, let's talk about the two studies that are brand new. The first one was on breast cancer patients, correct?

Dr. Longo: Yeah. We actually have three studies. Two we just published in the last 30 days on cancer, and one that we are about to publish. And so, the first one was on vitamin C combined with a fasting mimicking diet – which I'll call FMD so I don't have to keep repeating it. So, yeah, vitamin C and the FMD. And the idea with that one… It was only mice, and we're starting a clinical trial soon. And the idea was, can we come up with something that is completely non-toxic? Can we use two anti-aging interventions, vitamin C and FMD, to come up with something that only kills cancer cells? And it's remarkable how effective this combination is in killing cancer cells and doing zero damage to anything else. So, yeah, we really wanted to introduce this sort of futuristic idea about if you really understand the mechanisms of what you're fighting, and also of the body, then maybe instead of using chemo or something that toxic (even immunotherapy is fairly toxic, or can be very toxic) … Instead of using something that can be toxic, why not use something that is actually the opposite, that is actually beneficial to you? But it just happens to target certain cancer cell types.

That was one. Then we published a clinical trial in collaboration with a multicenter randomized clinical trial on breast cancer patients receiving chemotherapy, in collaboration with many clinics in Holland. And that was really remarkable. We were a little bit…not ambitious, in the sense that the primary end point we were going after was side effects. And there was interest in the results for side effects because basically we saw that the FMD replaced dexamethasone. So, it was either chemotherapy plus dexamethasone (this hormone that is given to reduce side effects), versus FMD plus chemotherapy. And they were about equivalent. So, it was interesting that now we can remove a major drug that is associated with all kinds of problems.

Chris: So, let me ask you this. In that trial, how was the fasting mimicking diet administered? Did they fast for two days before chemo, during chemo, and two days after? What did that look like?

Dr. Longo: There was four days of the fasting mimicking diet, that's called Xentigen. Three days before, and 24 hours after, the chemo. That's what the patients did for the trials that we've done so far.

Chris: That was different than the ProLon diet, in that it was very, very low calorie, right? Only 200 calories per day.

Dr. Longo: Yeah. They were trying to achieve in four days while we normally achieve in five or six. So, in this case it was very low calorie. Pretty high on day one, and then very low on day two, three, four. So, day one, I think, is 1100 calories. So, it starts fairly high, and then it drops drastically so that within those four days we get everything where we need to be – ketone bodies, IGF-1, IGFBP1, glucose levels, etc.

Chris: I see. So, you said that one of the findings of the study was that the patients who fasted and did chemo, basically didn't need this extra drug for side effects.

Dr. Longo: Right. Exactly. So, the side effects were equivalent, but now we had removed one drug. And that's already very good news, I think. But then, the secondary was, well, what happens to the cancer? And we didn't think we were going to see this very big difference between the women. Particularly those that did all the cycles of the fasting mimicking diet, versus those that did none of the cycles.

Chris: And how many cycles were there total?

Dr. Longo: Up to eight cycles.

Chris: And was it one a month? One cycle per month?

Dr. Longo: It was one every month or one every two or three weeks or so. I forget whether it was once a month, or once every two weeks. But yeah, so those that did all the cycles did very, very well. Almost all of them responded. I think the non-response rate was around 5%, and it went up to 27% on those that did not do any fasting mimicking diet together with the chemotherapy. So, yeah, there's a five-fold difference.

Now, you know, it's 65 patients that were in the dieting group. So, it's not a thousand patient clinical trial. But certainly, I would say, at least if you look at it from a scientific perspective, this is about as good as you possibly can do with the start. I particularly like it, as a scientist, the dose response. And I'll send you the paper, if you want to show it. You see that those that just didn't comply, so those that said, "I'm in this group, but I don't want to do it," respond pretty poorly. And then, the more cycles they do – three cycles, five cycles, six cycles, and then all the way to eight cycles. So, when you see that in science, I don't think the clinicians appreciate it as much as the scientists appreciate it. When you see that in science, when you see this dose response, it's very unlikely that it's an artifact. Very unlikely. It could be, but it's extremely unlikely. The chances of that are very, very small.

Chris: When you say dose response, you mean the increasing benefit with each dose, right?

Dr. Longo: Yeah. So, if you did zero cycles, you have one. Then you do one cycle only, out of eight. Then the people did the four cycles, out of eight. Then there were the ones that did six. And you keep seeing them moving up in percentage. So, what is the proportion of patients that are responding? And it goes up. Let's say, the non-responders are 27%. Then they go to 20%. Then they go down to 15%. Then they go down to… When you see that, it's very strong evidence, at least initially. It doesn't mean that you can conclude, "Oh, this works. We're done." But certainly, that's what you want in the first trial. You want to see a dose response. And you want to see that those that comply the most are, by far, the ones that respond the most.

Chris: So, I'd like to ask you about the cycles. So, when you say a cycle, does that mean they did four-day FMD with chemo? Was that what you mean by a cycle?

Dr. Longo: Yeah. So, let's say a cycle is six to eight cycles of chemo with, or without, the FMD. So, now you have both. So, if you look at compliance – and this, I think, was largely due to the fact that they did not have a registered dietician that was trained with this type of dietary intervention. So, I think, lots of the times we see that dieticians that don't understand this tend to tell the patient to eat more. "Why don't you have more proteins?" But the worst thing you could do is overfeed the patient. So, that's the training that a lot of them get – that doesn't mean that all of them get that. But anyways, the problem that I think was the consequence of that is that most people did one cycle, but then only 50% did two cycles. And then, it went down from there. So, it was remarkable that it worked in spite of the total lack of….

Chris: Low compliance.

Dr. Longo: …supervision, followed by lack of compliance. Because of course, I don't know for a fact. But I've seen it many, many times, so I'm speculating that they thought that this was probably not such a good idea. Because whenever we have the dietician, our compliance is 80-90%, sometimes 100%. So then, I'm very surprised when I see… And now, you have a multicenter trial with no dedicated dietician. Dedicated in the sense that they were trained by us and know what to do. And then, you see this compliance dropping to 30% or so. That's when you know that, probably, there may have been some discouraging from the dietician to the patients related to… But I don't know. It could be something else. But certainly, that's our speculation.

Chris: Well, that's probably the most plausible explanation in my mind, too. Because as someone who's been involved in nutrition, and trying to help people with diet and lifestyle changes to help survive cancer and prevent

it, compliance is the biggest challenge. It's very difficult to get people to change what they eat or to not eat when they're hungry. And it's also exciting to think about the future of this, because once you have clinicians and dieticians who are indoctrinated, that are fully on board with the program, then they can have those same convictions that you have, and they can really instill those into the patients and get that compliance up to 90% or 100%. And then, the patient gets the most benefit.

Dr. Longo: And I don't even think… We have many trials ongoing right now, so we know we don't even need that. All we need is a registered dietician that spends maybe a couple of hours, like two or three hours, throughout the six or seven or eight cycles. That's all you need. And that one person, if they're trained, if they know what they're doing, without promising anything… This was not about, "Oh, if you do this, you're going to be cured." This was more like, "This is a trial. Please try to do a right. Let me help you. If you have a headache, that's okay. If you're hungry, that's okay. It's going to go away." That kind of being followed by somebody who has a registered dietician degree, that was sufficient. Sufficient enough to get above 70%.

And so, I think that's good news. You don't necessarily need somebody like an oncologist that's got extensive training in oncology nutrition. You just need somebody that knows enough about the fasting mimicking diet to reassure the patient that it's okay. And in the new trials that I'm about to talk about in a second, we also looked at lean body mass. And actually, we saw an increase in lean body mass per cycle of the FMD. It was combined with a light muscle training. So interesting, right?

Chris: Yeah!

Dr. Longo: Everybody was shocked in the hospital because they sure that these poor patients were going to lose weight and they were going to become cachectic. And so, we begged them to keep the protein intake low – sufficient but low. And they insisted on keeping the protein intake higher than normal. So, we don't know what happened to the cancer yet. But certainly, because they started gaining weight, we think it was too much. There's no reason for these patients to be like gaining muscle – not just weight, muscle mass. They were losing fat and gaining muscle mass. So, yeah, basically demonstrating that we overdid it, meaning that we should have worried more about the cancer and less about the muscle, because the muscle was such a non-issue that they gained muscle mass.

Chris: That's really interesting. So, I read a summary about the second study we talked about here, that said that the women that were on the fasting mimicking diet were more likely to experience a 90-100% tumor cell loss, compared to the women who were not fasting around their treatment. That's a big number. I mean, that's a lot, 90 to 100%. 100%. That's all of it.

Dr. Longo: Yeah. But the impressive thing was there was a big change. It was not a 20% increase. It was like a two- or three-fold higher chance that they'll be 90-100% cancer-free. So, I think that what was nice, this is why this paper is a paper for scientists… I mean, it's for clinicians obviously, but it's also for scientists because it's fairly complex, if you look at it. But when you put it all together, you get the sense, in this case that you're talking about, we saw the clinical response. So, the radiology matched the pathological response very well. So, during surgery they took the tumor and then they'll go look at, in a blinded way, how many cancer cells are there. Or they looked at the tumor, the mass size, they match each other fairly well. So, the people that did the most cycles of the fasting mimicking diet, had the biggest cancer free (or 90% cancer free) response in the tumor. And they had the biggest response when they look at did CT scans and other radiological ascites.

Chris: That's amazing. One other thing that was, I think, worth mentioning from this study was that they had less DNA damage in their T-cells, right? From the chemotherapy.

Dr. Longo: Yeah. They had less DNA in their white blood cells. And this was already shown in a previous study. So, it's good we keep seeing this consistent protection of the normal cells. And in this case, replacement of the dexamethasone – protection of the normal cells, in spite of having the dexamethasone in the other group. And then, this at least initial very powerful effects on the cancer. Very much consistent with the mouse data. That's another thing that usually these papers, when they're clinical papers, they're viewed in a vacuum. They're viewed in, "Oh, this is it. This is what's in front of me. Tell me what the primary end point was. I don't want to hear anything else." Right? This is how the clinicians view it. We view it much more like, "Well, look at the 50 animal papers. Look at the previous six or seven papers on fastening and cancer, especially in chemotherapy. Look at all the results in this trial." And then, you start to get the sense that this is working. Now does it mean we know for sure? No. But is it beginning about as well as we could possibly have imagined? Absolutely.

Chris: I know you're excited. I mean, it really seems like a huge leap forward in this research. I mean, patients that were fasting around chemotherapy had less side effects. They didn't need the drug for side effects. Their immune systems had less damage. Were there any other metrics that you measured in their bodies that were affected in different ways? In other words, were there any other parts of the body or systems that were measured that had less damage from chemo?

Dr. Longo: Well, in this trial we did… And again, the side effects were fairly similar, but without one drug. So, the FMD without the drug was about the same as the other one. I mean, there were some things that trends for like neutropenic fever, it was not significant, but you could tell it was about health. So, the patients that seemed to be having these negative long-

term effects of the chemotherapy on the white blood cells, and then the fever that results as a consequence of that. There seemed to be a trend for being reduced, but it was not significant.

Yeah, the other thing, I think, that was very nice and consistent are these effects on insulin, IGF-1, glucose. And so, we now have no doubt about it, because I'll tell you in a second about the other two trials that are going to be published right now, pretty much. It's the effects on multiple factors that are very well established to be supportive to cancer cells. So, now we're going after insulin, IGF-1, glucose, leptin, some of these pro-inflammatory and anti-inflammatory facts, some of the insulin sensitizer markers. So, we're starting to see, in a very repeatable and consistent way, what it would take a minimum of four or five drugs to achieve. Right?

So, this is where we're starting to say, the way that cancer treatment is done, is very specific. And it's very good, because we always need the standard of care. If you remove the standard of care – like in this case, if you remove chemo, I doubt that the patients would have responded very well. So, have the chemo, the immunotherapy, the hormone therapy, etc. But then, have all these changes that seem to be making – as we knew very well from the mice that work – everything else struggle. Every cancer cell struggle and every normal cell respond in a very coordinated way, clarifying that this is nothing new. For a liver cell or for a kidney cell or for a brain cell, being under starvation conditions is just part of the normal routine.

Chris: I want to jump back to the mouse study really quick, because there's a question that's like rolling around in my head that I'd love for you to answer. In the mouse study where you gave IV vitamin C and the fasting mimicking diet, I guess there was a control group and then a group that had the intervention. What was the difference in tumor response?

Dr. Longo: It was huge difference. And the interesting thing, based on what I just said, even with the non-toxic vitamin C, if you give… And we tried it with many different types of cancer cell lines, all kinds. This is called KRAS, it is one of the most common mutations in all cancers. And so, if you give high dose vitamin C (injected vitamin C), the tumors respond. I mean, it kills tumor cells. But then what the tumors do, they increase something called heme oxygenase-1. And so, they have very high levels of this heme oxygenase-1. And this is a consequence of very high levels of something called ferritin.

Chris: Which is like a component of iron?

Dr. Longo: It binds iron. And so, together high heme oxygenenase-1 and high ferritin protect the cancer cell. Right. So then, when you intervene with the fasting mimicking diet, this brings it down. And really this

underappreciated… I call it that by confusion. I don't know if I used that term last time you interviewed me.

Chris: I don't think so. I love it.

Dr. Longo: It's underappreciated this confusion that is generated by this condition to a cell that is evolved in abundant or excess food. So, this cancer cell has always seen excess food, and all of a sudden everything is removed. Like now it gets high dose vitamin C. Normally it would have gone. Let me increase heme oxygenase-1. Let me increase ferritin. So, I don't worry about this vitamin C. I can handle that." But now, because the environment is completely different, you no longer have that option. You've got to keep HO-1, probably because if you don't keep HO-1 down, you're going to die of another cause. And that's a complexity that we think is so central in going after every cancer. Just by the fact that they're rebels that have evolved in excess food. And so, everything you move away with fasting is going to increase the complexity of the environment, and therefore the confusion – you can call it metabolic confusion – generated within a cancer cell.

Chris: Did some of the mice have complete tumor progression? Like elimination?

Dr. Longo: We didn't see… Now in the lab… I'll tell you in a second about the hormone therapy, and the hormone therapy, we got extraordinary results. And this is going to be published in the journal Nature very soon. For the vitamin C and FMD, we got a big effect on slowing down cancer. And once we had the chemo, we started getting a trend that maybe they were going down. But we never demonstrated cancer-free survival. And then, there was something that… We're now getting better and better. And now we're using lots of technology. So, I think that the next wave of papers, we're starting to bring in what's called systems biology. So, we can look at the network and now we're starting to understand. And very soon we're going to bring in artificial intelligence. And so, we can start seeing this metabolic complexity and metabolic confusion. How the cell is responding to this wide acting and specific intervention. And so, eventually we think very soon we're going to be able to point to how we get them all. How do they escape, and how do we prevent that escape?

Chris: Okay. So, talk to me about the hormone therapy study.

Dr. Longo: Yeah. The hormone is really remarkable because it's, of course, one of the most common therapies on the planet. Women that have estrogen receptor positive tumors, breast cancer, are treated with hormone therapy. And so, usually, let's say within a year or so on average, they progress. Right? So, the hormone therapy no longer works. And then, there is another drug called CDK4/6 inhibitor, and that gives them maybe another year or so. And so, what we're seeing is that if you add

the fasting mimicking diet, if you just have the hormone therapy, this causes a major delay in the resistance acquisition. But then, if you have two drugs, plus the fasting mimicking diet, not only do you see a delay, but you see a regression. And this is in the title of the paper. We bring the cancer down and down. And it never grows. It never takes over. And the other remarkable thing is it reverses resistance. If you take a tumor that is already resistant and you add the triple intervention, the tumor reverses course and starts going down.

Chris: Wow.

Dr. Longo: So, of course, it's a mouse study. But it has two clinical trials, 36 patients, of what you call a feasibility component, where they combine the FMD with the hormone therapy. And certainly, it's starting to see a few patients… I mean, we didn't have that many, 36, but a few patients that are now going for two or three years. And we see no evidence of them becoming resistant. So, of course we need to do a big trial. So, now we're discussing MD Anderson, UCSF, USC, and many top hospitals, the large trial, maybe an FDA trial, looking at this triple intervention.

Chris: But this is different in the sense that this is like a daily hormone therapy, not like a once weekly administered therapy, right? They're on a daily drug?

Dr. Longo: Daily. And the interesting thing, you know, according to what I have been speculating for a while is that the trick was not unique. So, for example, sugar had nothing to do with the effect. Right? So, we can add sugar, take our sugar, it makes no difference. What had the effect was the triple change in IGF-1 (insulin-like growth factor-one), insulin, and leptin. So, it seemed that by intervening in all three, by taking all three down… And more. It was just for certain those three, because we could show if we fasted them and then injected any of the three, the tumor could go back up. So, it wasn't sufficient to just go after one.

And this is what we're begging people to hear. You can't keep doing this. "I'm going to do this." You become resistant. "I'm going to do this plus this." You become resistant and you're out of luck. You have to have tools that are much more already at the theoretical level. They're much more likely to get them up. It doesn't mean it's going to work. But certainly, if you, at least theoretically… And now, it's no longer theoretical. We have mouse data, we have clinical data. But certainly, the promise is that if you have this revolution of the environment, that normal cells understand very well. And the cancer cells don't understand it at all. You are starting from such an advantage point that the fight becomes much, much easier, eventually.

Now, if you get to a certain point, then you can ask, "What would happen if you did three weeks of this?" Right? So, I mean, eventually we're going to slowly march down that road. What can we do? Is it just fasting? Or is

there something else that we can do to expand these differential effects, between normal cells and cancer cells. Eventually we might do two or three different things, like we did with the vitamin C. Right? So, you say, "Well, can I add something to the fasting mimicking diet that may make that separation even stronger?"

Chris: So, for those patients on hormone therapy, they were taking hormone drugs every day. How many times did they do a four- or five-day fast?

Dr. Longo: I think it was every four weeks.

Chris: Okay. So, they were doing it basically monthly.

Dr. Longo: It was five days. It was higher calorie five days.

Chris: Was it more like the ProLon calorie level?

Dr. Longo: High carolie five days, or a mid-calorie four days.

Chris: Got it. Is Chemolieve still a product?

Dr. Longo: It's called Xentigen now.

Chris: Okay.

Dr. Longo: The company didn't want to focus on chemo because it's obviously about so many different therapies now.

Chris: Yeah. So, those patients were doing closer to the ProLon type? Way more calories?

Dr. Longo: Yeah. This is either closer to ProLon or something in between the very low calorie and the ProLon.

Chris: Got it. Alright. And then, you have one other to talk about. Am I right?

Dr. Longo: No, no, no, this is it. Luckily for you, we covered all three of them.

Chris: Okay. Well, Dr. Longo, this has been so fantastic. I'm so excited for you. Congratulations. And this is remarkable research. I'm just so pleased and thrilled really just to know that you're doing what you're doing. Because as a patient advocate and a survivor myself, every step closer towards... Obviously improving survival is the biggest goal, but even just reducing side effects and treating patients with non-toxic therapies, like approaching that non-toxic level of care, is something I hope we get to in my lifetime. So, thank you again, for the work you're doing. It is so important.

Dr. Longo: Yeah. And I will say, as the cancer survivor and patient advocate that you are, I think it's important. I think the oncology field has created this very rigid, old style, "this is the FDA approval and nothing else." Right? And I'm not against the FDA. Absolutely. I think it's great. I think it's very protective of patients and protective against the BS or things that are quackery and not really validated. But I think the patient advocacy group needs to push the oncologist, the big hospitals, the government, to say, "There's a lot of patients…" And I don't know if you were in this situation or not…but, "There's a lot of patients that can't wait another seven or eight years."

And what we're missing, which is difficult… And this is why we're opening a clinic with my foundation in Los Angeles called Create Cures Clinic. And we have three physicians – we have a molecular biologist, and we have a registered dietician, and they work as a team. And so, the molecular biologist's job is basically to say, "Hey, there is not an FDA approval of this yet. But I think if we take the standard of care and we're respectful of the FDA and respectful of the standard of care, but add this, which is allowed by the law…" I mean, if you change the diet, you are allowed. If there's an oncologist. Particularly if you have an oncologist, a molecular biologist, and a registered dietician is a team, that's it. You can do medicine. You don't have to just have the manual of, "Is there a way that we can help this patient?"

Now, if the patient has a 99.9% chance of being cured, absolutely keep it by the manual. But if the patient is not in that situation, I think we're really missing… And the advocacy group needs to push this and say that we're really missing the need for this team to be created. First of all, bring in the molecular biologist and the molecular oncologist. Create the team with the internal medicine doctor, oncologist, molecular biologist, dietician, and push so that this patient may get benefits without risking. You know, we're not talking about, "Oh, let's do some crazy therapy and risk the patient's life." But if the patient is already in a bad situation, I think that it doesn't make any sense to sort of hide and say, "Oh, I hide behind the fact that it's not FDA approved yet," even though it doesn't need FDA approval. So, I'll give you a simple example. What should you eat between a cycle of immunotherapy and the other. You've got to eat something. So, who is going to give you that information? What you should eat between radiotherapy or chemotherapy cycle and another one? And what should you eat, based on the fact that you are muscular or you're anorexic? So, all of this is completely absent in the cancer field.

Chris: Well, there's one answer for everybody, right now. And it's eat ice cream, milkshakes, pizza. Eat as much as you want. Eat high calorie foods.

Dr. Longo: Ridiculous level of giving that advice. But let's say, the good places, like Loma Linda hospital. There are good places that are paying attention. So, now I think that they need to get together and the oncologist could say, "I already know insulin. I probably want it to be low. I probably already

know that glucose I like to be pretty low. And I know the leptin I like to be pretty low. Well, how do I get that?" Well, let's ask the molecular biologist. Let's ask the dietician. Well, it could be very easy. "Do this and this and this. Keep the protein intake low, that's going to bring IGF-1 down. And sensitize the patient. Maybe do a couple cycles of the fasting mimicking diet, even between chemotherapy or whatever else."

So, there are ways that, now in the clinic, we're handling it without violating any rules, without challenging anybody. We're not challenging the oncologist. We're not saying, "Oh, the patient should not do what you're saying." It's just a new team that is formed that I think we can see the big difference in the patients. And, yeah. So, I'll just conclude with that and say that I hope the advocacy groups can start asking for this kind of treatment. Because eventually, it's going to be for everybody. But it's very sad if you think about the people that didn't get a chance to have it. And maybe then, as we've shown in this paper, that reduction in insulin, IGF-1, and leptin could have saved your life.

Chris: I've got to ask you one more question before we go. What foods increase leptin?

Dr. Longo: Well, leptin, in our case, I think it's probably... I mean, I'm not an expert on components of food and leptin per se. Because it can be very complex to know. But in general, in this case, the starvation brings leptin down, right? So, the starvation response is associated with not just a leptin reduction, but a long-term leptin reduction. It's really remarkable. With the mice and the humans, it didn't just decrease temporarily. It decreased long-term. And this could be due to the fat. The fat itself is controlling leptin production. And so, now you eliminate the fat and now you can have long-term reduction. I mean, that's at least one of the hypotheses that we have in the paper, that the fat reduction, or at least the abdominal fat reduction, is now causing these long-term effects on leptin levels.

Chris: Got it. So, it's more about reducing external body fat – belly fat.

Dr. Longo: That's what we know so far. It could be other effects. But certainly, at least as far as the effects of fasting on leptin are concerned, it probably has something to do with the fat. Either the fat storage or certainly the modality or the mode in which the fat cells are operating. So, all of a sudden, they go from a storage mode – store, store, store, because I'm going to encounter a starvation period – to using it because I am in a starvation period. So, that could be the difference between high leptin and low leptin.

Chris: Do you have a timeline for the Create Cures Clinic.

Dr. Longo: It's up and running. Create Cures is in Los Angeles, it's in Santa Monica. We're already doing telemedicine. The team is up and going. So, now

we're starting to collaborate with all the oncology groups all over the world, by the way. But with focus in the United States. And we have another one here in Milan. And so, not just for cancer, but in general we see a big difference that this can make to the patient. Also because of time. This is another thing that people don't appreciate, how busy oncologists are going to be busy. How doctors are. And how it's difficult for them to say, "Let me stop and take four hours and go read six or seven papers." They don't have the time.

So, the molecular biologist in our clinic, that's all she does. She just focuses on: Is there a new study? What does this patient have? What is the genomic profile? Now we're starting to do microbiome profile to lots of the patients. So, you take the time, study these omics (this big data), and then go to the physician and say, "You know, we've seen this in this patient. What about this or that?" And of course, the oncologist or the internal medicine doctor can say, "No, I disagree." That's okay. I mean, eventually, it is the doctor making the call. But at least they're informed. And as a team, they can make a decision.

Chris: That's fantastic. Well, we'll link to the Create Cures Clinic in the show notes for everybody to find it. I imagine they're probably going to get a lot of calls and inquiries after this interview. I'm so excited. I didn't even know that was happening.

Dr. Longo: Yeah. It's a non-profit. They take insurance. But we treat everybody. So, independently… Of course, the actual cancer therapy is done by hospitals. But everything else, we try to help everybody, whether they can pay or not.

Chris: Sounds like a very good resource. I really love the fact that like, again, as a patient advocate, we are pushing. I mean, patients are asking every day, they're asking their doctors. They want to do more. That's the reality. Most patients want to do more. And we're trying to close this gap.

Dr. Longo: If you go to the oncologist and you say, "I want you to do more," the oncologist says, "Hey, I received one class on nutrition. I don't know. Why are you asking me?" And then, the dietician is going to say the same. "I was trying to make patients eat more." You know? So, I think that the advocacy group shouldn't be asking the oncologist to tell them what to eat. They should say to the oncologist, "You need that team." You know, I started a registered dietician program at USC and we train our dieticians. They all have to take my classes. They are a requirement. And I train them for however many weeks. And this type of understanding of the molecular connection between food components and cells and intracellular processes and bad cells and good cells.

So, yeah, that's what you need in the team. A few people. And of course, this dietitian may have just taken a few courses on that. But then I have a PhD that has four or five years in molecular oncology. So, in that team,

now you have somebody that understands the molecular aspects of cancer much better than the oncologist. So, now, this person can say to the oncologist, "Okay, let's get together. Because together you teach me. Or you make the decision clinically, but I intervene and I bring in the understanding of the molecular aspects of this particular type of cancer." Yeah. So, if you go to the oncologist, you're not going to get anything. So, the advocacy group needs to demand… It's not that expensive. Bring in these molecular biologists and bring in the dieticians and have them act as a team. The oncologist is still the boss, but everybody else can make a tremendous difference.

Chris: Fantastic. I love it. I'm so excited. Thank you, again, for your time. Thanks for watching everybody. Thanks for listening. Please share this video with people you care about. Obviously, this is very relevant, brand-new cutting-edge science. Pertinent to cancer treatment and survival. Exciting things are happening and we'll just keep you updated and keep pushing the ball forward. Thanks again, Dr. Longo.

Dr. Longo: Thank you. Thank you.