
Danny Lennon: Okay. Here we are Professor Ristow thank you so much for joining me on the podcast today. How are you doing?

Michael Ristow: Pretty good. How are you?

Danny Lennon: I'm doing very well. I'm very much looking forward to this conversation. I feel very privileged to be able to do so, and having been exposed to sum of the ideas that you've published on as well as with your colleagues I find it extremely fascinating myself and hopefully we'll be able to get across some of that to the listeners. So, maybe as a good start point can you maybe give people an overview of the primary research that you can your colleagues are involved in doing and how that kind of came about from your background in academia?

Michael Ristow: Well, sure. So, my academic background, and that dates quite some time ago, is clinical medicine and within that area specifically diabetes-obesity research. And over the years I slowly moved more and more into basic research and one topic I was always interested in is how do organisms and cells dissipate energy. So not only nutritional energy but also other sources of energy, and one very crucial component of the cell are the so called mitochondria which are power plants of cellular metabolism. So, more than 90% of cellular energy is produced within the mitochondria, and these organelles associated phenomena are the focus of my research for the last 10 to 15 years I'd say.

Danny Lennon: Sure. I think as we'll get to later you and your group came up with some really interesting and novel ideas, particularly as these mitochondria relate to aging and longevity. But with that idea just from a general overview therefore why are mitochondria typically talked about in the discussions related to lifespan regulation and longevity?

Michael Ristow: So, mitochondria not only convert energy they also generate what we thought are by-products commonly known as free radicals or reactive oxygen species. So, it has been in the biochemistry textbooks for long time that the main purpose of mitochondria is to produce energy and that unwanted side effects are these free radicals which unfortunately tend to damage cellular components and by that limit lifespan. This notion was first challenged in the late 1990s by other research groups mainly cancer biology fields where they realized that these free radicals are not just unwanted by-products but they also serve certain signaling purposes. So, free radicals exert very specific processes in the cell that are necessary in this case for cancer defense but maybe also other issues. What we did later on is observe a similar but at that time novel role for free radicals in the regulation of lives. So, again in the general consensus free radicals are bad, free radicals cause damage, and free radicals limit lifespan, induce all types of chronic diseases and so forth. What we in contrast observe in small nematodes or worms so called sea elegans is that when we increase free radical levels in these worms they unexpectedly would live longer, so by the textbooks we would have expected they live shorter but the opposite was the case. Secondly, if we co-apply so called antioxidants compounds that quench or inactivate free radicals this lifespan extending role of free radicals was not observed anymore. Furthermore, indicating that free radicals are really required for the extension of lifespan rather than limiting this effect.

Danny Lennon: Yeah. And that's where things get super interesting because as you laid out of course I'm sure many people typically associated free radicals with only negative downsides. We hear about free radical damage in the context of aging that theory you mentioned that had been conventionally around and I think maybe is still quite popular that is accumulation of free radicals is an important part of that driving aging, and so we want to go against that. But to kind of recap you said that you and your lab have essentially shown that increased formation of some of these free radicals or reactive oxygen species within mitochondria can increase

longevity. Is that what we're seeing here and is there a certain threshold so to speak for how much of that we need?

Michael Ristow: Well, we observed and others have confirmed that is that free radicals are not health promoting or lifespan promoting at any given dose, but what we see is that only at low levels free radicals have these positive effects. However, at higher doses they can do the opposite. So, this is a phenomenon called a non-linear dose response, also known as the term hormesis and this concept of low doses being healthy and higher doses being unhealthy dates back to ancient Greek and also Chinese medicine, so it's not novel al all. There are book from Paracelsus in the 15th century outlining this exact concept for certain medications, and so forth, and what we see for free radicals is this exact same phenomenon low doses are health promoting, lifespan extending. Higher doses do the opposite until the point where the organism gets killed by really high doses of free radicals.

Danny Lennon: Right. You mentioned there that important word hormesis and have talked how we know that at very high levels we see these negatives, but also if you were to go to the complete other extreme that's probably not a good thing either and a certain low amount of this can have a benefit because as hormesis suggests it's inducing some sort of stress. Is that a kind of fair way to put it, and if so what exactly is that stress that's happening and what's the adaptation I suppose that is happening within the cells that means that stress becomes beneficial?

Michael Ristow: If we expose an organism to low doses of, in this case free radicals, but this also applies to specific compounds and phytochemicals from plants and so forth is that the organism has to deal with them, these compounds be free radicals or others, by increasing the stress defense capacity of the organism. So, exposing an organism to low and non-lethal doses of a potentially toxic compound, toxic in the sense of higher doses will be toxic lower doses do not, is initiating a vaccination-like response. So, the organism gets primed to unwanted external measures and is better prepared to fight back such attacks from the outside. This also applies to free radicals that are produced within the organism, so repeated exposure to low doses of free radicals within the organism primes the organism to be better prepared to a higher external cues like that.

Danny Lennon: Right. So, this stress response or this hormesis is that isolated to the mitochondria where this is happening and having its effects?

Michael Ristow: We have been mainly looking at mitochondria, but it is not restricted to mitochondria. Mitochondria are of particular interest because major parts of the endogenously produced stressors in this case free radicals are coming from the mitochondria. But we have also performed studies adding toxic compound like arsenite and similar components to worms and we could observe the exact same effect at very low doses the worms would live longer and be healthier. In the higher doses as you would expect arsenite killed these worms.

Danny Lennon: You've talked about how your group has essentially been one of the main proponents of this idea that that at least some degree of reactive oxygen species or free radical production can have these beneficial impacts, and it's a more accurate way to view things than this black or white way of thinking that free radicals are always bad when it comes to something like aging. And I know some other groups independently had similar ideas I think Navdeep Chandel's group I think in Northwestern for example. How well accepted is the ideas that your group have been proposing, how have they been received to this point and is there any pushback still of people who are more entrenched with the conventional way of thinking or where is the overall landscape in this particular area of research?

Michael Ristow: Well, within the immediate scientific field there are numerous groups who have confirmed our findings and extended them. We have knowledge that this not only applies to worms but also to flies, and yeast, and mice and we have also done a study in humans showing that free radical formation during exercise is explaining why exercise is health promoting and there have been follow-up studies on that. So, fully independent of that this is epidemiological evidence indicating that antioxidants again compounds that interfere with oxidative stress do not exert health promoting effects in humans but rather do the opposite. So, there is epidemiology indicating the antioxidants increase cancer risk and that they do not decrease any disease risk, and so forth. So, I think scientifically this is all well established and there is little question on whether this applies or not. Nevertheless, the public opinion perception this wider parts is unknown despite New York Times and Washington Post and many other reported this repeatedly people still think taking antioxidant supplements

would promote their health and they probably will continue this for quite some time but I am not too surprised about that. The concept of antioxidants has been around for at least 30-40 years and these are readily available and attractive since people think by low investment they could effectively change their health outcome, which unfortunately is not the case but I am positive that it's going to take another 5 to 10 years and then the public perception of this would have changed, I hope.

Danny Lennon: And so, when we are talking about this overarching concept of anti-aging/longevity, as you have mentioned here mechanistically this work has kind of been well shown, has been replicated, you have other groups that have essentially shown similar to what your group has first put out. It's quite clear and logical to see how some of these things could relate to aging and longevity as well as having some of that data done in various different species like you say all the way from yeast upwards. I'm wondering when it comes to human data is there any big difficulties, and I think this probably extends beyond mitochondria research to anything related to longevity I guess, but some of the big challenges that occur with trying to do human trials especially to evaluate an endpoint like lifespan or health span. From your perspective how should people view the state of literature in terms of – they'll obviously hear about people questioning maybe the lack of human studies in certain areas and so on. How should we view taking the human data with a non-human data and where we can accurately draw conclusions, and then I suppose the second part of that question maybe touch on some of the challenges that we face in trying to get really good quality human trails done for something as difficult work as longevity and lifespan and so on?

Michael Ristow: Unlike in model organisms human studies are way more difficult since the life expectancy of humans evidently is significantly longer than the life expectancy of worms which live maximum of 30 days or flies the maximum of 60 days or mice that still live 3.5-4 years but that's a significant difference. But that's only one part of the problem the other part is that the study design in model organisms is very different from the study design in humans. The study design in model organisms is I can randomize sub-groups, one group receiving a compound that may delay aging, another group receiving a placebo and we can directly compare intervention in regards to effects on lifespan. I am not saying this is not possible in humans, but it's very difficult to materialize that and also very cost intensive. So, a study in humans to prove that

any pharmacological or nutritional intervention is the cause of the extension in lifespan would require several thousand individuals that have been treated with a compound or a placebo for at least 5 if not more years, and so forth. So, the interest in doing that scientifically certainly is significant, however to obtain funding to do such a study is extremely difficult. Why is that? For a pharmacological compound that is lowering cholesterol or blood pressure or blood glucose that is under intellectual property and may generate a significant return on investment, a company can certainly raise the finances for such a study. However, for a compound that is supposed to be given to healthy elderly people solely to extent their healthy period of life, that's what we call health span, is a very different issue. We should not do this with unknown compounds. We rather should do this with compounds that are on the market for a very long period of time that we are sure about safety issues, and so forth, and also these compounds should be non-IP protected anymore and they should be at a very low price range because otherwise the effects on health span and also social and health insurances would not exist anymore. So, we have the setting – the trial would be very expensive, the compound should be non-IP protected and very affordable, and it should be absolutely riskless or at least almost riskless and very few compounds in this regards match all these criteria.

Danny Lennon: One thing I did want to ask is that so far we have talked about on a mechanistic level what is happening here within the mitochondria, and the role of these free radicals, and how essentially this stress response and hormetic response can increase longevity?

Michael Ristow: Well, that depends on the compound. One well known compound in this field is a compound called metformin. Metformin is a drug that has been used to treat type-2 diabetes for many years and we are not the ones doing that, but there is a significant interest in materializing a trial where metformin will be tested on is it capable of extending the healthy period of life. Why do people focus on metformin, because there is evidence that type-2 diabetics who have been taking metformin profit so much from this compound unlike type-2 diabetics that have not been taking metformin but rather took other drugs that there is a good correlation of metformin being a promising compound. However, this is not a proof. This is just an indication of this is a good candidate. Animal studies have indicated that metformin maybe doing that and this altogether justifies to initiate a trial like that.

Metformin like many other compounds in this family of potentially health span promoting drugs do exert toxicity when it comes to higher doses, so S4 free radicals and S4 certain phytochemicals and there again is a non-linear dose response in this regard.

Danny Lennon: From your perspective and what you've seen within the literature when it comes to some of the potential pragmatic implications of some of this work. For humans where do you see the potential in the future in terms of actions and behaviors that would tie into this in terms of whether that's their nutrition, and caloric intake, physical activity, etc? How do these things connect to the issues we've talked about so far in relation to free radicals, mitochondria, and then longevity?

Michael Ristow: There is good evidence for certain behavioral issues being related to extended health span and also longevity in humans, and as you just mentioned regular physical exercise certainly has very good evidence in this regard, also of course, stay away from nicotine these are all well established. On the other hand, we all know that adherence of humans to a exercise prone lifestyle is limited and that's why we of course have to ask the question are there other ways by – pharmacological interventions that could mimic healthy lifespan exerted by exercise. This is where certain compounds come up and the idea here essentially is to compensate for the lack of exercise, and also for inadequate nutrition at least to a certain extent by such compounds. Metformin is just one example. I personally also believe that glucosamine which is widely used for joint problems also for many decades in humans is a good candidate which further needs to be tested, and then several other compounds could very well go into this direction. Does his make a healthy lifestyle, exercise, appropriate nutrition unnecessary? Of course, not but it at least in part could compensate for it. So, this is an individual perspective, but then there is also an economic perspective and this simply is based on calculations by researchers like Jay Olshansky who has very nicely shown that addressing aging or age associated diseases as a general phenomenon would spare so much money for health insurers as opposed to treating individual age associated diseases. That the return on investment not only for the individual but also for society and health insurers could be enormous, so we have a very rare win-win situation here to give specific compounds to healthy elderly people to prevent them from developing the typical age associated diseases cardiovascular, diabetes, cancer,

and so forth, by that improving their quality of life on the one hand, and also reducing health care costs significantly. I think this is the way to pursue and all we need for that is a better scientific evidence that these candidate compounds really are the cause for increased health span and reduction of chronic diseases in elderly people.

Danny Lennon: Sure. If I can ask about one of the compounds in particular, just because I know people listening will have heard about it before in relation to conversations around anti-aging and potentially how it affects sirtuin signaling as well is resveratrol and that it has been a mix over the years in terms of different claims and pieces of research that came out about it. At this particular time point what are your thoughts on resveratrol?

Michael Ristow: So, sirtuins are proteins in the cells that change the status of other proteins and there is pretty good evidence that activating sirtuins reduces age associated diseases and also extends health span. Many labs have been working on that. My lab also, but only to a limited extent, so the credit really goes to Lenny Guarente, David Sinclair, and others and the first compound they used to activate sirtuins was resveratrol and that's called polyphenol and that was the lead compound. However, it is interesting to note that all of these laboratories and inventors of certain sirtuins or the discoverers of sirtuins have essentially moved away from resveratrol because it turned out not to be active enough, and also not to be specific enough to be like the most promising compound and they have been moving onto a certain intermediates of nicotinamide metabolism and so forth, which are also available as supplements and companies have been setup, and so forth. So, to summarize I think sirtuins are a valid candidate when it comes to promotion of health span. I am not sure resveratrol is the most promising compound in this regard. However, on the other hand resveratrol does other things than just activating sirtuins, so it's certainly not useless I'm just not sure that this is really the prime compound to go for. We compared resveratrol with other polyphenols like EGCG a compound that is contained in green tea which is also very effective when it comes to promoting health. However, it has not been linked to sirtuins but rather to mitochondria. In light of balance out of these both naturally compounds I would probably go for the green tea and not for the resveratrol drench.

Danny Lennon: One thing I did want to ask and I'm particularly interested by is we obviously know some of these things can be influenced not only by physical activity, as you mentioned, or by some of these particular compounds but also through nutrition, as you've mentioned. But in particular a few aspects of nutrition that tend to get talked about or at least have been hypothesized in this area, so I would be keen to ask your thoughts on it. So, the ones that at least I've seen mostly commonly discussed in this area of how nutrition may influence longevity and lifespan, one tends to be low calorie intake or low calorie diets that has been looked at for quite a period of time, and then when more specifically looking at nutrients there is obviously a body of research that looks at some degree of protein restriction or the restriction of even specific amino acids like methionine, for example. And then another area tends to be looking at more on the glucose metabolism side and the potential impacts on insulin, and so on. When it comes to nutrition for either any of those three things and you can go in whatever order you wish, so caloric intake, protein, and maybe glucose/insulin. What are your thoughts on how they may potentially play a role in human longevity?

Michael Ristow: I think the best scientific evidence we have for a general reduction in caloric uptake, which is known as caloric or calorie restriction, evidence is more than 80 years old and it has been to a certain extent translated into even humans but primates show the exact same effects, and so forth. So, I think from a scientific viewpoint that is certainly the intervention we have best evidence for. When it comes to adherence we all know that it's not easy to stay calorie restricted schedule for a significant period of time. Some people manage to do that but generally adherence and compliance is limited. So, what people have investigated is a regimen where we either stop nutritional uptake every second day or interventions like what we know as dinner canceling, but also breakfast canceling and so forth. The idea being that the human metabolism is not really adapted to nowadays nutritional habits, but rather to what was occurring 20,000 years ago and at that time humans would have access to food only on rare occasions. So, maybe every second day they would have access to lots of food, but then they involuntarily would fast for a day or two. And our genetic equipment is exactly made to cope with these circumstances, so our lifestyle nowadays to have three or four meals per day is really not compatible with this genetic equipment. The concept behind that is called metabolic flexibility and the idea is to refrain from food uptake for more than 12

hours, better 14 hours will switch our metabolism into a so called catabolic state when the body starts accessing stored energy resources and accessing energy from there which is mainly fat tissue. And the switch between catabolism, so using our own resources, and anabolism use to build up fat tissue is probably what we're genetically equipped for and what's probably also health promoting. So, the general reduction in food uptake, the global calorie restriction I think is pretty well established. However, the much easier to obtain target is have certain periods of fasting be 12 to 14 hours of an entire day. So, every other day breakfast canceling, dinner canceling maybe not as good but almost as good as calorie restriction. That was part one and part two you asked about certain macronutrients being responsible for unwanted effects of nutritional uptake. That is more difficult to answer. And you already mentioned that protein uptake in general, but also specific amino acids have been identified to contribute to aging, and also reduced health span and I fully support this view. However, is rather unsure to which extent in a dietary approach this can be applied to humans, so we don't know about that. The same applies for carbohydrates, especially rapidly metabolized carbohydrates like sugar or readily accessible starch. I personally think sugar and starch are a significant problem of metabolic diseases namely obesity and type-2 diabetes. This however not automatically implies that reducing carbohydrate uptake and replacing these by fatty foods would automatically promote health, because people tend to replace carbohydrates by meat, especially red meat. We know independent of these studies that red meat also is not that healthy. I think from what we know nowadays reducing processed carbohydrates is certainly a good idea. Avoiding excess protein uptake certainly is a good idea and when replacing carbs by fat the fat ideally should be of plant origin or fish or something like that but not red meat and similar products.

Danny Lennon: Okay. So, just a couple of things to follow-up first on the caloric restriction part of that obviously with any data where we have someone on a calorie restricted diet there one particular or I suppose two main confounders which are, I guess you touched on also, of knowing where the exact benefit from the caloric restriction itself came versus the ability for someone just to maintain a lean physique or lower bodyweight. And then, second to that is it the caloric restriction or could we get the same benefit from let's say higher average calorie intake but with those intermittent bouts of say either fasting periods or intermittent

caloric restriction over time. Obviously, this is tough to tease apart but in your opinion do you think those benefits of the caloric restriction are distinct than separate from the ability to maintain a say lower bodyweight or a lower body fat percentage?

Michael Ristow: I am a bit reluctant to give a straightforward answer here because really the evidence is limited and certain parts conflicting. What we know from slightly overweight people from several studies in recent years or maybe the recent decade is that slight overweight is not a problem as long as these people stay physically active, and they get into this catabolic state I was talking about earlier. So, endurance exercise over the period of time will automatically put your body into the catabolic state, which would support that calorie restriction is not mainly about reducing bodyweight but rather staying metabolically flexible. On the other hand, there is also opposing evidence, so that's why I'm really at the moment scientifically not in the position to promote one or the other concept. What we do know however is that reduction of bodyweight only is helpful to a certain extent and that there is a threshold in the lower range where it is not problematic is okay. On the other hand there is also evidence that limited overweight, so before it's called obesity is totally okay as long as metabolic flexibility, and also physical activity is maintained that's probably the two key messages I can get across at the moment.

Danny Lennon: And so, with that Professor Ristow I wanted to maybe come towards a conclusion by maybe giving the listeners some couple of key takeaway points from everything we've discussed so far. Are there any kind of concluding remarks that you would give on what conclusions from the literature that you feel are pretty clear right now, and then maybe second to that are there any potential practical implications of these findings for the moment or where do we need to go next in the future. What is your kind of concluding remarks you would like to leave people with?

Michael Ristow: When it comes to specific components within foods the message is simply try to get the food that you think this compound is contained in. For example, if you want to go for EGCG drink green tea and avoid extracts or anything that pretends to be green tea because here we have dose response again. These can become very toxic and have significant side effects, but this also applies to other health promoting compounds. Try to go with the source that's nutritionally available while try to avoid supplements. The supplements rarely do the exact same thing the corresponding

food does, and supplements can rarely mimic what certain foods do. Lastly, be reluctant to go for specific supplements when it comes to extending health span or lifespan. Most of these have in the best case been studies model organisms and even those that have been studied are known to have an effect in model organisms but this does not necessarily translate into humans. I think to be sure we should wait until there are human studies available, which as I said initially are difficult to obtain. On the other hand, companies have understood that this is necessary a role from authors I hope metformin will soon be initiated in practical ways as a clinical study, and I also think that other compounds like glucosamine will follow-up soon.

Danny Lennon: Is there anywhere online that people can keep up-to-date with you either on social media, ResearchGate, anywhere they can find access to you and your work?

Michael Ristow: I'm on quite a few social media. I think most active is my Twitter and Facebook accounts, which are linked, so the content *** [inaudible 0:41:56] and what I am trying to do on a daily basis is give updates on new scientific articles from the field of nutrition, mitochondria, reactive oxygen species, and so forth. Some of them are very scientific and probably specifically directed to more a specialist audience. Some of them are more general, but that's certainly the way to go. So, just type in my name and you'll find that. We are also on ResearchGate and so forth, but this is not the primary medium, so I think Twitter and Facebook is the way to go.

Danny Lennon: With that we come to the final question I always end the podcast on, and this can be to do with something completely outside of what we've discussed today, if you wish, and quite a big broad question, so forgive me ahead of time. But it is simply if you could advice people to do one thing each day that would benefit their life in any aspect what would that one thing be?

Michael Ristow: I think the easiest way is 5 minutes of exercise or 10 minutes of exercise is doable almost everywhere. It's accessible to everyone at no cost and it requires a minimum change of individual lifestyle, so that's certainly the way to go. I am not saying there aren't other options, but I think this is the most general advice.

Danny Lennon: Thank you so much for your time today Professor. I really enjoyed this discussion, and I've got a lot from reading your work. So, I

appreciate you taking the time out to come and discuss some of it.

Michael Ristow: You are very welcome and thank you very much as well.