

## **Valter Longo, PhD: Differential Stress—The Effects of Fasting on Cancer**

*Interview by Craig Gustafson*

*Sponsored by the Oncology Association of Naturopathic Physicians 2014 Conference*

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*Valter Longo, PhD, will speak at the 2014 Oncology Association of Naturopathic Physicians February 14 to 16 at the Arizona Grand Resort & Spa in Phoenix, Arizona. He is the Edna M. Jones Professor of Gerontology and Biological Sciences and Director of the Longevity Institute at the University of Southern California, Davis School of Gerontology in Los Angeles. Dr Longo's studies focus on the fundamental mechanisms of aging in simple organisms, mice, and humans. The Longo laboratory has identified several genetic pathways that regulate aging in simple organisms and reduce the incidence of multiple diseases in mice and humans. His laboratory also described both dietary and genetic interventions that protect cells and improve the treatment and prevention of cancer and other diseases in mammals. Dr Longo's most recent studies are on interventions that can affect stem-cell based regeneration to promote longevity. The Longevity Institute in Los Angeles, directed by Dr Longo, includes over 40 faculty members focused on topics ranging from regeneration to dietary interventions to engineering all aimed at improving health and lifespan in the near future. Among the accolades received by Dr Longo are the 2010 Nathan Shock Lecture Award from the National Institute on Aging (NIA/NIH) and the 2013 Vincent Cristofalo "Rising Star" Award in Aging Research from the American Federation for Aging Research (AFAR).*

*Dr Longo was born and raised in Genoa, Italy and received his undergraduate degree from the University of North Texas, where he majored in biochemistry with a minor in jazz performance. He received his PhD in biochemistry from the University of California, Los Angeles (UCLA) in 1997 and his postdoctoral training in the neurobiology of aging and Alzheimer's diseases at the University of Southern California (USC). He started his independent career in 2000 at the USC School of Gerontology, one of the first and leading programs for aging research and education.*

**Integrative Medicine: A Clinician's Journal (IMCJ):** In February, you will be speaking to the Oncology Association of Naturopathic Physicians. What will the title of your presentation be?

**Dr Longo:** It will probably be "Fasting and Fasting-mimicking Diets in Cancer Treatments."

**IMCJ:** How did you first become involved in the concept of deriving health benefits from calorie restriction?

**Dr Longo:** I first became involved many years ago as a graduate student at UCLA. I was one of the students of Roy Walford, MD, one of the pioneers of calorie restriction. Later, I moved to my own work on starvation—he was working on the standard calorie restriction, which was a 20% to 30% restriction in calories, independent of the type. Instead, I went to another lab and started work with fasting, originally in microorganisms, and then eventually in mice and humans.

**IMCJ:** Much of your work is focused on antiaging research. How did this evolve into developing a new approach toward cancer therapy?

**Dr Longo:** I was looking for more than just what discoveries and ideas could do to aging, but also what would maximize the impact—what things were needed by people. I thought that since we were experts on cellular protection, even though aging does cause stress to cells in many different ways, I thought that chemotherapy was most likely the highest level of toxin that a human being was likely to encounter.

So, if that is the number one most likely chemical a person is going to be exposed to, then what can we do about it? Was there an intervention that nobody had been

thinking about, which had to do with protecting normal cells that also affected cancer cells? That is where we stepped in.

**IMCJ:** Your lab had developed expertise in cellular protection. How does fasting contribute to that?

**Dr Longo:** Cellular protection is negatively regulated largely by glucose and protein amino acids. We had discovered these two key paths in yeast and then, eventually, we moved our work to higher eukaryotes.

The two key pathways are activated by proteins, amino acids, and sugars. When activated these pathways—these genes—make cells much more sensitive to all kinds of toxins. So if you fast—for a yeast, a worm, a mouse, or now, we think, a human being—these pathways are shut down. But there is one exception, which is the cancer cell, because the same genes that control protection are also the ones that are always on in cancer cells. That genetic expression provided the foundation for what I call *differential stress resistance*.

**IMCJ:** You are saying that not only does fasting protect healthy cells, but it makes the cancerous cells more sensitive to chemotherapy.

**Dr Longo:** Yes, starvation shuts down these pathways in normal cells and the normal cells go into a shielded mode. The cancer cells cannot—regardless of the type of cancer. Then it gets better, because it turns out there is another problem that the cancer cells have: the inability to adapt to extreme environments. The reason for that is simply a fundamental property of damaged DNA. So if you take a cell and randomly damage its DNA, it becomes progressively dumber, right? Meaning that it can do pretty well in standard conditions, but as you change the environment, it might be unable to do certain things that it used to do. The beauty of fasting is that it makes the environment so extreme, that now cancer cells—not only are they nonprotected, but they have become sensitized. This is what we refer to as *differential stress sensitization*.

**IMCJ:** You conducted a trial on mice that offered strong evidence for fasting in cancer treatment. What did you observe in that study?

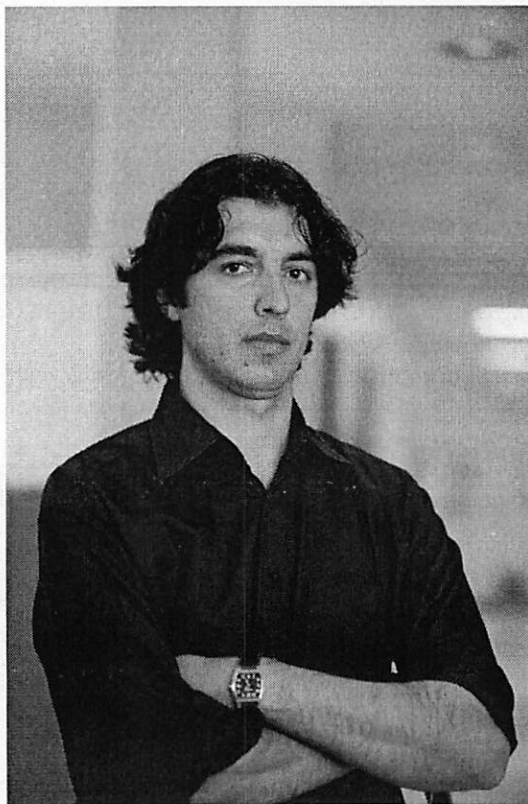
**Dr Longo:** The first study was the proof of principle. We used different types of cells in the mice and just wanted to show, in fact, that this worked. We hoped to document that we could starve the system—starve the mice—and they would become protected against multiple types of chemotherapy, but the cancer would not become protected. In some cases the protection was remarkable, so with several different drugs, we kept 100% of the mice alive if they were fasted before the chemo, and 100% of the mice died if they were on the normal diet before the chemo.

**IMCJ:** This was your first animal study. Have there been more?

**Dr Longo:** We have done many now; at least 6 or 7 have been published. All have confirmed our results. And, of course, the follow-ups were not just observing the health of the normal cells but also the cancer cells. Last year, we showed that if you combine multiple cycles of fasting and chemotherapy—depending on the tumor and its stage of development, which are all metastatic tumor models in mouse trials—we could get anywhere from 20% to 60% cancer-free survivors. So basically, these mice were cured by the combination, but they did not become cancer-free at all if given either fasting or chemotherapy alone. So fasting alone makes it a little bit better, chemotherapy alone also makes it a little bit better—fasting had about the same effect as chemotherapy actually. But combined, you get 20% to 60% of the mice that become free of cancer.

**IMCJ:** How was fasting employed in the cancer therapy? And to what degree did you have to go to achieve the result?

**Dr Longo:** This was 3 days of fasting, which is pretty extreme for a mouse. Either before chemo, or better: Do 2 days before and 1 after. And we knew that this was pushing the mice to the limit, but we were interested in achieving certain markers to feel that the fasting was effective. We monitored several growth factors and other molecules in the blood, and once we got there we felt that it was the right amount of fasting.



**IMCJ:** For mice, it sounds like 3 days of fasting is about optimal. What are you projecting that it might be for humans?

**Dr Longo:** We are now doing a number of human clinical trials, and the standard now is 3 before chemo plus 1 after, so it is 4 days. Now, it is not necessarily complete fasting. Because of concerns about safety, we had to keep complete fasting to 2 days before and 1 after. And then we moved to what we call *fasting-mimicking diets*, used 3 days before and 1 after. They include a few calories so the patients can have food, although it is not very much. They are very calorie-restricted—less than 300 calories per day on some days but over 800 calories on one of the days—but it is much easier on patients, and oncologists, than just telling them to drink water. These are also high-nourishment diets, to prevent and even reverse the micronutrient malnourishment of cancer patients.

**IMCJ:** Do you feel that it would still be effective for cancers accompanied by cachexia? How would that impact treating a cancer with fasting?

**Dr Longo:** First of all, cachexia is not very common, meaning that it is common for people at very advanced stages, but not very common for the great majority of patients who are getting treatment. Now we have followed more than 500 people outside of clinical trials who have done fasting together with chemotherapy while being monitored by their oncologists. So far, I do not remember very many cases, if any, of people reporting that they had to stop fasting because they were becoming cachectic and were advised to stop. At the same time, in the clinical trials, we excluded people who had lost more than 10% of their body weight. The reason, of course, is that there is a major concern for someone who has lost a lot of weight. At that point, an oncologist should step in and ask whether fasting is appropriate or not.

What we have seen with people who were cachectic already—there were a few participants who decided to do the fasting study anyway, because they couldn't take the chemo anymore—is that they reported doing much better. Even though they were already somewhat cachectic, they did much better—when they combined the fasting with the chemo—than they had done before.

This makes sense if you also look at our animal studies. The mice lose weight because of the fasting, but gain weight after being given chemo and food whereas the mice that were on a normal diet started losing weight when given chemo.

**IMCJ:** Do fasting and calorie restriction have any role in cancer prevention?

**Dr Longo:** Yes, a major role. Luigi Fontana, MD, and I wrote an article a few years ago on that. There are many

studies showing that calorie restriction prevents cancer, at least in mice. Now, mice do not get the same cancers that humans do, so we have to see what the effects are for humans. But in monkeys, both of the studies—one done by the University of Wisconsin, the other one performed by the National Institute on Aging—suggest that the monkeys under calorie-restricted diets have reduced incidence of tumors.

**IMCJ:** If somebody were interested in pursuing fasting for longevity or cancer prevention, how would that look?

**Dr Longo:** I would first of all explain the separation between calorie restriction and fasting. They are completely different things. Of course, fasting entails calorie restriction; however, calorie restriction is just a little bit less calories than baseline and it is chronic—for the rest of your life, basically. And we know that situation is just not feasible for the great majority of people. People may or may not benefit from it, but it is very, very difficult to maintain, and I would say maybe one in a thousand people would be able to do long-term calorie restriction.

Fasting—periodic fasting—is what we focus on. Periodic fasting really does not entail any drastic changes except for the days when you fast. And it does not entail, for example, chronic weight reduction. You can be of normal weight and just do periodic fasting. So I really think that is the way to go. You may have heard about the Michael Mosley diet, which was in part based on our work, but he came up with something called 5:2. And 5:2 is basically normal food for 5 days, and just about 500 calories for 2 days a week.

I do not think that 5:2 is going to live up to my longevity component, nor the compliance component. We think that 5 days a month of a fasting-mimicking diet is a better way to go. So we are running a clinical trial now with over 30 people enrolled already. They seem to do very well on it and compliance is 100%. People who needed to lose some weight lost it, while people who need to keep their weight up were able to regain it, so we feel that this is the way to go.

For somebody who needs to lose a lot of weight, or struggles in maintaining weight, 2 meals a day instead of 3 is also beneficial, in combination with monthly periods of the longer fasting-mimicking diets. Now the fasting-mimicking diets should be medically supervised and should not be very low in calories. For disclosure purposes, I should note that I have a company that is making food kits for fast-mimicking diets, but I think that people can eventually think of their own version. The problem with people and doctors making their own version is going to be safety, compliance, and efficacy as determined by clinical studies. I really think that even though medical food does not require FDA approval, the type or size of study that the FDA requires is really what is needed to optimize the efficacy and the safety but also the acceptance by the medical community.

**IMCJ:** You mentioned, in contrast to the fasting-mimicking diets, another scenario where 2 meals each day are consumed instead of 3. How would you observe that type of diet?

**Dr Longo:** This is what I have been doing for 5 years. The scenario is for you to only eat twice a day. The problem, of course, for a lot of people is malnourishment. Doctors often tell you eat 5 times a day for 2 reasons: The first is that in some cases they do not really understand the consequence of that—and the consequence is obvious, 70% obesity or overweight-ness in the United States. But the second reason is to make sure people get everything they need, and that is a good point, right? If you are eating all the time you are probably not missing anything. If you only eat twice, and are not followed by a dietitian, or a doctor who knows what they are doing, you could become malnourished.

So, 2 meals a day; it can either be breakfast and dinner or I think breakfast and lunch is the way to go. But there must be medical supervision—which does not mean that somebody has to be in the hospital; it just means that there has to be a health care professional following the person to make sure that they get everything they need.

I don't like the 24-hour fast because I think it is just too extreme for people. But 2 meals is much, much more manageable. Some of the centenarians and other people out there have been doing this for a long time, without any doctor instructing them. That tells you how easy it is to do it. But 24 hours without food, that is much harder.

**IMCJ:** What more will attendees at the OncANP conference learn about how fasting impacts cancer by attending your lecture there?

**Dr Longo:** I will show some data from the clinical trial, so that attendees will be able to see that, and I will talk a little bit about these fasting-mimicking diets that eventually are going to be available for them to recommend to patients.

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