Researching Cancer Bioenergetics For Future Solutions Transcript

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Introduction and Tomas Duraju2019s background

Hi, everybody. Welcome back. I am incredibly excited about this very interesting conversation we are about to have with Dr. Tomas Duraj from well, currently from that from Siegfried's lab in Boston, but also has an incredible background.

He's a medical doctor, so he's very accomplished at the bedside, but he's also a researcher and has a PhD in that level. So also equally as accomplished at the bench.

And in my years of knowing Dr. Tomas I have gotten to understand that he loves both equally and that he's always trying to find a way to kind of bring the two together.

So I'm excited about where this conversation is going to take us today. Some sort of heady, heady discussions around metabolic, in the cancer space and what this means and where we're going to go with it.

So welcome Tomas I'm really glad that you're here. Thank you. Thank you for having me. It's a pleasure. Absolutely. So first of all, you are, like I said, no stranger to both patient care as well as sort of peer reviewed publications and the laboratory side of things.

Tell us a little bit about what got you involved in this space of metabolic oncology. What drew your your interest and your attention in this arena? so, you know, I, after doing my my medical degree, I was sort of interested in, kind of going to it, like, like a layman from outside to do research side about these new concepts in metabolic, approaches to, to the cancer treatment and to other diseases in, in general.

And that was in the time where, ketogenic diets were kind of having a resurgence in, in the, in mindshare and, so, so I was trying to understand, how these things work at a, at a physiological level.

And there is a lot of biology behind it. Yeah. And I was also struggling on a, on a personal side, also struggling with, being a little bit, overweight and these, these concepts naturally fit into, you know, in doing the weight loss and all these things.

So I kind of came into it from like, like a side, opening.

How metabolic oncology became the focus

Let's say, but then then I the, the focus on, on the research is really what, what drew me and, it's where like, a lot of, a lot of open questions remain for metabolic treatments, especially for, for cancer.

And that's kind of what I'm where my focus is right now. I love this because you talk about, you know, kind of what we're going to chat about. Take on this overarching piece here is this there's a lot of differing opinions and interpretations of the data.

Number one. So we're going to kind of unpack that, even our the way our experiments are designed, maybe inherently flawed and maybe areas of where we can improve upon or just have an understanding of that, where we're prioritizing research today in the cancer environment and maybe what might be hopeful on this in the future where we could put that.

And then the other piece is like, how do we make this moving from kind of an intellectual exercise into a clinically relevant exercise? So I know that those are areas that are very near and dear to you, because as a researcher, you get put into a camp that has a clinician, you have a different understanding and a different need for this information.

So can you talk to us a little bit about these discrepancies and what your where they're sort of holes in, in the narrative and in clinical application.

so I think one of the issues that we have, in, in the field in general, and both on the research side and on the, on the other side, is that right now there's different interpretations of what kind of metabolic, against us metabolic disease is and, and the metabolic treatments, how they would be structured.

And this, this comes from on an underlying theoretical background or theoretical framework that that you would look at. It's also like the traditional perspective in, in the research field is that we have to differentiate this cancer as a, as a metabolic disease in the sense that cancer has, you know, like a hallmark of metabolic reprograming as a genetic hallmark of, of cancer as a consequence of the, the mutational burden.

And then you also have cancer as a, as a mitochondrial disease, as you know, originally proposed by the Warburg at the beginning of the the 20th century and then, in recent times continued by Thomas Friedman, a couple of other research groups, around the globe and this, this understanding, it is kind of the foundational background and perspective.

It's important because when you go to design treatments and when you even like experiments in the lab, and you tailor the clinical practice with different, you know, end points or end goals and of course, there is also like a third camp, I would say, or third, perspective where and I would say this is the most prevalent one in, in, in the research world, and that is that cancer is everything.

I don't know if you've seen the, the, the latest update to the The Hallmarks of Cancer. you know, it's I think published now in March, in cell and it's, it's titled Embracing Cancer complexity.

So it's like now everything is cancer, every single kind of observation that that you have. And I think this is missing the point because, you know, they mention a little bit about precision nutrition and fasting, mimicking diets on on PI3 kinase inhibition, together with the ketogenic diet as a part of of the the dietary aspects determine cancer.

That's in genesis on cancer development. But then like everything is put under the umbrella of of cancer and that is fine as like a reduction is approach where, yes, in 50 years or maybe 100 years.

So with big data, we will be able to kind of reduce it to the atomic level.

Competing views of cancer metabolism

Every single molecular pathway will be completely characterized, and we will be able to perhaps develop treatments based on that. But, you know, everything is interconnected.

So it's going to be difficult. And I think what kind of differentiate us a little bit, as a, as a research perspective is that we are focusing on the, on the bioenergetics.

So if, if you, if you have a car and you ask the question, how can I stop the car from from moving? So we would, you know, we would take a look at the gas, we would say, oh, maybe if the Garstang is empty, the car will not move.

Or if, if we look at the brakes, if you look at the signaling, okay. If we reduce the signaling, to, to move the car, then the car will not move if we push the brakes.

But right now, in research, like, everything is cancer. So the I would say the priorities are not clear. everybody is trying to chase these trends and trying to, you know, look at everything in, in in the maximum delay possible, which is it's fine to it's producing a lot of data and a lot of information, but there's only a limited time, that, that you can spend on, on every single thing.

So we are looking at cancer, focusing purely, I would say on the, on the bioenergetics, a little bit of biosynthesis

too. But so bioenergetics is the ATP, what is the ATP coming from.

And this is of course different from the, you know, mutations and genes and tumor suppressor genes, locking cancer into a proliferation mode. And then then the cell kind of response to that by reprograming metabolism, that's kind of traditional perspective.

We think that it is the loss of function or better, you know, insufficiency in oxidative phosphorylation. Maybe you can define these terms a little bit, afterwards.

So it's a insufficiency as the loss of function in oxidative phosphorylation that leads to an upregulation of substrate level phosphorylation. And this then of course it's accompanied by by genetic reprograming as a as a secondary kind of observation in this atomistic framework where where cancer cells revert to this ancient pathway of of energy production.

And this also accompanied by mitochondrial reactive oxygen species and and mutation. So, you know, the question would be of course, once cancer has developed we will observe the mutations.

So if the mutations are there what does it matter. What is first, what is the chicken or the egg. in the late stage we will have to deal with both the and that is true.

But the the approach is trying to target the, the genes kind of the genetic product, the gene products really. It's you know, we are not fixing really the, the genes.

the gene therapy is not really considered like a, like a very promising avenue in the, in cancer. But we are trying to target the gene products. There is a lot of heterogeneity at when the cancer has already developed, and it's very difficult to to target the gene products.

So we think that perhaps, focusing on the metabolism there, it actually matters where the whether the mitochondria is functional, how much functional it is, whether it's sufficient or insufficient, how much subset of phosphorylation this other pathway of, of energy production.

how much it works. So, so when we try to target metabolism, we first need to understand, for better or for worse, I would love to only, focus on the therapeutic aspects.

And that's where I think that's where we need to do more work. But at the same time, the the understanding of the biology determines how we approach the, the development of the treatments.

What I think is so interesting and you're talking about, you know, we've spent the past hundred or so years really looking at this as a genetic disorder.

And you are suggesting from your research and other things you've learned that it's a little bit upstream from that, that it's more like it's about the genetics or more of the byproduct of a disorder that's happening at that metabolic mitochondrial level.

And so what it sounds like to me is you're also interested. You are recognizing the importance of studying kind of at the bench side, these very singular or even myopic pathways, which are important.

We need to have that understanding. But it seems to me, and please correct me if I'm misunderstanding this. You also have a more of a global understanding, kind of there's like, what does that pathway land within?

Like what is a tumor microenvironment? What is the healthy microenvironment around the tumor. And how all of those interface. And that's where I think you're talking about how do we make this more clinically relevant.

because it's one thing to keep treating it in a petri dish or in a cell line study or in an animal study, but it's different when it actually comes to the patient themselves.

one of the things I think is, is interesting is how would you describe what you just talked about to one of your patients? Well, I when, when I, do client consultations, I do not, I do not shy away from the, the complexity of, of the biology.

I think it's the language, you know, the metaphors and the examples, need to be adjusted for, for the understanding. But I, I think it's necessary within the, the patient autonomy and the scientific literacy.

I do think that some, some basic, understanding of, of the biology is, is important, not just mostly also to do when you have to have informed consent, you have to understand what exactly are we talking about? So.

Well really within like the clinical aspects, I think it's better to focus on not, you know, not not talk about the country, and the, the mitochondrial kind of dysfunction and how the electron transport chain works and all these things. But, for the patients to understand more on the side of the, the clinical kind of the long term outcomes that come from clinical trials and the different, levels of, of evidence that we have for, for different, therapies, and with the understanding that there are certain, certain types of cancer and certain types of diseases where you have to kind of lower your standard, for, for evidence, of course, it would be ideal if we had phase three clinical trials for every single intervention, under the sun.

But some of these, some of these will be, quite difficult to to do just due to lack of financial incentives to, to do them. So I think for, for the patients, it's very important to understand, you know, the difference between median overall survival and progression free survival and, the long term survival.

I always try to encourage them to ask as much information from, for the standard of care that they are being offered as, as possible and to understand, you know, they don't have to be statisticians, but they have to understand what these things mean, because sometimes, when when doing, you know, in the, in the standard practice, there's not that much time.

And sometimes, you know, you hear, oh, we're going to provide you the maximum benefit, for example. And this means something very different if you have, a GBM, if you have a blastoma brain cancer.

Why bioenergetics may matter most

also rates for the most aggressive or if you have like a stage one prostate cancer or breast cancer, the the maximum benefit definition in these two cases is very different.

The long term survival is very different. so I think it's necessary to still go from, from the biology because we have like we are fighting two battles.

I would say we have the theory and the therapy and in, in, in the Doctor Siegfried lab, we are not just in the middle, we are trying to wrestle with both.

But I think if if we don't understand the biology enough, then we will pursue therapies that have, you know, have a lack of, of a basis in, in, in no, no biological basis, such as, for example, Oxus inhibitors.

I'm sure you've seen the, the recent clinical trials with this electron transport chain complex one inhibitor, has a very long name as something, something.

And, it led to a lot of toxicity. And, you know, I think when they were testing these things in, in preclinical systems and in the mice, even, sometimes it's easy to forget that there is, there is a human attached to the tumor also.

And something that, you know, it would be obvious that if you are going to target, oxidative phosphorylation, there will be a lot of toxicity. even so, even with this kind of very discouraging result in the, in the clinical trial, there's still the idea that, you know, there has been a lot of research, development, kind of investment into this idea of targeting all fossil.

They still, couple of research labs that still continue to, to pursue this. And even though I think it's not the most sensible thing to pursue. So I think that the biology informs the treatments that, that you try to develop.

And in the mitochondrial metabolic theory, we are looking at the Oxford insufficiency and the subset phosphorylation dependency. And maybe maybe I could define these terms.

And this is what for for us. What drives the the malignant transformation. I love it. And you know, I think this is a good opportunity because you have talked about you alluding to this a lot, but to get really specific and very briefly to, define some of these terms that you've been throwing into the conversation here, because it's very, very much to your point.

There is a big disagreement in like on these therapeutic targets and what potential outcomes we can expect. And so when we talk about these, targets, I mean, first of all, you talked about this article just came out this year on this.

Everything's a target, you know, at conflict. And and so that's one, one level that well, that's never going to get us very far because it's it's almost too vast right of going.

And so you talk about some of the targets like oxy boss, oxy phosphorylation. You talk about fatty acid oxidation. You talk about lactate, you talk about amino acid.

there's so many of these tools. Can you give maybe a high level overview of what are the biggest targets we're looking at now in the bioenergetics metabolic sphere first.

So let's define that first. And then we'll follow up with what do you personally think might be some therapeutic priorities. on now and in the on the horizon.

yeah. So as you said, in within metabolism itself, if you take the perspective that, the metabolic reprograming is a consequence of, kind of the, the gene, gene changes the gene mutations in, you know, oncogenes and tumor suppressor genes driving mutations, kind of locking the cell into a proliferation mode.

And then the cell adopts by up regulating whatever pathways it deems necessary for to enable this proliferation. Then, there will there will be a threshold of, of different things that you can target, which will be different between the normal cells under and the tumor cells.

And this this is true. but you, you you forget, let's say you, you forego the, the fact that you also have the normal cells operating their normal metabolism.

they are sensitive to too many of these things, you know, like targeting oxidative phosphorylation, targeting fatty acid oxidation, lactate oxidation, not production, but the oxidation of it, different amino acids.

it is possible and, you know, different researchers are pursuing these therapies and they will provide benefit. But for in, in our mind, this would not be the, the first step or the first priority.

So if I take a step back, maybe I could explain. so we think that, each of our cells has, has a condition. So, is that is the sum of all the, all the mitochondria that we have in any given cell in our adult tissues, we would have like 100 or 1000, up to a thousand of of mitochondria.

Are you saying Mitochondrial Kingdom is what you're kind of referring to this like collection of the ecosystem of the mitochondria? Okay, cool. Yes, I, I like to think because sometimes, you know, we have in our mind this, this image of this one, one giant mitochondria inside the cell and doing everything, you know, the poor mitochondria is overworked, producing all the energy from from the pictures that we have in, in, in biology.

And that's not that's not the case. So I think it's important if it's like a functional some of this 100 or 1000 different mitochondria, they all they all have their own mitochondrial DNA.

They all have independent function. They travel across the microtubules. They have, you know, it's like a little organism that we have within each of our cells.

This is, you know, from the endosymbiotic theory of, of the mitochondrial origin, like a prokaryotic cell, that only could do such little phosphorylation, engulfs a mitochondrion, oxidative bacteria, that produces the energy for us right now in the presence of oxygen, through the phosphorylation.

So if you have this conundrum, this, this whole kind of functional sum of, of different mitochondria, they're doing their own thing. They are being recycled.

They are like a dynamic system. Yeah. Over time, if if these mitochondria suffer chronic damage, and this is not immediate. This is over time. If you if you destroy all the mitochondria within your cell, the cell usually dies.

So it's more a gradual, chronic damage. and you can have genetic predisposition, predispositions for this damage. So, you know, many of these, genetic, cancer syndromes such as, neurofibromatosis, only from any, Lynch syndrome.

These, these all, also, let's say you have to define the damage, but certainly they lead to substrate level phosphorylation dependency and oxidative insufficiency.

And so we would say that the the damage or the the change in the, in the mitochondria, the metabolic reprograming driven by the mitochondria is necessary and sufficient for cancer development and for sustaining of the cancer phenotype.

But the the genes, as you know, there is some tumor tissues that have no, no detectable mutations. So they are there. So they they, you know, in certain circumstances you could say they are sufficient, but perhaps not necessary or they are necessary, but perhaps not sufficient.

Or sometimes they are not neither necessary, not sufficient. but the, the, the changes in metabolism certainly seem to be present at all in all cases.

if you don't have a cell that is upregulated in some of phosphorylation, you know, the common name would be fermentation, but I prefer substrate or phosphorylation because it talks about where the energy is actually produced.

Right. these these two forms of energy determine what the cell will be doing, whether it's oxidizing nutrients or whether it's it's fermenting them. Now, if we concede that, cancer cells have a dependency for substrate level phosphorylation, that is a dependency to upregulate these, these pathways, that produce energy.

So that's, phosphate, fossil lesser kinase and pyruvate kinase in the glycolysis pathway. And succinctly like this in the mitochondria, these are enzymatic reactions that give you ATP and cancer cells, have a dependency to to these pathways to obtain to obtain their energy instead of oxidative phosphorylation, which is what you would expect in the in the normal cell.

And now this is where we this is kind of our whole thing. That's that's where we want to target.

Defining oxidative insufficiency and substrate-level phosphorylation

That's where we want to develop the, the treatments that will target the substrate of phosphorylation instead of the, oxidative phosphorylation. Because, yes, there is and maybe, maybe this is something we could touch upon the arguments against the mitochondria, metabolic division of cancer.

And I know this is getting into the weeds. And, you know, I'm not the biochemistry, but I think it's it's very important because we never thought about it.

And, and and it's then it's kind of difficult because we are trying to convince, not only the patients and we believe the patients will be the driving force to kind of change the system.

But at the same time, the, the clinicians and the researchers, they look at it and they say, what? Why? Why are they not talking about the things that are more, you know, still in the air?

And I think this is something that we we have to do. So the counterargument is, of course, that, yes, if you have a system where you measure, oxygen consumption as a marker of, of, of the phosphorylation in cancer cells, you will still be able to detect it.

Now, it's very difficult to quantify it. to say exactly how much is contributing to actual ATP production and the efficiency of the system is also very important.

So oxidative phosphorylation, as you know, one, I'm sure, and a listener, you know, remembering from, from biology classes, it's a very involved and evolved system.

It goes through different steps of glycolysis. It gives you a little bit of ATP to, to subsidize the phosphorylation. Then pyruvate enters into the disease cycle, gives you another a little bit of ATP through substrate or phosphorylation.

And then this fuels, you know, the reducing equivalents, maybe added fuel. The electron transport chain can be a small the gradient, and at the end you get some amount of ATP, you get, you know, the, the, the number I learned was 36 no longer now it's between 30, 32.

and this is because the efficiency can change depending on, on the system, on the structure of the mitochondria, on on whether all the complexes are in their, you know, little generations in the, in the membrane on the cardio lip, in, on, on the enzymatic activity of of every single enzymes involved in the process of, of the lipid membrane.

All these things determine how much ATP you get. So if you if we claim that there is a loss of, you know, efficiency in the system, of course it's you still can detect it and you still can measure it.

But we we think that whatever the number is, it is insufficient to, to keep the cell alive by oxidative phosphorylation alone. So this is one of the things that, this is what I work in the lab, basically, I'm trying to I have kind of three projects I'm trying to look at to try to advance a little bit to the clinical side, more of a synthesis of, of the different ideas and where we could go next, from, from this they, you know, it's not a baroque perspective.

It's very focused perspective on just the bioenergetics. And then, I'm looking at the gravity effect. Well, this is another different thing. I want to do for another time.

This, this, this artifact that, that you have in, in, in vitro systems that you have how the sun behaves in the presence of glucose, which is very interesting.

And then I'm trying to go one by one to the different fuels that either a fuel substrate or phosphorylation or they fuel, obviously with the phosphorylation. And, the the big question in biology and, and many researchers, consider this in cancer metabolism.

I've been very happy to see one of the top leaders in, in the field also like ask the question, isn't it strange that we have been chasing basically, a cancer cell that would be able to survive using only oxidative phosphorylation, let's say 90% of its energy as the normal cells.

And we cannot we can't seem to find is this cancer cell. And so I'm trying to ask the question and go one by one through to all the different nutrients, to see if, if the nutrients that only feed into oxidative phosphorylation can keep the cell either alive.

I think again or growing here I think they cannot. So, so if we define cancer as a, as a cell that keeps growing and growing and growing and dividing, and then I think the the Oxus insufficiency term, where the, the Oxus is

insufficient when you have to upregulate substrate like phosphorylation to keep the system going.

And so it's just kind of like a circle of definition. If the cell is substrate level phosphorylation dependent, that means that Oxus is insufficient. And if access is insufficient, that means that, you know, it's either dead or it has to regulate substrate on phosphorylation.

So I'm I'm trying to go one by one through to all the different kind of nutrients and metabolites that that could give us a clue. And, I mean, I'm sure you would think and of course, the logical question is whether this behavior of the cell in cell culture is the same as in, in, in the animal.

Yeah. And, you know, this is of course, the answer is yes and no. Yeah. I you often hear and we hear this as a criticism that that humans are not mice, you know, that's true.

Humans are not mice, but both humans and mice are eukaryotic mammalian cells of multicellular organisms. And and biology is biology. So I think, you know, if and let's.

Patient across all animals basically. Yeah. You could you could argue that some some species of animals have like certain evolutionary adaptations. I don't know, I like the naked mole rat.

Maybe maybe. Yeah. You know about it. It's it's, it seems to be adapted to hypoxia. And there's something very interesting going on with the Warburg effect.

Like, it seems not be able to upregulate the Warburg effect, this, this organism, because it's spent so much time in environments where there is no oxygen that instead of, regulating lactate production, it seems to kind of lower the whole metabolism down.

And of course, as you know, they are very resistant to to cancer development, although some of them supposedly have been able to, to develop cancer. So, unless we are talking about something very specific, I think most of our eukaryotic cells, our cells in our body in, in the minimum requirements for either ATP production or biosynthesis or the most essential pathways are evolutionary conserved.

it is when you talk about like the optimal conditions, you know, most research is developed with and this is why it's once again important, the theory and the theoretical background.

Because, when you go back to how the, the cell culture and systems and subduction media was developed, you know, how Egle in the 1959, this was the cell culture media was developed trying to maximize growth because you wanted to have as many cells as possible.

To work on yet to study on. Right. Exactly, exactly. You wanted to have a lot of cells to, to get a lot of protein and to look at the genes and to try to understand, you know, how how all these systems are working in kind of optimum maximum growth conditions.

Now, when you start to strip things away, we skip all this like nobody. Well, not nobody, but the, the purpose of of 50 years of research where we kind of ignored metabolism and we focus on the molecular studies, we can assume that this is the baseline.

And now everybody will be doing this, in, in, in the trying to get the cancer cells to grow, instead of trying to focus on what, what are the minimum minimum requirements for either viability or or cell proliferation.

So that is kind of I think a lot of work needs to be done. There has been some some work done about it trying to kind of make a little bit more, representative, types of median, you know.

To what we would expect in, in the natural form, not in a. Right in, in the plasma. The the problem is, of course, when you have cells in culture, they are kind of consuming everything that's there.

So you have to replenish it. Whereas in, in our blood it's always flowing. but yeah, I would say in vivo, in vivo the if people and in vitro the fundamental constraints are the same.

So couple recaps and kind of I would love to clarify because again, I, I love this stuff. And I could literally eat this for breakfast every day. But I'm imagining there's some listeners here, like now going, what the hell is going on?

And so let's simplify some things.

What fuels cancer cells use

So first of all, what you're describing is this concept that we're trying to understand the, the, the number, the quality, the efficiency of our mitochondria and how it may play into, all diseases, you know, not just cancer, but the cancer itself has a unique behavior, different than diabetes, different than cardiovascular disease or Alzheimer's.

you know, some of those other conditions that are also metabolically mitochondrial, you know, disease based, in that there's a shift you're talking about.

There is a reprograming of the resources that those cancer cells take on that's different than, say, the cells in Alzheimer's, cardiovascular, etc.. And what you're describing here is there becomes a, a certain dependency that is also not static, that becomes very dynamic as what I like to describe, cancer cells are very opportunistic and they are very, adaptive.

And they will if you starve one bit of their fuel source, they will find another. These are resilient little buggers and they find their workaround typically.

And so you are studying all of those possible workarounds. Is that is that an oversimplification. no it's not it's it's it's true. you know, I, I've yet to see.

So it is true that cancer cells are very adaptable in the sense and I think there is a danger here to, to fall to 3D ology and I, I do it all the time in the sense that, you know, you have your little cute cells growing in the dish and they kind of try to scramble different nutrients together as if they had a mind of their own and that they could make decisions.

Oh, I don't have enough glucose. I'm going to use glutamine. I think that's this is not how it is in. Okay. It's a it's a mechanical response to, its gene determinant.

It's it's within the programing of the cell is. You know. Respond and adapt to, to the conditions that, that it is in. but going, going through the different nutrients.

So there is a. Limit to seeing, carbohydrates, fats and proteins. And then of a variety of things within each of those categories. Is that what you mean? Correct.

But so basically different metabolites that can feed into. All right. So I should give a step back. So there is only two forms. There's only two forms for eukaryotic cells.

you know we don't have photosynthesis. So we cannot unfortunately generate ATP from, from the power of the sun. So our cells only can do either substrate or phosphorylation and to the mitochondria oxidative phosphorylation.

These these two pathways, can use different metabolites to, to go through the pathway. But the purpose of you know, you see me as falling prey to the, the, the objective, let's say the end result, not the purpose.

The end result of these pathways is the production of ATP. So you can have different. Just the energy currency of the cell. All right. So, so without energy, we I think we can, agree that there is no life.

Nothing can survive indefinitely without energy. You can you can hang on for a little while, but, after a certain period of time, and ATP is very quickly used through the cell.

So if you if you are unable to sustain, a continuous production of ATP, of energy, the cell is that okay? So that would be ideal for, for if you are talking about cancer, of course we would try to reduce the amount of ATP.

And if the cancer needs more ATP then it's able to generate the cell. Is that the cancer cell? Is that problem solved. But of course it's it's difficult to get there.

So so you you have different metabolites, which, which come from, from carbohydrates proteins and fats. The little kind of broken down, molecules, that feed basically into these, only these two pathways, substrate of isolation.

this basically three one. One part. So I was just like reiterate, some people understand they're sort of like a fork in the road and those substrates can go went down one particular path or down another. Yes.

The issue is also many of them do both. So that's. Not. Difficult data. So so for example glucose in normal cells goes through substrate level solution.

And then the majority of it's gives you ATP through oxidative phosphorylation. But in cancer glucose goes mainly through subcellular phosphorylation in the cytoplasm gives you two net ATP.

And then it leaves the cell as a lactate. And some portion of it also to pyruvate goes into oxidative isolation. But it's it's a it's a lesser amount.

So it's tricky. But some some are only for oxidative phosphorylation such as fatty acids and ketone bodies for example. And some of the amino acids do and some are both for example, glutamine technically goes in the substrate or phosphorylation in the mitochondria and looks like it's, mitochondria associated expression.

And then a portion of it goes also to oxidative phosphorylation. And we think it's less than what you get. So it in the end it depends on the flux through the pathway.

So the more you you go to the battery. And if you have a lot of glucose that goes to glycolysis on that glucose goes through the glutamine lysis. And it gives you a lot of ATP through the way the substrate of phosphorylation is much weaker.

then this is enough to keep the cell alive. And now when you try to force it so you remove these two fuels because you can either inhibit them, two metabolic inhibitors, or you can remove them, and then you force the cell. Okay.

Now you use only fatty acids, or now you use only ketone bodies or not. Now you use only certain amino acids. in general they cannot survive. similarly they cannot grow.

So yeah. So from this understanding that that's kind of the whole point when you try to develop therapies, we are not saying targeting all the other things doesn't make sense.

Eventually if you have if you if you prioritize these two pathways first and you actually make sure you inhibited them correctly and you we would say you have to adapt to the ketone body metabolism, maybe there we could we could go into the ketogenic diets and the dietary aspects of it that that is to protect your normal cells.

That has not so much to do with the cancer cells. So if you target these two pathways efficiently, so substrate low phosphorylation from glucose, glycolysis on glutamine analyzes.

These are the two main that that cancer uses. Then if you see a cancer as you know, surviving cancer cell that is able to oxidize just enough lactate or just enough fatty acids to stay alive without growing, but of course, always with the with the danger that if if glucose and glutamine come back into the into the microenvironment, they will resume resume proliferation.

Then you can figure out, oh, maybe make just a touch of, you know, and also there are lactate oxidation inhibitor that that would make sense. But we are now doing the opposite.

We are we are giving you a chemotherapy, a standard of care. And now we want to like give you one extra thing like, oh, let's inhibit transporting complex one and let's see what happens.

And of course what happens is you get toxicity to the to the normal cells. So. Right. And I just. Caught in a moment here of just this because boy this goes really fast in these conversations.

So I want to bring this back to some clinical relevance for folks. But number one, what you're talking about is how we we really could start and simplify things that would probably be effective.

And, you know, the literature suggests 70 to 90% of the cases. If we start on these two pathways, and then the whatever sort of, escapes that approach is worth in evaluating, because you can't no one fits into the one size fits all treatment.

And so if we start with kind of the most prioritized, which you just described of these two possibilities of blocking glucose or blocking glutamine, we will capture, the attention of most of those cancer cells, you know, stalling their growth or killing them straight out.

And then if there's a workaround, we then go to that as the next priority based on the individual and how they're expressing. So those are really cool. And this is where the studies are.

We're getting maybe a little too out there when everyone is trying to target all the pathways all at once. First of all, that's entirely impossible and entirely too toxic and overwhelming for the body.

And I think they forget. They forget. There is, there's a patient there to. Complete. It that you can target the pathways on. It works great. We have done it.

And you can kill cancer cells very easily. But that has been always the kind of the Holy Grail. And sometimes taking the patient along with it, you know, like, great, you don't want to kill the cancer cells and the patient.

And it's tricky here is like cancer cells are one personality within the body. And healthy cells are a different. And so you have to both be supporting the healthy cells while targeting the cancer cells.

This is also what a lot of the intellectual bench side forgets, is that there's this other component that needs to be dealt with in real time at the same time, which is why you are so beautiful in this place, because you've got the medical background, the clinical aspect and the the research aspect.

And so when you think about today, what are your when you take this information that you're learning in the lab to the bedside, what are for you today?

Maybe your top three areas that you're most excited about and most likely would offer to your patients, today. And then perhaps talk about what's, very briefly, what's on the horizon in these last few minutes together.

yeah. So, I think if we can, you know, invest a little bit of the time, maybe, the, the design of the therapies, maybe you could go a little bit into into detail on that.

That would save me also time.

Why standard metabolic targeting can be toxic

So I've limited my you probably have more, much more clinical experience at this point because I've limited my, my clinical consultations a little bit just because I'm, I'm so, so in love and interested in the, in the research that I, I focus mainly on that.

I still do have some, some time in prisons for for, for helping patients. But my, my focus is I just I out of intellectual curiosity, I, I'm trying to understand, what the optimal, kind of therapeutic approach would, would be.

there is still a little bit of work to do on, on that front before, we jump to, to kind of broad statements of, of, of every single patient should be treated with this very specific protocol right now.

And it's the kind of the, the issue or the danger is that we are we have a lot of doors open and we are trying to explore them all at the same time. And, and we get distracted sometimes with, with kind of projects that are interesting but, but do not lead to, to helping the patients.

And I, I would say most of the research that is being done at this very moment, unfortunately it is not done to help the best. I I'm sorry to say that, but it's true.

It's not. True. It's it's done to sustain the research itself. And that's fine. I mean, knowledge for knowledge sake. And I love knowledge. And the more knowledge you have, I mean, the more I feel I like it. But it's good to have it to, you know, it's good to have it on permit.

And I'm sure, somebody is working very hard that a very specific transporter that you have in cancer or on this bacteria or on the zebrafish. And 50 years from now, somebody will Google it and, you know, or whatever the search engine will be at that point.

And say, oh, wow, this this guy, this guy knew 40 years ago that this is the most important thing ever. But, for for the patient right now, I think we could go to two and this will be in the upcoming publication that I coauthored with, with a colleague.

And we have, a lot of colleagues from, from the field on, on it with us, to try to kind of set up the, the groundwork for the metabolic treatments from our perspective.

And this is always kind of the case, that our perspective is very focused on. It's slightly different from, you know, the male perspective, which is fine.

I mean, but we only have one life and we can, you know, I can spend 40 or 50 years. Well, I hopefully I live a long time and I can only focus on one thing.

So, I cannot do everything at the same time. So, we would say that the first thing that you would do if you are diagnosed with cancer, you would initiate, a ketogenic diet.

And when we talk about a ketogenic diet, this has a very specific objective change in, in the biology, basically, what you are trying to do is to reduce, glycemic and to regulate keto anemia.

And this is like an area under the curve over time, you are trying to play your your normal cells, which are competing for the resources with the cancer cell, and you're just lowering the substrate availability of the of the glucose.

Especially you are providing ketone bodies to to your normal cells, and you are putting the whole system into like a nutrient scarcity state, like a metabolic pressure on the cancer cells where there is still there is still glucose in the in the environment.

I can't really get rid of it. Right, right, right. Yes. You're not totally getting rid of it. For that, you would need metabolic inhibitors to specifically target either glycolysis directly and you know, to dig, for example, to the exit.

Glucose is kind of the most famous one. But there is there is many others. You could also target glutamine with Dawn. Maybe we could also mention it briefly and or you could do it indirectly with, you know, metformin as the two inhibitors, you know, a couple different things that would like, just steal the, the available glucose, glucose from, from the tumor.

But you are also lowering mTOR insulin, insulin signaling this it's very low. It's physiological minimum. You got to basically put in the whole system into into your normal cells are doing good.

They have enough for for their needs. And your forcing the cancer cell to oh, you should be using the oxidative phosphorylation and that that's why it's important that in in our mind Ox was is insufficient.

It is there and it's, it's being used by the insufficient to keep the cell going. If you target some level phosphorylation. So while you're doing this, that's like the first step, here, as I mentioned, I would encourage, encourage the patients to, to speak with their oncologist and to to get a very clear understanding of what they can expect from the and the standard of care.

Right. And and this is where I see a lot of failure in, in, in our part two where you know and I know I know some patients kind of doesn't want to know.

So maybe the family members. But you have to know the long term, outcomes, the long term ten year survival of, of your tumor so you can make informed decisions whether you should intensify these emerging treatments.

They are still evidence based, but they are still emerging. Or you say, hey, I mean, this is great. I'm just gonna do surgery. And, one quick round of chemotherapy, maybe I can do some some fasting around it to to reduce the toxicity.

And the tumor is gone forever. in 95% of the cases, it's not expected to come back. So maybe this is enough. Maybe I don't need to worry about learning.

What's the consumer, what's sustainable? Phosphorylation and all these things. But if I have a GBM and you know, the ten year survival is is 0.8%, then then maybe I have to.

So after you learn about what's the outcome and as you know, we focus mainly on on GBM, on global asthma, which is a model. It's a it's a good model because the metabolism kind of fits very well with, with these, concepts.

But at the same time, and I would like to reiterate here that so far from from the literature and from my own experiments, we, we all all tumors that we know of, you know, even prostate cancer.

Okay. So it's going to oxidize some fatty acids. That's great. Is oxidative phosphorylation sufficient to keep it going. And are dependent on subcellular phosphorylation.

And so far the answer seems to be no in in these very specific conditions. So this also mentioned we we always jokingly we we got the CPT. We have this prize that we announced of like 100 bucks to $100 to, to anyone that can find us a cancer cell.

That would be that would have Oxford sufficiency. That is done in the absence of explanation. Yeah. Would be would be able to to live and I would increase it to, you know, I have the opportunity with you.

I would increase it to $1,000. I'll give it my money. Yeah. Just to make it up to. No. Yeah. Just to make it more enticing. you people can email me. I love it. I'll give them the.

I'll give them the conditions of the of the prize. So very simple. Basically remove the substrate or phosphorylation metabolites that feed into this, that includes everything and other things.

And if there is a tumor cell that can grow like crazy using only oxidative phosphorylation, I can retire. That's great. I can go back to Spain to write novels, sci fi novels and, and, you know, live a happy life.

And I don't have to worry about this anymore. So, so, okay, so once you know what type of cancer you are dealing with, then you would bring in the, the standard of care, if it makes sense.

In some cases, it makes sense. In other cases it doesn't make sense. In some cases there's a little bit of conflict, you know, like radiotherapy for brain cancer, for example, or radiation therapy is great.

It kills cancer cells. But at the same time the brain is just not there, not the location that you would irradiate because you damage too much the normal cells.

So it is a risk benefit ratio. And unfortunately for GBM it doesn't work any anyway. So I would encourage patients to at least long about. Right. For the long term. Exactly. So, so it would bring aspects of the standard of care I think for example, temozolomide for, for GBM is is great.

It's fine. And then you would bring some repurposed drugs and you know, this probably you would you have a lot of also like a broad overview of that. And we like not all for example, but there's many others.

You know that's a cycling. And so from folks to inhibitors, different, different repurposed drugs that are being investigated. And they, they do not necessarily target metabolism.

They can target or for the pathways as well. some systemic treatments such as hyperbaric oxygen might be relevant. See how those add extra oxidative stress into that environment.

Yeah. Yes. And they can or if you are forcing the mitochondria of the cancer cell to oxidize the fuels, and we know it doesn't work as, as efficiently as, as it should.

and you even provide even more true, you know, hyperbaric oxygen, for example, of these things to even force it more to produce reactive oxygen species.

You can kill kill the cancer cells. And then the point would be to bring in the metabolic drugs. where would you start? So that's the whole point. We would start targeting substrate of isolation of glycolysis and such little phosphorylation of amino acids.

And you could do, metabolic stratification to try to find out for the specific tumor, you know, in PDX models, in patient derived xenograft or organoids, you can try to measure as much as you can to oh, this this cell is also very dependent on fatty acid oxidation.

And so.

Clinical priorities and future directions

That's where you go from the nuanced individual approach to know where some of the workarounds might be. Correct. although I think if, if on on basic principles, if the targeting of glycolysis and glutamine lysis is sufficient enough, it will stop proliferation.

Now, of course, your normal cells also need a little bit of these pathways. It's not like you can just completely remove. We need our healthy cells depend on glutamine.

That's the main, amino acid they need to survive. And so if you just bring in across the board glutamine inhibitor, you will take the person out with the tumor.

And so you're right. Concepts of proof yes. Yes, yes or no. So so there has been these studies with the pegylated glutamine is that they did together with the on this but probably late at late latest trial with, with dawn.

So six years or 5 or 6 years or five or, six, the other five or so. And the leucine is, is on this, is this glutamine analog that, that I'm sure, our listeners are familiar with because we, we we talked about it, quite a lot.

So that's an inhibitor of glutamine, but it also inhibits or other enzymes, for DNA synthesis appearing on pyrimidine synthesis. And it's doing several things.

It's basically inhibiting all the enzymes that are required for, for glutamine. But in when, when you lower glutamine availability in in the plasma acutely.

So this contaminates or asparaginase. it seems to be fine. The body can can tolerate it for the short term and the same for, for the, for the don, don administration. Intermittently.

Exactly. Press. it's it's fine. It's more of a chronic if you if you instead of pulsing it if you press it for too long. Yes you will, it will damage the normal.

So so I know this is a point of perhaps not contention, but, we, we talk about Don a lot. And I would like to clarify. Dawn is a chemotherapy. It's a research phase.

Chemotherapy. It's it's a, glutamine analog. that's in the research kind of field. And we have no vested interest in it. It could be any other glutamine inhibitor or, that we could use.

And we have no patent on Don. It doesn't need to be Don. Don is just as, as an example of of targeting the pathway. If any other glutamine inhibitor can target the pathway as well, that is fine, I do.

Personally, I would like to try to get, a pilot, clinical trial with, with Dawn for GBM, specifically, something very, very small, very easy, but easy temptations give them a, well measured ketogenic diet where we know in real time, you know, ctmc in that we know what the glucose and the ketone bodies are doing, actually, and try to measure as much as possible and give them a portion of the standard of care, ideally without radiation therapy or just delayed a little bit and then give them, Don and I, I would predict that we would see a very good result.

now of course, difficulties. Don has no patterns. So, I mean, we are not against patterns. And if, changing the molecule and, and having a patent would entice whatever venture capitalists or investors.

That's in the. Studies, right, to help us do the science so we could give it to, we could apply it to the patients better. I'm open to that. You know, that's just how the game is played.

Button. so these these kind of steps will be conceptualized in, in the paper that that, should be available quite soon. it's. Very exciting. This way.

And I think this, this would be for me the kind of the rational approach to, to cancer treatment. And it has a lot of flexibility. So that's another thing that it's, it's difficult to to wrestle with is that clinical trials you know, there's this whole field of personalized medicine in the conventional world.

but then you cannot have personalized medicine and then complain that each patient gets something different and you cannot translate. You can't have them both.

So that's why we have to come up with new models of research and new new translational methods and, you know, different things along those lines. I think I think platform clinical trials would be a way to do it.

But they are so, so expensive. Oh my gosh. So so on the clinical trial side, there is a lot of you know, if you, you know about it, if you read about how clinical trials are done, it's all a game.

You know, it's all out you you have a product and you want to get it to market and then you cannot you get the data later. You first actually. Get it to your desired result is that's the way to put it.

And I will say it for you too much because I know you're in the, academic world where you have to pray. Be careful what you say, but I'm not. I'm just a I'm just a, savvy consumer and studier of this information, but too much.

My gosh, there's so much we could keep going on here. But I think big picture is I want folks to be watching for the publication that you and Dr. Siegfried's lab are about ready to publish on this topic, if not, by the time the listeners hear this, that should be out there, which is exciting.

I want folks to understand that this is nothing is set in stone. These are theories. They are not truths. And it is an ongoing process of curiosity. And the next iteration, the next step of this, there is also the place of just thinking that there is just one target and one treatment out there.

I don't believe that's ever going to be the case, and that will continue to exist for okay. And that we get to continue to learn in this field together. And, I feel so grateful of your passion in this because you are helping us iterate to the next level and give us hope on the horizon.

So thank you for your gracious time, your brilliant brain, and your beautiful heart. Thank you. Thank you so much. And, you know, I think we, as we build, build upon the, you know, the knowledge that we have and we, as, as all together, as, as, you know, clinician practitioners and researchers and researchers in the metabolic, you know, metabolic treatments field.

If we we start agreeing on the this that the most kind of fundamental definitions from there hopefully will get the incentives to to align so that we can actually bring this to, to the patients.

So we need to change a little bit the way we are doing the the clinical research legitimacy is also very important. So so doing the trials for in my mind, even though the patients will request these therapies, and before.

They're available, you know. We will have to go to, to some form of clinical testing or even just clinical experiences that can be shared. Use case reports, for example.

And I don't I don't I don't think there will be like a one day revolution where everything will click and suddenly this will be like, the new standard of care.

This will be more gradual, probably, but hopefully we can get the momentum going and, and slowly over time, I just it, it angers me a little bit or it saddens me more than anger.

that I'm sure in 50 years time, you know, we'll look back and the people that are kind of making the roadblocks at this moment from just, just every everybody is trying and everybody is kind of feeling that we are doing everything we can.

But they will say, oh, it was absolutely obvious this was, you know, it was clear that this was the way it's just some time to, to get there. So yeah, this is kind of recorded and I want to note, you know, I, I will probably contribute like 0.001% this whole thing.

But I think it's dangerous also to, to feed the ego too much. So I think we should not do that. But just, just sort of just out of curiosity, I actually I really want to try to understand the, the biology and how this can then be translated into the, the complexity of the, of the patient, of the human, the whole system, which is where also a lot of the difficulties, like you can have very clear mechanisms and then to bring it into the, the human.

This is where the, the, the rubber hits the road so that this is, this is what we focus on. And sometimes in, in a like a more combative fashion, I would, I know the new, new researchers that are coming into the field from the outside.

I would like to welcome them to, to also your house. Yeah, yeah. Yes, yes. Because we had a small lab, you know, David versus Goliath, and it's, we cannot do it.

It would be so nice, you know, if I could outsource some of these research questions that I feel are like the most fundamental thing that we could ever ask.

I was only doing it. It would be great if there was, like, 100 other research labs. Instead, there's at least one more. Yes, yes. That's true. but, you know, instead of spending 20 years looking at this very specific mutation in Chinese or whatever, if we could try to first get a very good grip on, on the basic bioenergetics, and then we could move forward with these more kind of specific questions.

So that's why. I love it. It's like leaving this that creating kind of our own, conundrum of research would be super cool, out there too. So I hold let's hold that vision true here.

And doc, thank you so much. Thank you Nasha Thank you so much.