Diet Doctor Podcast with Angela Poff, PHD (Episode 44)

Dr. Bret Scher: Welcome back to the DietDoctor podcast, I am your host Dr. Bret Scher. Today I'm joined by Dr. Angela Poff. Now Angela is a research associate in the Department of Molecular Pharmacology and Physiology in the University of South Florida and she's working in the same lab as Dr. Dominic D'Agostino.

But she's really flourished in her own right and has sort of taken over the cancer side of that lab looking at nutritional interventions for cancer. And it's a really exciting field because when you think about how prevalent cancer is, pretty much everybody has been touched by cancer, either personally or by a loved one.

And cancer therapies, although you can say we've progressed, probably haven't progressed as quickly as many people would've hoped with this sort of genetic basis of cancer. Well, now there's this resurgence of this whole other concept of the metabolic basis of cancer. And how can we treat metabolic disease? With diet, with nutrition. And specifically with a ketogenic diet and maybe even exogenous ketones.

Now there's a lot of excitement about this field, but as you'll hear Dr. Poff and I discuss it, still a lot of preclinical evidence, which puts us in a bit of a tough balancing act of how strongly to promote this because people want a cure, people want something to help, they latch onto anything. And if we have something that can help them, we should be promoting it.

But does the strength of the evidence support the strength of the recommendation? So we do have to be a little bit careful when we talk about nutritional therapies for cancer. They play a role for cancer therapy and for helping the patient, but exactly how strong can a recommendation be? And I think that will be an important take home from this discussion with Dr. Angela Poff.

She's got a ton of knowledge, she's done a lot of experiments in this field, so I hope you enjoy this and really come away with a few nuggets of what it means for nutritional therapy for cancer therapy, what the state of the evidence is now and

maybe how can you take some of this either personally or to help a loved one who is maybe suffering with cancer. So enjoy this interview with Dr. Angela Poff.

Dr. Angela Poff, thank you so much for joining me on the DietDoctor podcast.

Dr. Angela Poff: Absolutely, very happy to be here.

Bret: So here we are at the fourth annual Metabolic Summit... Metabolic Health Summit, which you are one of the organizers of, and this is a fantastic event and you and Dr. Dominic D'Agostino are like the power organizers and you happen to be in the same lab at the University of South Florida where you are a research associate. And how did you get lucky enough to stumble into his lab and be able to work with him?

Angela: Yeah, you know, so I joined Dominic's lab about a decade ago as I was finishing up my undergraduate work. I knew that I wanted to be a scientist, so it was kind of the only thing I ever wanted to be since I was young and so I knew that I wanted to do research.

I went straight into a PhD program after my undergraduate and kind of how these programs work, you typically show up at the University and you enter into like an umbrella program where they have a lot of different departments under the program and then you meet with all the professors and you learn about what kind of research they're doing and then you choose one to do your doctoral thesis with.

So at that time Dominic had just transitioned into a faculty position at the University of South Florida and so he was wanting to start up his own lab. And at that time he was doing mostly neuroscience research, so he had been funded by the Navy to look at mitigation strategies for central nervous system, oxygen toxicity seizures. And as we know, ketosis is a potential therapy for seizures and that was an application that he was studying-- My headset is going to fall off... Sorry about that.

Bret: That's okay, adjust it as you need it there.

Angela: Thank you. But he had some interest in the cancer field so I remember that he was presenting about his lab and where he was wanting to go with it, and most of

the talk was on the neuroscience side and then I think at the very end he had like this one slide about, "I really want us to think about this diet for cancer".

And I just remember like in that moment my whole kind of mindset shifting, because I'd never thought-- I knew that diet and nutrition was important for like prevention of disease and maintaining health but I'd never kind of viewed it as a tool to actually potentially treat disease, especially for something so severe and complicated as cancer.

Bret: Right.

Angela: And it just really intrigued me and so I went and met with him and just hit it off. He's such a kind person, such as a genuine person and so smart, and so I decided, "Yeah, I'd love to join your lab". And so at that time it was literally me and him and we kind of hit the ground running on getting that cancer research aspect up in his laboratory. And so since then I've kind of spearheaded the cancer program in Dominic's lab and he kind of spearheads the neuroscience side of the lab.

And a decade later, you know, we still work together in that set up, and it's been great, we have a lot of students and people in the lab working on various projects. It's really expanded since those days. So it was completely by chance, I was totally lucky to end up at that program and to meet Dom.

Bret: That sounds really interesting so it was more sort of the nutritional intervention for cancer and not so much the ketones in the beginning that brought you in.

Angela: Absolutely, yeah.

Bret: And then the ketone part has sort of built up from there. And it almost sounds like selling you short to say you're in his lab, because you've been so prolific on your own and have done so much to advance this field of nutrition therapy for cancer. And I love when I read about what you're interested in... non-toxic metabolic targeted therapies for cancer... And just that statement says so much.

One, non-toxic... why? Because so many of our cancer treatments are toxic. Wouldn't that be wonderful if we could find something that's non-toxic? And then the second part, metabolic targeted therapy. So, that's the part I want to unpack a little bit,

because when I was going through medical school and residency, it was sort of this genetic boom of the genetic cause of cancer. And it almost seems like it's a "new revelation" that cancer also has this metabolic aspect, but in truth there's nothing new about it, is there?

Angela: No, there's really not. It's something that we've known for a very long time about cancer, that it has this metabolic face to it, that it was probably one of the first things we truly knew about some of the mechanisms that are happening in a cancer cell, what sets a cancers cell apart from a normal healthy cell.

And so Dr. Otto Warburg who is a German biochemist in the early 20th century had done research looking at the metabolism of cancer cells and found that they were very different than a normal cell of the same tissue type, and that they preferentially will utilize large amounts of glucose metabolism and they don't rely as much on oxygen - oxidative phosphorylation and oxidative metabolism to fuel their growth.

Bret: So even in the presence of oxygen the cancer cells prefer to use an anaerobic metabolism that doesn't use oxygen, even though there's plenty of oxygen around.

Angela: Yes, exactly. So they do both... and the degree to which they do both varies by cancer type. So, sometimes in this conversation it can become-- it's difficult when you talk about cancer because there's a lot of nuance that has to be provided and we don't always have the time to provide that kind of nuance. But they're not fully glycolytic.

They definitely do retain some level of oxidative metabolism and some cancer types more so than others. But it's almost a universal feature of cancers that there's heightened a glycolytic metabolism and the more aggressive the tumor is the more metastatic it becomes, that feature exacerbates even further. So much so that this is actually a diagnostic tool.

It's the basis of a diagnostic tool, the FDG PET scan that is basically just radioactively labeled sugar and the patient consumes this and then the tumors take up the glucose, the sugar, at such high rates that it will visualize them on this PET scan.

Bret: So it's not that other cells aren't taking up the glucose. It's just that the cancer cells are taking it up by such a greater degree that they just light up in comparison to normal cells.

Angela: Exactly, that's the case.

Bret: Yeah, so you said there is a lot of nuance here and we throw the term cancer out there like cancer is one thing. And there is, you know, blood born cancer, solid tissue cancer, and even the solid tissue cancers are different, then there are different stages, so, absolutely we can't talk about cancer in one thing. But, when we talk about the metabolic versus genetic aspect of cancer, I mean is it one or the other? It's either metabolic or it's genetic, or both?

Angela: They're completely inseparable. So Dr. Adrienne Scheck in her presentation she likes to show an image of these spools of yarn. And she will show this spool of yarn that says the genetic features of cancer and another one that says the metabolic features of cancer and then she says, "In reality this is what it looks like." And it's a bunch of kittens playing with both spools... it's complete chaos. And that's 100% true.

So the same genes that we know of as being heavily mutated in cancer that are stimulating, you know, cell proliferation, inhibiting apoptosis, all of these things that we think of as being those fundamental genetic kind of features of cancer, they also control metabolism. So you can't even really separate them. And a lot of these genes, when they're mutated in the ways that are typically seen in cancers end up with this more glycolytic metabolic phenotype.

So the glycolytic anaerobic phenotype of cancer is actually something that we see in proliferating cells in general. So stem cells for example, have a more glycolytic phenotype typically because they are proliferating. So it's also just a natural feature of a rapidly proliferating cell to do this and there's some important reasons for that.

And kind of the biggest idea is that glycolytic metabolism, if you're not fully oxidizing the substrates through the respiratory chain and completely losing carbons to CO_2 production, you can actually shunt those carbons towards biomass synthesis. So this

is actually the idea-- there is kind of this-- two competing theories on why tumors are glycolytic and I think it's true that both sides of the coin are kind of true.

So essentially, this glycolytic phenotype allows these carbons to be preserved and instead of being fully oxidized you get to package, repackage them into new lipids, new proteins, new DNA, which if you're a growing tumor, you have to be able to grow.

Bret: Yeah, especially when you're growing that quickly.

Angela: Yes exactly. The other side is the argument that this glycolytic phenotype is a consequence of mitochondrial respiratory insufficiency and that they are glycolytic because they have to be, because the mitochondria are damaged. There's evidence for both and I think both are probably contributing and depending on the cancer, you know, one is maybe more contributing to one type of cancer versus the other.

Bret: Yeah, and I've heard you actually say this before in some of your talks that when you talk about genetic mutations for cancer, it doesn't mean that every single one of those cancer cells has the same genetic mutation, which is something I haven't really thought of before, but kind of make sense that you can have different mutations.

So, if you use one of these gene targeted therapies, you may be getting the majority of the tumor cells but not all of them, but if you focus on the metabolic side as well, chances are you're getting practically all of them... would you say all of them?

Angela: I wouldn't say all of them for sure. So we know that different-- and even different-- this is what makes cancer such a beast... we know that different regions of the tumor show different types of genetic mutations, some are more oxidative, some are more glycolytic than the other regions of the tumor... this is also related to the oxygenation status of that region of the tumor.

So another area of cancer metabolism that we target in the lab, in the hyperbaric lab that I work in at the University of South Florida is targeting the hypoxia that's present in tumors. So as tumors grow, they have to form new vasculature to provide blood to that new area of the tumor, but they're doing this, the angiogenesis that's

stimulating these new blood vessels to growth, is happening under the direction of these mutated gene pathways.

So it's not a normal process in these-- These vessels that form are insufficient, they are immature, they have leaks, they have holes in the walls and so and they can't keep up sometimes with the growing tumor. So throughout the entire tumor you have everything from complete anoxia sometimes--

Bret: Lack of oxygen.

Angela: Yes, complete lack of oxygen... and the core of the tumor where perhaps there's just no blood vessels that are close enough to be able to get oxygen to that region and then a gradient of hypoxia depending on how close you get to a vessel and what kind of functioning it has, to a fully oxygenated region. And that level of oxygen also will contribute to the glycolytic versus oxidative capacity of that part of the tumor as well.

So it's quite complicated and all of these things are kind of converging at once, but it results in this real mixed bag of the tumor metabolically, genetically. There are regions, sub-regions throughout the tumor that have different mutations, different metabolic features that mean any single targeted therapy is less likely to actually impact the entire tumor. And indeed that's what we see. This is why most targeted drugs end up with resistance.

You may apply a drug that is targeting a mutation that is even if it's present in 80% of the cancer cells, you still leave 20% behind. And now there is ample room for those 20% to repopulate. And that is repopulating from the portion of cells that were resistant to your treatment in the first place and now the tumor that recurs is resistant to that treatment.

Bret: Yeah, so that was an important statement you made that any one single targeted therapy basically is unlikely to succeed. So to put things in perspective, when people say a ketogenic diet or exogenous ketones may be helpful in cancer therapy, would you ever recommend them as a solitary cancer therapy?

Angela: The data does not support that at all.

Bret: I think that's important to clarify. So we really talk about an adjunctive therapy.

Angela: Integrative, absolutely. And it all depends on how important the specific mechanisms that you're targeting are for that tumor. Even with a ketogenic diet, this is why I think that the ketogenic diet seems to at least in the preclinical studies where it's mostly been studied in cancer, seems to have an anticancer effect in a majority of the cancer types that it's been tested in, not all... it's important to know first of all... but it is influencing many, many things.

So unlike a targeted cancer drug that may be influencing a specific genetic mutation, the ketogenic diet is changing hundreds of metabolic pathways at once. It's also influencing a large number of signaling pathways simultaneously through epigenetic alterations.

So I think that the ketogenic diet because it's influencing so many things at once, that's why we see that at least the preclinical literature suggests it may be effective to some degree in a larger number of cancers.

Bret: Now you use this word "preclinical", so I think it's important for us to be very clear about where the evidence lies and right now the vast majority is in mice, is in animal studies, with very little human data... is that an accurate statement?

Angela: Yes, I would say that. Luckily, there are a number of clinical trials ongoing that seems to be increasing yearly, which is wonderful. I would say there's probably about 20 registered clinical trials right now.

Bret: Great.

Angela: -Yes, which is excellent. It is difficult to get a diet trial in general, but in cancer, especially--

Bret: Is part of that because who's going to pay for it? Because nobody's going to make money off of a dietary trial? Or is part of it just because of resistance from IRB's that no, you know, we need to focus on drugs because they're more effective than diet, like that type of philosophy?

Angela: All of the above. Our understanding and appreciation of the impact of diet on cancer has changed rapidly in the past decade. Anyone that's actually familiar with the literature on diet and cancer I don't think can any longer claim that it makes no impact. So thankfully people are now opening up, but it's kind of a whole brave new world where that's concerned. There are complications. So for one thing, you know, we study in the lab of the effect of cancer cachexia, the effect of diet on cachexia.

Cachexia is the wasting that occurs in late stage cancer. So where you'll lose body fat, but most importantly muscle mass. It contributes to the morbidity and mortality of patients significantly and is even thought to be responsible for mortality in about 20% to 30% of cancer patients. So when you're talking about a diet, especially a diet that is publicly used to lose weight in a cancer patient, there's a lot of fear there which is totally fine and understandable about how do we walk this line.

Bret: Right.

Angela: It's interesting because from our lab's perspective, we understand that the state of ketosis, the metabolic state of ketosis, is actually a muscle preserving state which goes back to being necessary to preserve muscle function during fasting or starvation. So there are actual signaling effects of ketones to help maintain muscle during ketosis.

But from a clinician's perspective this is so important and historically we've only kind of-- the advice has always been eat whenever you can to keep your body weight up. For a good reason, I understand that because they know that if a patient with terminal cancer starts losing lots of body weight, that's a very bad prognostic factor.

Bret: Yeah, I remember seeing some handouts that recommended like the Dairy Queen slurry with all that-- like so much sugar in it. But it was just get whatever you can in your body. Which drives up your sugar, drives up your insulin and could potentially fuel tumor growth. But is the ketogenic diet effective simply because you lower glucose and you sort of starve the cells of glucose or is it more complex than that?

Angela: It's so much more complex.

Bret: Does it have to do with insulin itself and the ketone bodies themselves? Like how do we better understand the mechanism and does it really matter?

Angela: I think so, I think it matters a lot. Because for one thing when we're applying for research grants to study this, people really want to see mechanistic information. We want to know why it's working. The glucose story is scratching the surface of what's actually happening and that's something I really like to talk about a lot, because it kind of gets pushed as, oh, we are starving cancer of glucose. End of story.

And that's really the beginning of the story. So, glucose levels of course do go down on a ketogenic diet. Not necessarily vary significantly depending on where your baseline was of course. And that will reduce glucose availability to the tumor. There's human data showing that in patients on a ketogenic diet from these studies, about 20% less glucose being taken up by the tumor.

That's going to be tapping the brakes, some, on those important proliferative pathways that really thrive on that high glucose flux within the tumor, but that's not a starving the tumor of glucose, right? For me I think perhaps at least as important is the insulin story. So as glucose goes down, insulin goes down. Insulin is a very important growth factor for cancer. Many, perhaps most cancers overexpress insulin receptor, have overactive insulin signaling which contributes to the growth and proliferation.

Bret: Yeah, and I think that's a factor that probably isn't talked about nearly as much as it should be, insulin as a growth factor. I mean, we know that bodybuilders use it as a growth factor for muscle and cancers can use it as a growth factor. Maybe not all cancer types uniformly, would you say that?

Angela: Yeah, almost anything you can't say "uniformly" in cancer, unfortunately. Some tumors are notoriously high insulin users, others not as much, but the majority definitely do have at least elevated insulin signaling. And then beyond that you have a host of other sequelae from ketone metabolism; either the state of being in ketosis or direct signaling effects of ketones themselves that are going to be impacting the tumor as well. So we know that ketones serve as histone deacetylase inhibitors.

Bret: So, describe what that is for people who may not know.

Angela: Yeah so kind of the easy way to explain that is ketones will physically interact with the DNA in a way that causes certain genes to open up their expression. Tumors take it-- the very smart-- they take advantage of every opportunity they can to put on the gas and take off the brakes when it comes to proliferation and survival of these cells.

And so they actually silence-- we have a host of genes that are inherent important genes to tell ourselves to stop dividing when you shouldn't be dividing. As an adult, not many cells in our body are actively dividing at one time. But those genes are still in our DNA from when we were growing in development to do that. So cancer finds a way to turn those genes on and to turn off the genes that are the housekeepers saying, hey wait, let's pump the brakes, or there's something wrong with that cell, we need to initiate cell death, so that it doesn't become cancerous for example.

And they do this in one mechanism, they do this through mutations, but another way is that they actually epigenetically silence those genes. So literally the DNA, the chromatin around those genes gets twisted up tighter and tighter so that they can't be transcribed and then translated. So ketones function to reopen up DNA in some important targets that we know cancer might be benefiting from.

So we actually see that tumors may be-- you know, cancer may be inhibited by ketones, because the ketones are actually re-expressing these tumor suppressor genes simply by a signaling mechanism. This has nothing to do with their energy status. So ketones have two complete faces. They can be burned as energy and make energy ATP or, you know, they also can just physically interact with other proteins, they bind to cell surface receptors; we're now learning more and more about the receptors that ketones bind to and what, you know, effects happen in the cell, downstream of that.

And then they also interact with the DNA, they also interact directly with components of our immune system. So there's even data that suggests that that component of ketones signaling is contributing to the anticancer effect in at least some of these

preclinical models where ketones influence the immune cells ability to recognize and then target the cancer cell. It's amazing.

Bret: It does sound fascinating and it's a very important topic, because then it gets into the discussion of, okay, a ketogenic diet, a ketogenic lifestyle will affect the glucose and the insulin components of it and give you the ketone bodies to have all these extra effects. But does raising that ketone level with an exogenous ketone, perhaps, does that provide even greater protection or even greater effect of the ketones by raising levels?

So when it comes to general health concepts of a ketogenic diet, you know, I generally say you don't need to chase ketones. Because there is a ketone level-- a beta hydroxybutyrate level of 3. Any better than a level of 1, when it comes to insulin sensitivity and weight loss...

Angela: Right.

Bret: ...probably not.

Bret: But for something like a cancer treatment does that make a difference?

Angela: It could, it really could, but we don't know. But theoretically-- I like to think that you kind of have to view everything that's happening in the tumor. All of these different mutations, the phenotype, the metabolic phenotype it's expressing, each subset is more or less important for a particular type of cancer. So one tumor type might be really, really dependent and thriving, because of this high glucose metabolism.

And maybe they have some of these weird epigenetic, you know, suppression going on, but it's not really that important for the success of that tumor, at least at that time. In that state a ketogenic diet that lowers glucose may be important and the ketone story might not be as important, because they're not as dependent on the mechanisms that this ketones signaling would target.

But what about a tumor that is really, really benefiting from the epigenetic silencing of these tumor suppressor genes? And maybe they are actually more oxidative in its capacity than a normal cancer. Well, in that case maybe the glucose side of the

ketogenic diet is not as important for the tumor, but the signaling part is really important.

Bret: So this is going to make studying this very difficult because you're going to need different protocols for every different type of cancer. Now, I want to walk through this a little bit more.

So when we talk about the ketogenic diet, are we talking about the specific type of ketogenic diet for cancer therapy, like the 4 to 1, where there's four times as much fat as there is protein and carbohydrates combined, which is not probably the average ketogenic diet that most people are eating. So do we have to make that differentiation when we talk about a ketogenic diet for cancer therapy?

Angela: I think we will. I think that most of the research that's going on is looking at those more therapeutic types of ketogenic diets, something more akin to a classical ketogenic diet like is used in an epilepsy, something like a 4 to 1. And it's interesting in the preclinical literature you'll even see-- so yesterday at MHS we had a presentation from Dr. Barbara Koffler. -She uses and 8 to 1 diet...

Bret: Wow!

Angela: ...in her mice. Yeah, I know, it must just has been straight oil. But this is because mice are a lot more resistant to getting into a state of ketosis than humans. So it's all very complicated, like knowing what to study in the preclinical models, how to translate that into the clinical trials as were designing them.

In my opinion at this point and I think this is what's been done mostly trying that strict therapeutic level, giving yourself the best shot, giving yourself the best shot to reduce glucose, reduce insulin, while also getting ketones higher, that makes sense as a let's get into clinical trials in this way and then we can tease out... in what situations might just simple low-carb versus a ketogenic also be effective? That might be the case.

This is what we have seen in epilepsy. For the first several decades it was all this 4 to 1 ketogenic diet and within the past couple of decades people have started saying, okay, a low glycemic index treatment is actually sufficient for this type of seizure

disorder or a modified Atkins or a modified ketogenic diet is sufficient, but we're just not there yet.

Bret: And modified Atkins is probably I think what most people are eating for a ketogenic diet. And you brought up the point about the mice and how it's hard for them to get into ketosis, so there's a study published recently that said a ketogenic diet is beneficial for the first week and then after that it actually induces diabetes. And got all the headlines. And it was a mouse study for the 10% protein diet with hydrogenated soybean oil as the fat.

So the type of fat in these mouse studies makes a difference too, because that's not what people are eating. So the different types of fat may have different types of effect. So that's one of the problems when trying to extrapolate mouse data to human data as well. So we clearly need more human data. So when is that coming? Hurry up... when is it coming?

Angela: It's on the way. I wish research was faster than it is. So there's a lot of inertia in science. But, you know, even just seeing from when I started this research about 10 years ago, it was not something, at least in the cancer field, but there were obviously some studies here and there.

But it was not something that was being discussed on a main stage and it was not something that most oncologists had heard of or were open to in any way. We at that time, you know, in those early years would reach out to local cancer hospitals and just try to get perspective or, you know, even just like, "Can we come and give a presentation about this, talk about this?"

And there's a lot of pushback. Fast forward, a few years later, and we're getting contacted by those oncologists, because they want to know, right? Things have changed so quickly.

So I would say even for, you know, science where things move slowly, this is accelerating very rapidly, in part because conversations like you and I are having right now, getting information in people's hands that they can go back to their oncologists and ask questions and oncologists now, you know, realize, "I need to learn more about nutrition."

It's not something that I covered in my training. And so, you know, that's why these kinds of conversations are so important, just getting the information out there so we can all move forward together.

Bret: Yeah, I'd love to hear that, how it started, with you knocking on doors and now people are knocking on your door, wanting more information. Yeah, that's just fantastic. So the other thing though to get into, we talked about the specific type of ketogenic diets, but also the specific type of cancers.

So I think this is important because from what I understand renal cell carcinoma and melanoma are two cancers that really don't respond to a ketogenic diet or may even worsen with ketones at least in mice compared to other tumors. Now is that true and why would there be a difference?

Angela: Yeah, possibly. Definitely, possibly true. I am by no means of the opinion that the ketogenic diet is going to be a one-size-fits-all for all types of cancers. Cancer is way too complicated for that. I would say the preclinical data suggests that the majority of cancers seem to respond favorably to a ketogenic diet. There's a portion that, from the preclinical data, seems to not really care that much, then as you mentioned there have been a couple of papers here and there that showed in this model we saw a promotion.

Bret: A promotion of the cancer growth.

Angela: There's a lot going on my head right now about some of the complicated sides of why that might be. So, let's take the melanoma example. That model is a BRAF V600e mutated melanoma.

Bret: I'll pretend I understand that.

Angela: Okay, it is a important mutation that is present in a lot of melanoma patients and it is a mutation that affects one of the major signaling pathways in that tumor that really helps it grow and proliferate rapidly. That paper showed that the elevation of acetoacetate could actually promote the growth of that model. This is interesting because this seems to be a signaling effect of ketones.

So that same mechanism, the acetoacetate simulation of that pathway is something that's also been reported to happen in skeletal muscle, which is why skeletal muscle can be preserved in models of skeletal degeneration. So this is a signaling effect, a unique signaling property of acetoacetate specifically that promotes this pathway. This pathway happens to be really important for a melanoma that carries that specific mutation.

Bret: So not all melanomas.

Angela: No, I mean it might be heightened to some degree, but that's a common mutation and then if you had that mutation then acetoacetate itself might promote it. Okay, so that's what they saw in that model. We actually just had a speaker yesterday presenting her data, looking at other BRAF V600e mutants that she was able to further elevate beta hydroxybutyrate and she didn't see that effect.

Bret: So it was specific to acetoacetate and not to beta hydroxybutyrate, which are two different ketone bodies.

Angela: Yes, there are two different ketones. So this is why it's so complicated. These are the details we have to work out, because it's possible, it's absolutely possible that there's a cancer type that has a mutation and then this signaling effect if it's there it's going to drive that tumor to grow. But remember, you are changing tons of things within the tumor.

So how important is glucose metabolism in that tumor? Is it as important as that signaling pathway or more important? Even then you might have a net negative effect on the tumor depending on the importance of the things that are being targeted.

Bret: So some of this can drive people crazy because we don't have all the answers. We are in the very early stages. But if somebody or somebody's loved one has cancer and wants to try this, they want to know that they are doing more benefit than any potential harm.

And so there still is a bit of a limbo, but is there any-- can you draw any lines to say for these cancers, you know, even though it's not guidelines, even though I can't tell

people individually, I would say, in general try it for these cancers and for these cancers maybe not? Of course in addition to radiation, chemotherapy, surgery, whatever the general recommendations are from the cancer doctors.

Angela: I am a very strong proponent of the data that supports this as an adjuvant as most promising. And there's even data that suggests that there's a really nice synergy from ketogenic diet with the standard of care therapies. So that's absolutely my position.

So, obviously I'm not a medical doctor, I am a scientist, I can only speak to what the data suggests is happening and what might be most useful versus not. I don't give any medical advice of course. I would say that there are types of cancers that there have been a lot more data in, which is why they are the furthest along in clinical trials, they have the most clinical trials; a great example would be brain cancer.

So the most preclinical data for a ketogenic diet for cancer comes from brain cancer. Brain cancer, especially GBM, glioblastoma multiform stage 4, brain cancer. Also, even with standard of care it has a very grim prognosis. So in that setting it really is the perfect scenario to test this out. And that's why there have been the most number of trials, right?

So there's a lot of preclinical studies and there is some clinical data that shows that this might have a nice effect there. All the other cancer types, it's mostly coming from preclinical data, saying that we need to test this. I would say the ones you've mentioned, you know, the melanoma story, that's obviously complicated, especially for those BRAF V600e mutated patients and we need to be more cautious.

And then the renal cell carcinoma that was interesting because that was basically a portion of renal carcinoma patient will present with a paraneoplastic syndrome called Stauffer's syndrome that basically causes inflammation in the liver and liver failure. And so the study that showed this might not be a good idea for renal cell carcinoma was not because it was promoting the tumors. The tumors were actually growing more slowly in those mice. The mice died because they developed this paraneoplastic syndrome and caused liver failure.

Bret: Interesting.

Angela: So, which also speaks to why this is so complicated and why a patient has to have the oversight of their oncologists and their team on board. It's not just what happens with the tumor. I mean, there's so many other things going on in the body when a patient has cancer and is going through treatment. And there needs to be a really close eye on all of these other things.

Bret: Great point. And then so the next step though in talking about cancer therapies and nutrition and lifestyle changes is the tolerability of the therapy, whether it's the tolerability of radiation or chemotherapy. And this is where we get into that point of the statement we started this interview with, the non-toxic metabolic targeted therapies; so, the non-toxic part.

Because, let's face it, chemotherapy is toxic and people can get severe side effects. So, does the ketogenic diet, and then we can also talk about plus minus fasting, help with those side effects of the chemotherapy?

Angela: It's possible that it could. So there is some data that suggests-- largely preclinical data again-- to suggest that some of these things are more well-tolerated. Also, it's possible if there's some kind of synergistic effect between combining these therapies, it's possible that we could actually use lower levels of these drugs that would reduce toxicity.

This is all theoretical, of course, at this point. Those things would have to be pinned down in a clinical trial. But for a few reasons, we think that, yeah, it might actually improve other aspects aside from just effect on tumor. We need to be thinking about quality-of-life.

Bret: Right.

Angela: That's really important and there is human data from small trials showing improved quality of life, better emotional functioning scores, better sleeping... people also like-- you know, some of the other added benefits of... you know, I have lost this excess body weight, I am feeling younger, healthier, more energetic. We think that for those reasons people might be able to actually tolerate some of the side effects of the standard of care treatment better. And we are starting to see emerging data that supports that.

Bret: Yeah, that's a great perspective. We are treating the cancer, but we're treating the patient too, we're treating the whole person to get them feeling better and help the body with its own sort of anticancer fighting ability perhaps.

Angela: Support the immune system, absolutely.

Bret: So, when we talk about the ketogenic diet or ketones in general helping with the chemotherapy, one of the things that's gotten a lot in the news lately is the PI 3K inhibitor. So can you give a sort of a basic overview of what a PI 3K inhibitor is and what the data has shown with ketogenic diets?

Angela: That's a great question. So this is a pathway that is-- you know, we keep talking about these signaling pathways that are important for cancer cells; so this is one that is heavily often mutated in a lot of cancer types and helps promote the cancers growth. It's also driven by insulin signaling. So that that was a really interesting paper.

In that basically they showed they had developed these drugs against PI 3 Kinase inhibitors-- they were PI 3 kinase inhibitors to target that pathway, but they weren't actually doing very well, they didn't have great success. And what they found out was basically... the tumor was reactivating essentially insulin signaling around it just as like to bypass the inhibitor.

And so what they found was it can do that. The tumor can reactivate the insulin to like circumvent that drug in the context of a standard high carbohydrate diet, but if you put a ketogenic diet on top of it, it's not able to mount the insulin response that compensates and overcomes that drugs effect. And so the background diet made all the difference in whether or not this drug actually worked. So that was such a great paper.

Of course, it was done by incredible researchers that are just at the top of the field and published in a very high impact scientific journal. But that showed unequivocally diet matters not just from its own impact on cancer, but it actually impacts our ability-- the chemotherapy drugs that are being used and their ability to do their job as well, which is pretty cool.

Bret: Right, I think that's so important. Now, we're talking a lot about treating cancer. And cancer, like we said in the beginning, comes from stage one to stage four. So, stage 1 localized, stage 4 metastatic and different versions in between. Do you think this tool of a ketogenic diet or even exogenous ketones can be used across the spectrum?

Or do you think it's going to be much more effective in stage 4 in the metastatic disease and less so in the early on? Because like you were saying, when it's metastatic it's growing faster, it's more glycolytic, that's where you can sort of impact it more. Or can it still be effective sort of in the early stages of cancer?

Angela: Yeah I would love to say there's data on that. There's not, but I can theorize when I would predict to be true. Which is kind of interesting, because I could make strong arguments for either being the case. The tumors are more glycolytic, more dependent on those glucose pathways. The more aggressive they become, the more late stage. But in almost all cases, prognosis is going to be worse the further a cancer gets overall.

Usually by this time the tumor is really resistant to a lot of therapies. So even though maybe the intervention of ketosis at that point could impact on its own stronger, you don't have as many options. So with cancer and just how aggressive and smart it is, I'm a big, big proponent of as early as you can get it, and as early as you can start fighting it, the better. But there are reasons why it could potentially be applied across the board, but that's something we have to tease out for sure.

Bret: What about prevention? I'm sure most people listening to this don't have cancer, but you know the statistics are that 1/2 of all men and 1/3 of all women are going to get cancer at some point in their lives and 1/4 of all men and 1/5 of all women are going to die of cancer.

So even people who aren't personally touched by cancer yet, in the back of their brain they're probably thinking "Can this be a prevention strategy?" And of course we don't have the data, but is there enough theory, theoretical reasons to say, yes it could be?

Angela: Sure, from a theoretical approach, it makes sense that it would. You are influencing pathways that we know promote tumor growth. There's also data that suggests consuming a high glycemic diet, a high glycemic load diet increases your risk of developing many cancer types.

So just first of all, not eating, you know at least a high glycemic load diet should, you know, theoretically the data suggest that it would lower that risk at least or maybe neutralize that increased risk. It also, you know, just things that-- it targets things that we know increase your risk of cancer: obesity - strong link between diabetes and cancer.

So you're lowering your glucose, you know for the most part you're seeing lower A1c, you know, all of these things are independent risks for developing cancer. So it makes sense, we don't really have data because it's hard to do that kind of trial. What we're talking about is, you know, decade-long data following people eating in a certain way... and do they have lower cancer risk?

Bret: Now, the flip side of that coin though is that ketogenic diets that are considered relatively high in animal proteins, even though you can argue if it's high or not, stimulates mTOR, mTOR is thought to promote growth in cancer cells as well as normal cells... and we have no idea what that means clinically, right? It's more of a scientific finding at this point. Does that play into your decision at all?

Angela: Somewhat... so, you know, there has been some in mice, so take it for what it's worth. There was data looking at ketogenic diet over the lifetime of a mouse and then also cyclic ketogenic diet and these mice had less tumors than their age counterparts.

So, theoretically you're getting the enhanced mTOR signaling, but, you know, it's not-- I don't know, it's so hard to say. I would say overall when we look at all of these independent changes that are occurring, the bulk of them seem to be moving in a good direction that suggests a lower cancer risk.

Bret: Okay, that makes sense. Now let me ask you another opinion question. You know, scientists get squirmy on opinion questions, because there's no data. But do you think that maybe some-- Do you think maybe we can be hurting our mission

more than we're helping it if the message out there is that ketogenic diets cure cancer?

Angela: Absolutely. I think it's a very irresponsible way to talk about it. It's a conversation that really requires nuance and, you know, buzz lines like that just don't provide that context. The data also does not suggest that. I mean, even in the most successful preclinical studies showing a nice impact, the mice were not cured almost ever.

There is one study... Adrienne Scheck performed a study in a brain cancer model and the ketogenic diet on its own prolonged survival, radiation on its own prolonged survival... In that model when she combined radiation and ketogenic diet she saw a complete remission, sustained complete remission for like a year, which is a long time for a mouse; they only live about two years. In those animals, in like 80% of those animals that got the combination therapy, that's the closest I've ever seen to a cure. But again it wasn't just the ketogenic diet and it was in a brain cancer mouse model. Right?

Bret: Right.

Angela: So saying that ketogenic diet cures cancer is irresponsible. It's not reflective of the data, it is inhibiting us on so many levels, because it instantly puts up the defenses of any oncologists that we need on our side and you don't want to turn on inappropriate defenses against that. Because people are making claims that aren't backed up.

Bret: Right, so instead the message of it could be beneficial as an adjunctive therapy to help traditional therapies to help reduce the side effects and the efficacy of therapy. So maybe is worth giving a try.

Angela: Yeah.

Bret: Which is not as exciting as a message.

Angela: No, it's not. But, you know, it's the truth.

Bret: And I think that's important. You know, having the strength of the recommendation match the strength of the science. Which right now the strength of the science is not strong, but this is a clinical situation where people are desperate for answers. They are desperate for something better. It's one of the sort of the scariest diagnoses you can have, even though more people die of heart disease. I think the diagnosis of heart disease is much less scary than the diagnosis of cancer, because--

Angela: It doesn't seem so imminent.

Bret: Yeah and it's sort of less of the unknown. So people are grasping at straws and so they want to latch onto anything that can help and this is one thing that could potentially help. So if people want to learn more about your research and what you're doing and what's coming next how can you direct them?

Angela: Yeah, absolutely... so I have a scientist page on Facebook that I'll share a lot of research on... just Angela Poff, PhD on Facebook, Metabolic Health Summit - this is a platform that myself, Dr. Dominic D'Agostino and Victoria Field, we're the three organizers of the event.

But it's not just a one weekend event a year, we put out information throughout the whole year. So we are on all the social platforms. And our website is metabolichealthsummit.com And so we we're constantly putting out more information. So I can be contacted there or you can find out more about what we're doing through those resources.

Bret: I really appreciate you taking the time especially since you're so busy organizing this event, which I have to say it's been a wonderful event. And the quality the speakers and the engagement of the audience has been phenomenal. So thank you for that and thank you for all the research you are doing. I'm really excited to see more coming out of your lab.

Angela: Absolutely, thank you.