Ronald W. Davis, PhD | What's next?

https://www.youtube.com/watch?v=pFzOrknOylA&index=17&list=PLl4AfLZNZEQPxjqF4ojAO3wdCFMeriNBK

I made my previous talk a little on the short side to give me some time to talk after Robert (Dr. Robert Phair, Metabolic Traps: A new way to think about ME/CFS https://www.youtube.com/watch?v=uej1LXzRbnY&index=16&list=PLl4AfLZNZEQPxjqF4ojAO3wdCFMeriNBK) talked. There's several things I'd like to try to cover with that. One is I'd like to try to explain how an awful lot of research is goes out. Right now we're sort of in the, I would call, observational phase of research. We're trying to learn a lot about the disease at the molecular level, not symptom level, the molecular level. All these talks that's whether it's about collecting that information. Then what sometimes happens, and this is not improper things to do because you're trying to understand it, that is you take those observations and you're trying to understand what's going on and so you start to propose a hypothesis of what may be going on. You go and look at all this data and say oh this one supports it, oh with this idea this supports the idea and that's called cherry-picking. Now it's not a horrible thing to do because if there are enough cherries that you can pick and it kind of supports the idea that's useful because it says well it's possible that this might be the explanation, but it's not really useful demonstration that it's right because you cherry picked. So what you really have to do is to say is if this idea is right then it predicts this will happen. There's no bias in this, I haven't cherry picked anything. Your back is up against the wall, this has to happen or I'm wrong. Right, so that's just what Robert just did, he said if this trap is right it predicts these things. Now what usually happens when you do science is you've just shown yourself wrong and so that's what science is all about, constant disappointment [laughter]. So now that doesn't prove he's right but it's very strong support because it was done in such an unbiased fashion. So then what you do, of course six patients well maybe the best ones is probably not enough, so what we need to do is do more patients. Well that we'll add to, it seems to be a constant theme.

Now, I mentioned biomarker (Ronald W. Davis, PhD | Biomarkers https://www.youtube.com/watch?v=W11GdwrmZVI&index=15&list=PLl4AfLZNZEQPxjqF4ojAO3wdCFMeriNBK), well this ratio that he's [Dr. Phair] showing you is a biomarker. Now it's a really good biomarker if it turns out that's what's causing the disease because now we're right at the heart of the initiation of the disease. If you have that you have the disease, if you don't have it you don't have the disease, that's perfect. It doesn't matter if another disease shows that well they have it too because it's exactly what's causing the disease. So this is one of our problems, that we're kind of struggling with is, in our lab, biomarker testing, we have to go and look at other diseases like MS with our biomarkers. Then we started thinking about, okay, what happens if they show the same thing as ME/CFS, does that mean it's not a very specific biomarker. Well not necessarily, it also means that maybe they have ME/CFS. There's nothing saying you can't have two diseases at the same time. But it also could mean the fact that something like MS could actually be caused by initially having chronic fatigue syndrome. You have to have it for six months after all to be even diagnosed. So it's possible that your immune dysregulation, because we see a T-cell activation going on, actually causes MS. When you talk to the immunology people and ask is that possible, they said well yes but no. I said what do you mean by that. Then they said, look because yes it's certainly possible that happened but no-one would ever consider it. That's because if all the symptoms that you have are caused by the one disease that they've diagnosed you with, you can't possibly have two. So, it would never be considered that you have ME/CFS as well and so it's hard to figure that out. But if we can figure out the real cause of this, and this is really what the cause is, then we can tell you, you also have ME/CFS. Now there's a value in

that, from the point of view of funding, because now you're just upped the number of people who have it by a lot right. This is why we really want to push this a lot to try to see if it's right or not and do more patients.

Now, the other problem we have is that we want to do some modeling and what I mean by modeling is we want to try to see if we can reproduce this in cell culture. What happened in our working group meeting the last three days is one of the scientists I invited said, “Heck I will make a yeast model for this. It's going to be really easy, all I’ve got to do is take out the genes from yeast to do this and replace them with the human genes.” That's actually pretty easy to do and it's very likely that they'll work. Then someone else came up to me and said, “I'll make a model of this in the nematode, all I’ve got to do is convince a graduate student to do it.” [laughter] That's easy right. Then another person at the meeting said I'll make a mouse model. That's what getting these people together means and those can speed up the experimentation, because it's hard to experiment on people but one of the components that we need is kynurenine, not easy to find and it's not been tested in human use. So we've looked hard for that. So when Jonas [Jonas Bergquist] was there we were talking about this problem he said, “Oh no problem absolutely, we just made a bunch and we've tested it on humans. It's being tested in clinical trials for migraine headaches.” So I said okay you get to do the experiment, we'll send you our protocol but you need a mass spectrometer to test the patients. Now, did he show you all those mass spectrometers he has in his lab, [laughs] no problem. But that's what getting together means and especially when people are really focused on a problem, trying to solve a problem. This is more about the patients than it is the scientists, that's a great state to be in. So this is all about trying to solve a scientific problem so that's why I'm so excited about it. We have a path forward we know that it might be wrong, very common when you have something like this, that it is wrong but sometimes it helps you get to the right answer.

Now what we found here is that tryptophan is high and what we've also found is that kyneurine is low. That's not a hypothesis, that's an experimental measurement, and the experimental measurement also says that the enzyme IDO1 is inhibited. That's real, that's what's actually happening in these patients. Why is it inhibited? Now Robert [Dr Phair] has a hypothesis it's a trap inhibiting it. It could be something else but if we find that the traps not right then what is inhibiting it. So you see how it, goes that leads you. Now is it significant the tryptophan is high, well maybe serotonin will be high but the other thing is kyneurine is low. Is that a problem? Absolutely, why? Because kynurenine makes a compound called NAD [nicotinamide adenine dinucleotide]. NAD is used in 400 reactions in your body. All 400 of those are not going to work very well, is that going to make you sick? You bet it will. In addition to that it's [NAD] necessary to make ATP which is for your energy. It's a very important molecule and it's low. There's one more thing and that is kynurenine levels control the immune system, does that sound familiar? So without kynurenine you can't suppress autoimmunity, does that one sound familiar? So that does not mean that that's what's happening right but it gives you a path forward. So Michael [Michael Sikora - Sequencing Clonally Expanded T Cells in ME/CFS https://www.youtube.com/watch?v=_Alla0IT59E&list=PLl4AfLZNZEQPxjqF4ojAO3wdCFMeriNBK&index=13] is very aware of this and we're going to try to incorporate that and maybe do some testing of that type. We need to figure this all out but we're in a great position to do that. I think this would be important.

It’s important to point out that to do all these kind of things the rate limiting step in all this stuff is having enough funds to hire enough people to do it. You've seen he [Dr. Phair] mentioned Julie [Julie Wilhelmy, scientist in Dr. Davis’s lab] is one of the best pair of hands, the best pair hands I've ever seen too, and it’s not surprising she's involved in half a dozen projects because we need

someone really good to do it. So she has very limited time. We have a really good person with mass spectrometry, 7% of his time can be devoted to this project. So that's why it's taken months to do this stuff, we don't have enough people. If there's any big donor out there this is the time to get the money. I got to tell you we got to figure it out, is this right or is it wrong, and we want to do that as fast as we can and then if it's wrong move on to the next idea.

Now the other thing I wanted to mention is the fact that it hasn't escaped our attention that we're talking about tryptophan and things that you can buy. What happens usually with patients if they see “Oh my gosh, that might make me well” and they start experimenting. This is a dangerous pathway to experiment on. We know for example if you take tryptophan you can actually cause autoimmunity. Auto-immunity is not necessarily curable by present technology. We were talking about some of this stuff a couple nights ago with with the people there. One point one person pointed out, yeah it's really dangerous when patients start experimenting because there was one possibility for a disease and they needed a particular drug but it wasn't available. So they contracted a company that synthesized it for them and they gave it to them. That is not tested in any animal models and they took the drug and it killed part of their brain and became totally paralyzed and then died. So it's really dangerous to self-experiment on you without really the people who know what's going on. That's why we're so strict about drugs and they have to be tested. If you make a new drug or a new company makes the same drug that's been made before it has to be tested because you can get yourself into big problems. So I'm urging people do not experiment with this pathway!! Give us some time to figure it out. Then you can see some immediate problems if this is all true the tryptophan levels can be very high, which will make your serotonin levels very high. The problem with that is that the body will self adapt to that and it reduces the level of receptors to make you less sensitive to serotonin. If you try to get yourself out of the trap, and this is what we have to be really careful about, your body's not used to the right level of serotonin and what is it gonna do to you? It may be awful, we don't know. It's certainly involved in the brain and we just don't know what would happen. The problem is by self-experimenting on these kind of critical pathways you can make yourself much much worse and that whatever you did to yourself might not be curable. **So I’m just urging people please don't self-experiment!** Give us the time to figure out the right way to do it and that's what we'll be trying, if we think it's right, that's what we will be trying to do. We're going to be working with the doctors and we're going to be working internationally with this thing. I'm hoping it's right because it would lead to an effective treatment and it might even lead to a cure but we have to test it and we have to build the resources to do that. So thank you very much.

[Applause]

Thank you to our wonderful volunteer transcribers for transcribing the Symposium.