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Welcome to IFL Science – The Big Questions, the podcast where we invite the experts to explore the biggest mysteries of science with your host, Dr Alfredo Carpineti.

I: What we eat plays a massive role in our well being and it is only natural to wonder how that affects our bodies' natural defence mechanism. So, our big question today is how does your diet impact the body's ability to fight diseases? To answer it, we are joined by Dr. William Lea, Physician, Scientist, President and Medical Director of the Angiogenesis Foundation and author of *Eat to Beat Disease: The New Science of How Your Body Can Heal Itself*.

Dr. Li, thank you very much for taking the time to talk to us. Can you tell us about who you are and what you do?

R: Yes, thank you Alfredo it's a pleasure to be on. So, I'm a physician, internal medicine which means I take care of men and women, young and old, healthy and sick and my orientation has always been to try and preserve health, maintain peoples' health, and when people fall off the rooftop of health, to try to get them back on as best as possible. I'm also a scientist, a research scientist. I spent the last 30 years studying a field called angiogenesis. Angio: blood vessel. Genesis: how they grow. So, I'm an expert in circulation is my area of research. I'm also an author, I wrote a book, a New York Times bestseller called *Eat to Beat Disease* and a new book coming out called *Eat to Beat Your Diet*, which is really all about how the science of the body informs how our food affects it. This comes from my background in biotechnology. I've spent almost three decades working with biotechnology to develop new treatments for cancer, complications of diabetes and vision loss. So, my whole emphasis throughout my career has been developing the scientific evidence that allows us to know, using the principles of science, how something actually works.

I: Thank you very much. Can we start by, if you can tell us a bit about angiogenesis and what is it's role in many diseases?

R: Right, so first of all, angiogenesis is really the process. Our body grows blood vessels, and these blood vessels actually form a defence system in our body. Let me explain how that works. There are about 60,000 miles worth of blood vessels in your body and in mine, most adults, and this is an extensive network, these are the highways and byways by which the oxygen that we breathe into our lungs is delivered to our cells. This is also the channels by which when we eat nutrients or take medicines frankly, that they deliver the medicines also to our organs, our cells, and our tissues. So, having this channel is absolutely vital for our health. Now, what happens and why is it called a defence system? Well, what happens when you don't have enough blood

vessels? Our organs starve, they don't have enough oxygen or nutrients and we know this happens if you have a stroke and you don't have enough blood vessels. Your brain tissue dies, or if you have a heart attack, you don't have enough blood vessels growing, your heart tissue dies. If you don't have enough blood vessels growing in your leg, you get gangrene. Toes turn black and you need to have an amputation. So, we kind of know that importance of circulation. When there is not enough you want to grow more or bypass. On the other hand, there is this whole side of the equation where you have too many blood vessels, more than you need and that becomes equally dangerous when you have an overage, an excess, because too many blood vessels can actually feed disease. What do I mean by that? Well, turns out that microscopic cancers are pretty common in the body but they're entirely harmless because they don't have their own blood supply, so they sit as microscopic pinpoint size tumours until your immune system wipes them out. That's because they don't have a blood supply. So, healthy bodies have just the right amount of circulation, angiogenesis, the growing of the circulation as a defence system. Not too few, not too many, kind of like *Goldilocks and the Three Bears*, just the right amount. When you don't have enough or you have too much your body is out of balance, your defences are down, and you are more vulnerable to disease. This is where both medicines but especially foods can make a difference.

I: Very interesting, So the whole point is that diseases are caused by angiogenesis when that becomes unbalanced.

R: That is actually correct, and this is a true principle for many of the health defences in our body as well. I wrote about five of them in my book, *Eat to Beat Disease* and really, our health defences were formed when we were still in our mom's womb. So, when our mom's egg met our dad's sperm, we became a ball of cells that ultimately developed ears, and chins, and knees, and livers, and lungs. Throughout that process, so too formed our body's health defence system, so we were hard wired at the moment of birth from our very first breath, to have these health defences firing on all cylinders to protect us from harms inside the body, things that can go awry. We need to have balance; maintain that balance and you maintain your health. But also, from harms from outside of the body, including in our environment. We live now increasingly in a degraded environment making our health defences even more important than before.

I: I'm aware that there are anti-angiogenic drugs that can fight some of this imbalance and some of them are being tested. So, there are clinical trials when it comes to fighting cancer. Some of these trials are also using them together with other immunotherapies, drugs that can help fight tumours. What are the expectations from these scientific investigations?

R: Actually, since the late 1980's I've been involved with pushing and helping and fostering the development of anti-angiogenic drugs for cancer. So, the good news is that after all these decades of effort we actually have about a dozen approved drugs used to treat cancer showing survival benefit. So, we already know that they work. One of the other major spheres of cancer research has developed successful immunotherapies. Now, immunotherapies work on...if angiogenesis therapies work on one aspect of our defence systems, immunotherapies work on another defence that also our diet affects and that's our immune system. Who has not thought

about our immune system? Your immune system in the last two or three years, with what the whole world has gone through. However, most people think about the immune system as protecting us from infections from the outside world, but it turns out our immune system is equally important, if not more important, for protecting us from harms inside the body. By that, I mean cancer. So, these little tiny microscopic tumours that form in our bodies from childhood, by the way here's the little footnote for your viewer and listeners; [unclear 0:07:43] microscopic cancers, we all live with cancer as an invisible disease and the reason is because cancers are from mutations in the body. We've got 40 trillion cells in our body, and they all have to divide, reproduce, replicate themselves in order for us to maintain alive. This is why we are here tomorrow and the next day. Turns out that as our DNA replicates, so reproduces itself, at a small scale it tends to do it perfectly but on a large scale, 40 trillion times, mistakes get made. In fact, this has been calculated that our DNA on a daily basis, every 24 hours, makes up to 10,000 mistakes every single day. Each of these mistakes is like a mis-spelled word in a document that we are typing and, fortunately, our body has a spell check. That spell check fixes these errors and lowers the risk of actually developing cancer. Some of them already, of course, escape the spellchecker and form a microscopic tumour. Without a blood supply and angiogenesis defence it can't grow but then what happens, is that these little, microscopic tumours which don't cause disease, sit there, like a time bomb frankly. But then our immune system swings by, our immune cells conduct surveillance. It's like cops on a beat, policemen patrolling the streets of a good healthy neighbourhood and seeing the drug dealer sitting on a street corner. Maybe not doing anything, but what our immune system does is pick up that errant microscopic cancer and puts them in the cellular paddy wagon and takes them away and that's basically how our body cleans up cancers that form inside our body all the time. So, immunotherapy, which is also an approved treatment that can improve survival in some types of cancers, actually is being hailed really as one of the major revolutions for cancer treatment. This is perhaps the most natural way of treating cancer. Not by poisoning the body with chemotherapy in hopes of getting a little more tumour but actually by activating and unleashing our own immune system to go and do what I talked about, that cop on the beat, better so we can go after even established cancer. So, this actually works pretty well but not in every patient. Foods can actually make immunotherapy work better. This has actually been shown in some very large-scale clinical trials. But let's talk about the anti-angiogenesis because these two defences actually work together. Turns out that when large cancers are growing, they have already recruited a private blood supply. Now the difference between an avascular, a tumour that lacks blood vessels sitting there – and this has been studied in a lab – and frozen in size, when the blood vessels actually reach it because the tumour cancer cells can release natural fertilisers. These are angiogenic factors. They hijack our system. When new blood vessels grow into this tiny, microscopic cancer, the tumour can grow 16,000 times in volume in just two weeks. It's an explosive feeding and nurturing of the cancer and it makes sense, right? With no food you can't grow. With food you suddenly allow propulsive growth. Now what happens is that the immune system has to spot these as well, the bigger the cancer the easier it is to spot. Makes sense if you are a hunter out there you see the big animal, it's a lot easier to see than the mosquito. The interesting thing is that the tumours releasing these growth factors that recruit blood vessels also do something very sneaky. These same growth factors that attract blood vessels to them also repel the immune cells so even though we have got blood

vessels, the factors, the proteins, these are vascular growth factors, repel. They disguise the cancer and then they prevent our immune cells from getting into that tumour. So, anti-angiogenic therapy not only cuts off the blood supply to the growing tumour, thereby starving it, but it also decreases this repulsive force, like the repulsion of immune cells so you hit two targets at the same time. You get rid of these extra blood vessels, and you allow immunotherapies to penetrate better. So, the expectation for these very exciting studies is that you can take immunotherapy that already works very well in some patients and make it work better, partly because you are starving the cancer and partly because you're allowing more immune cells to penetrate and attack the cancer.

I: That is fantastic. Well, I can only say let's hope that those expectations are met and surpassed. One of the theses stresses the importance of us not just fighting cancer and tumours when they are already established but, since you mention how it is so common to have microscopic tumours, the important of prevention. So, with that in mind, how can diet impact angiogenesis?

R: Right, well, it's really important to understand that prevention is something that is in the hands of individuals, citizens, ordinary people like you and me whereas when the line has passed with prevention, that's in the hands of doctors and the health systems and the medical centres. So, prevention is actually something that isn't the responsibility of the health systems. That's very important to understand. It actually flips the equation to actually put it on to giving us the opportunity, ordinary people and this is where actually food comes into play. We know, we've known since the 1970's, that cancer is preventable because the development of cancer involves many different stages. You know, when you construct a building, a skyscraper, you start with the ground floor, you build the foundations and then you start building every floor up and up, and so too a cancer grows. You start from the ground floor, in the body. The cancer needs to establish its footing and then it can actually get bigger and bigger. Every single layer, every floor, every storey that the tumour gets bigger and more aggressive is an opportunity that when you finally get a big skyscraper you have to destroy it using more powerful drugs, including anti-angiogenic and immunotherapy but traditionally chemotherapy and radiation. So, what's the opportunity to prevent it in the first place? Well, you know, you really don't want to be talking about drugs because drugs have side effects, they're not universally accessible and they're expensive and we can't possibly afford to treat everyone who might develop cancer with an expensive drug. Enter the dietary approach. We have known for years bad diets can promote cancer, so for example the World Health Organisation has recognised processed meats high consumption as a carcinogen, and it's associated with the development of different forms of especially gastrointestinal cancers. So, we know bad things that you eat can actually make cancers grow. We're now beginning to discover that eating beneficial foods, certain foods, can also prevent cancers from growing. This has been shown in the laboratories, been shown in clinical studies and been shown in large population studies. Let me give you a couple of examples, and by the way, some of these may surprise you because of the urban legends that surrounds food. There are so many well-intentioned people that come up with ideas and spread them through the social media that some of the ideas that are not maybe rooted in science become the law. This is one of the things that I try to do, I try to address some of the urban legends and try to bring the science to the table. Let me tell you something. So, many

women will have heard that if you have had a history of breast cancer or you're trying to prevent breast cancer you should try to avoid soy at all costs. Tofu, soya milks, soya beans. There is a common belief in the public, in the mainstream, that eating soy is dangerous for women because of breast cancer. The reason that is given is that soy has a phytoestrogen, a plant-based oestrogen and some human breast cancers are sensitive to oestrogen. So, the idea was that if you want to avoid at all costs anything that could spark an oestrogen dependent cancer, you want to avoid soy. Now that's not true. It turns out that the – and by the way, even doctors, even oncologists actually start quoting that urban law – so here is the real science. It turns out that it is true, some human breast cancers are responsive to oestrogen, not all, but some, and it turns out that soy beans contain a phytoestrogen, a plant based oestrogen but if you compare the chemical structure of the plant oestrogen with the human oestrogen, left and right, they look nothing alike and in fact, it turns out according to science, that the plant oestrogen blocks the human oestrogen. It's mother nature's tamoxifen, which is used to treat breast cancer frequently. The other thing that plant oestrogen does, the phytoestrogen does, and we have identified them, [unclear 0:17:14] is the name of one of them. These are called bio actives, mother nature's pharmacy, not with a ph with an f, pharmacy. Turns out that mother nature's pharmacy with genocine has developed something that not only blocks oestrogen receptors in human breast cancer cells but is also anti-angiogenic, and I've actually done research on this to show potentially that the phytoestrogen in soy prevents tumours from growing blood vessels. Now, that's nice in a laboratory, it's been published over and over again. There is no doubt that this is actually a true scientific fact. What about in humans? What happens when the rubber meets the road? Well, there was a paper published in 2009, so this is not new information, but it's not well known yet, but in the journal of the American Medical Association, which is one of the gold standard journals for medical research and it's called the Shanghai Breast Cancer Study, women's breast cancer study, and they studied 5,000 women who were at the highest risk for breast cancer. These are women who already had breast cancer and they studied how much soy they had. When they found that those women who ate more soy had 30 percent better survival, less mortality. If they also had their cancer successfully treated, those women who ate more soy had about 30 percent reduction in the rate of recurrence of the cancer as well, it doesn't come back. A critic would say, "Well, that's just one study." So now there is meta-analysis in which they have looked at 14 consecutive studies looking at soy, breast cancer, and mortality and in no case – zero case – is soy consumption associated with more death and in every case, consumption of soy is associated with better survival. So that's a very compelling set of data to show that soy can inhibit anti-angiogenesis, is beneficial to women, and can actually improve survival and outcomes in a particular form of cancer that people care about, breast cancer. Same is true for prostate cancer with tomatoes. Eating cooked tomatoes, two to three servings a week has been shown to reduce the risk of prostate cancer in men by about 29 percent, almost 30 percent, and this has been studied in more than 30,000 men over 25 years to look at this correlation. So again, when you go into the lab like I have and studied what's in a tomato, we've identified one of the molecules called lycopene, it's a carotenoid, helps to make the tomato red. It's a powerful anti-angiogenic substance that cuts off the blood supply of feeding cancers. Just two examples.

I: That is fantastic and makes me feel very happy that I am Italian and I'm constantly having cooked tomatoes on everything. That is great news. Thank you so much for those two

examples. I have heard of other studies, for example in mice that looked at calorie restricted diets which appears to slow down tumours and I know there are other studies looking at other anti-angiogenic diets etc. So, as you discuss, it's clear that many products that we eat and drink increase the risk of diseases. Others, as mentioned, soy, tomatoes appear to be preventative or at least give us a reduction in risk or a reduction of a recurrence of disease. So, our big question for this episode, how does one's diet impact the ability to prevent disease and how does one's diet impact the ability to fight disease?

- R: Right, so, I think you're getting into two things that are related. When it comes to food and health, what my research has uncovered it's not just about the food because we hear so much in the realm of marketing. There's this superfood or this super supplement and these are mostly marketing messages. There is no such thing as a super food or a super supplement. It's really the human body that's quite remarkable. It's a super body. So, when it comes to food and health what I say is it's not just about the food, it's about how our body responds to what we put inside it and if you put certain foods in and strengthen your health defences, you are much less likely to develop diseases like cancer but also many other diseases as well, including obesity, metabolic syndrome, cardiovascular diseases. The list goes on. If you have already developed a disease, the horse is out of the barn, so to speak. Foods still make a big impact and we have seen this perhaps most profoundly in cancer. We have talked about immunotherapy earlier and one of the big frustrating things about immunotherapy is that in some cases, like in my own mother's case, she was 80 years old, diagnosed with cancer of the uterus, an endometrial cancer and it has spread throughout her body. In the past that would have been untreatable frankly for someone so elderly, wouldn't have been able to tolerate chemotherapy. We gave her just a little bit of radiation and we gave her immunotherapy, activated her immune system and with three treatments only over the course of nine weeks, never receiving chemotherapy at all and with no side effects in her case, all of her cancer disappeared completely and she is alive and well eight years later. So well that her oncologist isn't even following her anymore, she is absent of disease. So, we are beginning to see, if you have a good strong responsive immune system, we can achieve things. Even at an elderly age that we would have thought impossible a decade ago. However, only 20 percent of people respond in such a dramatic positive way. We want 100 percent of the people to respond in that way. Although this field of immunotherapy led to the awarding of the Nobel prize in 2018, the reality is that we are still beginning to make big discoveries of how to make this work better. With diet, it turns out that a colleague of mine, Dr Laurence Zitvogel at the Institute Gustave Roussy in Paris, which is one of the most influential cancer research centres in Europe found in 200 patients who were getting immunotherapy for various cancers, that those who responded well had the beneficial desired outcome, when you looked inside their gut microbiome, regardless of the cancer had a particular organism, a healthy gut bacteria called *Akkermansia Muciniphila*. One healthy gut bacteria was responsible and seemed to be correlated with a response. The people who didn't respond had no *Akkermansia*. They were absent this one bacteria. Now obviously, responding to immunotherapy has to be more than one bacteria present or missing but the impact of this bacteria was studied in the laboratory and then back in the clinic. It turns out that this bacteria, *Akkermansia Muciniphila*, which is a normal healthy gut bacteria that are very sensitive to antibiotics. Think about how many patients take

antibiotics out there, very easy to get rid of them. This bacteria communicates with the immune system. Now, when I went to medical school, I was taught that your immune system lives in the thymus gland, in your spleen and lives in your bone marrow. Turns out that your immune system, 80 percent of it, is actually in the wall of our intestines. Most of our immune system lives in the gut. Now what else lives in the gut is the bacteria. So, the bacteria live inside the gut, but the immune system lives in the wall of the gut, so think of a garden hose you've cut in half, the bacteria is inside the hose, but the immune system is inside the structure of the hose itself. So, they talk to each other. *Akkermansia* can talk to the immune system just like college roommates living in a dormitory with very thin walls can shout at each other to order the pizza for the evening, right? So, this is what actually happens. *Akkermansia* plays a critical role in activating and instructing the immune system. Now, you cannot really take *Akkermansia* probiotics, there is no easy way to replace *Akkermansia*, but you can grow it with food. This is what's remarkable. Food as medicine can help grow *Akkermansia*. What other things are known to grow *Akkermansia*? Well, *Akkermansia* loves to live in the mucus in your gut and there are certain foods that will help grow this mucus. Pomegranates, pomegranate juice, cranberry, cranberry juice, and grape juice are all known to actually grow *Akkermansia* by helping the gut secrete mucus. Now, I have done this with patients that have been on antibiotics, and you measure in their poop, their microbiome, zero *Akkermansia* and then you put them on a dietary regimen and in three or four weeks we have been able to grow six times above the population levels of *Akkermansia*. Then they go on to immunotherapy and they become remarkable responders. Not a clinical trial but based on the knowledge of the science I have been helping patients this way and we have had some really remarkable responses. So, food as medicine, food and medicine – foods can make medicines work better. This is also true by the way for activating our immune system beyond the microbiome – oh another study by the way, just let's talk about cancer again. MD Anderson show that for immunotherapy that dietary fibre makes a huge difference. So, they calculated in a study that people who are for every 6 grams of dietary fibre that the cancer patient receiving immunotherapy receives; this is in patients with melanoma's, a deadly form of skin cancer; for every six grams of dietary fibre, they reduced their mortality by 30 percent, reduced mortality by 30 percent. Now, how much is in 6 grams per day of dietary fibre? Well, 6 grams is what you would get in an average size medium pear a day. Quite remarkable, right? So again, this is not food replacing medicine, I'm not a doctor going on a soap box saying, never mind your medicines. I actually help to develop medicines. What I am saying is that food is a tool in the toolbox that we're beginning to really understand now, the biology, the mechanisms, the molecular physiology of how this can actually not only help prevent disease but help make disease treatment even more efficacious. My new research now is really on human metabolism because this is really the next level of where we are going. In my first book I wrote about the research I had done over the last 30 years which is really about health defences and what I've been doing more recently is thinking about the interconnection of our health defences in a healthy metabolism. When our metabolism is healthy, we wind up actually being able to resist diabetes and obesity and all of the complications that come from that, including dementia. So, it turns out that metabolism is connected to our health defences, they're linked together with our diet and largely what we've thought about our metabolism is actually not correct either. The same way there are these urban legends about soy, metabolism is also not true. So, I am very excited, my new book *Eat*

to Beat Your Diet, not a diet book, it's a trick title. It sounds like a diet book but what it is, it shows you that you don't need a diet to actually improve your metabolism and if you're interested in actually unleashing your potential for metabolism to get to a next layer of health, you can eat foods that proactively activate and optimise your metabolism and yeah, along the way you actually pare off excess body fat, maybe shrink your waistline as well, but overall attain a much higher level of health. So, we want to fight cancer, we want to fight blindness, we want to fight cardiovascular disease; absolutely. But, for those of us who also want to optimise our baseline health, people go to the gym, they ride a bicycle, they work out but how do we use our kitchen? How do we use our refrigerator? How do we use our pantry to actually optimise our diet? There is a way of working out our metabolism at the same time.

I: That is fantastic. Thank you so much for taking the time and explaining all of this to us and to our listeners. Thank you.

R: My pleasure.

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