The Stanford Genome Technology Center
and
CFS Research Center at Stanford University
and
Open Medicine Foundation

PRESENT

Q & A Regarding 21-Feb-2017 Research Update Video with Dr. Ronald W. Davis

00:18 - Ron Davis: Hello. This video is a follow up to a video that was done a little over a week ago, where I'm going to answer questions that were submitted about the previous video.

00:32 - Janet Dafoe reads a question: With the red and blue chart of metabolic pathways, you implied that ME/CFS is not like conventional mitochondrial disease, but more like a supply problem. Is that right? Like, if the mitochondria are a factory, it's the factory itself which is broken, and usable fuel piles up outside; whereas with ME/CFS the factory itself is in working order, but it's just not getting any fuel supplies delivered. Have I understood that right?

01:02 - Ron Davis: Yeah, I think that's a really good analogy of what's going on in this disease. It's clear from Dr Naviaux's work, and others', that it's a hypometabolic disease with a large number of things that are very low. Some of those things are the raw materials that go into the mitochondria to generate energy – and that's what we think is the primary problem in causing the fatigue.

01:30 – Janet Dafoe reads a question: Is it still the case that the problem could also be not having enough of something in the blood, that should be there ?

01:39 – Ron Davis: So we've tested serum from patients, that show a change in [MPS ? *mitochondrial proteins ? impedance ?*] – we don't know exactly what it is that causes that change – it could be something that's in the blood, that's a positive thing that causes the change – or in fact, you're right, it could be something that's insufficient. Now, one of the likely cases is the fact that it might be a metabolite, or several metabolites – because this is

a hypometabolic disease. So we have done another experiment, where we have actually filtered the serum, to see whether the signal is in the material that goes through the filter, or something that is retained by the filter. These filters are filtering out molecular species. What we've found is that most of the signal is filtered out – which means that it's very large, which means it's probably a protein. If it were a metabolite, we would probably have seen it's the filtrate causing the problem – which we did not.

02:45 – Janet Dafoe reads a question: Would blood from patients suffering from other forms of chronic fatigue, also show a similar impedance signature, or is the ME/CFS signature unique and distinguishable from other kinds of chronic fatigue, and therefore viable as an unambiguous diagnostic for ME/CFS ?

03:05 – Ron Davis: Well, we haven't done enough tests at the moment, to understand that. We will look at a number of fatigue situations, other diseases that show fatigue, as well as sports fatigue, and see if we see similar signals. This signature can still be quite useful, if in fact it shows up in all different types of fatigue. We would then have to work out some way to distinguish the types of fatigue, and one way to do that distinguishing, is to look at chemical reagents that will change the signal.

And if, for example the pyruvate that we've used, causing the signal to go away, we would look at whether the signal goes away in these other fatigues. So this gives us a lot of dimensionality to actually do a fairly complex test that may be very specific for Chronic Fatigue Syndrome.

04:10 - Janet Dafoe reads a question: I've been ill with ME/CFS for almost 40 years, and am now 73 years old. Will you be able to help us 'oldies' ?

04:20 – Ron Davis: Well I'm very sad to hear that. My guess is that it's a fundamental process that's wrong in patients, and that if we come up with some process to reset the body, it will work on anyone, regardless of your age, or how long you've had it. We do think that maybe the disease changes with time – and so we'll have to be very careful to look at that when we do testing – we'll test people who've had it for different lengths of time.

04:55 – Janet Dafoe reads a question: Are you able to say anything about the involvement of the enzyme mTOR, or the complex mTOR C1, in the disease?

05:04 – Ron Davis: Well this is a very interesting question. We have found two patients (and we haven't looked at that many), that have a mutation in the mTOR. The mutation that we have found, is fairly rare in the population, according to the literature. This is a little odd, and would imply that mTOR is an important part of establishing this disease.

One reason why that's important, is that you don't want to take something that inhibits mTOR. There are a number of drugs out there, that are used for other purposes, that are inhibitor for mTOR. These might actually cause you to get Chronic Fatigue Syndrome, or in fact might make it worse. Some of the antibiotics are drugs that will inhibit mTOR – and so

that could actually be making you worse, by taking an antibiotic that you think is clearing you of an infection. That's why I've often said, it's very important to know that you have an infection, before you try antibiotics.

06:15 – Janet Dafoe reads a question: How effective would pyruvate be, either to ingest, or to drip through a line? What sort of volume would be necessary? Is there a reason it wouldn't be practical at all?

06:28 – Ron Davis: I said in the video that we've tried adding pyruvate to our assay – and it makes the cells normal. Now, what we don't know: is it making it normal because it's now a food and fuel supply that's bypassing a block – or in fact, is the pyruvate 'blocking the blocker' so to speak – we don't know the answer to that.

So, the problem with pyruvate is the fact that (1) it's not very soluble, so to take it as a pill, it won't be absorbed very well, and you can't take very much – if you take a lot, it will go into the lower intestine, and cause bacteria to grow, and cause a great deal of discomfort. If you use it as an IV, you will also have to be careful not to overdo it. Now the other problem with it, is that it's likely to be converted to lactate – and lactate can create problems. So it's not obvious that pyruvate is something we should be trying at the moment. That is something that will be tried out in some sort of modelling system, to see whether or not it could potentially be a useful drug.

My bet though, is that we can find something else, that will actually block it more effectively than pyruvate.

07:58 – Janet Dafoe reads a question: Does anyone think it probable, that an existing drug will cure ME/CFS ? Will it be possible to take a guess, at a personalised cocktail of substances for a patient, and test that for a particular patient, with the chip ? What is the difference between finding a cocktail that replenishes what's missing, versus 'turning the key' as Dr Naviaux has discussed ?

08:21 – Ron Davis: Robert Naviaux has suggested that this is a 'cell danger response' in the body, and that it's a metabolic state that is designed to protect the organism. He believes that we should be able to find something, to turn it back on. I think that's highly likely - that that's what's going on with this disease, given everything we've done. And we certainly have not found anything that's inconsistent with that.

I think that's what we want to look for, as a drug. It's likely that a single drug will work; it could be though that we have to use combinations of drugs. That's easily tested with this device [chip] if we get to that point. I'm optimistic that we can find something; I don't think that it's likely to be a cocktail of different nutrients – that's what a lot of people have tried, and it hasn't really worked. I think it's going to be a drug – and possibly a very surprising drug, that nobody'd ever occurred to them that it would actually work.

09:38 – Janet Dafoe reads a question: If this process is a protective mechanism, could it be a bad thing to turn it off?

09:45 – Ron Davis: I don't think so. I don't think it would be bad to turn it off. I think that would be the natural course – that it's designed to come 'on', and protect the individual, and then in fact should reset and then go back on – that should be the natural pathway. Something is happening that prevents [the reset] from happening – and that would also be something we should be trying to explore.

It's possible (at least, this is a hypothesis that I have) that we have been trained socially to always 'push through' things. You certainly see an awful lot of athletes that have this disease, that were extremely active, and they've learnt to 'push through' when they get tired. It's possible that this mentality of 'pushing through' (which causes crashes) is what keeps people in this state; and [without it,] naturally they would change and reset and go back to normal.

We've certainly seen cases where, like a viral infection, people are sick for some time, and then they recover. It's possible that that's the normal mechanism – and they've rested, and they've recovered. And it's possible that if they've tried to "push through" that illness, too early, that's what's caused them to continue to have the disease. **In other words – the "crashing" reinitiates the disease, over and over again. And that's what keeps them in it, year after year.**

11:23 – Janet Dafoe reads questions: How soon do you expect to start testing treatments, using the assay you have developed ? How long do you expect it will take you, to test all currently existing drugs and compounds, using your assay? Do you, and your team, have certain drugs, or classes of drugs, that you feel are particularly promising, that you will test first ? I'm not asking what they are – more just asking if you've got a good idea about what might work. How likely do you think it is, that your assay will uncover a currently existing drug, that eventually turns out to be safe and effective in ME/CFS ?

12:05 – Ron Davis: Well, an example of this is that we've tested all of the FDA-approved drugs in use. We also have a drug that affects every gene in the genome of the yeast organism – there's 6000 genes, and we've found a drug for all six thousand genes. So some of this, when you have an in-vitro assay, can move very fast.

The other thing to keep in mind, at least initially – that a drug may be designed for a specific target, but it probably interacts with a number of other things – and if you use a higher concentration, you will get a secondary and tertiary effects. For example, Rituximab is an antibody that destroys B-cells, but it's possible that it interacts with other things – and that can be seen more clearly if you use it at a high concentration. So we do these screens – we're going to do them, not [just] at a low concentration that is generally prescribed for these drugs – we'll also look at them in high concentration.

It's possible that we can find something that will work, at high concentration – but not be the target that the drug was originally developed for. Now, at these high concentrations there will be side effects – but as Dr Naviaux explains, it's possible that all we need to do is

to trigger the body to go back to normal – and so these side effects may not be so bad. This is not a drug that you'll probably have to take year after year; it may be that a single dose will cure you.

13:53 - Janet Dafoe reads a question: How do your research findings fit in with Dr Naviaux's 'Cell Danger Response' hypothesis ?

14:00 – Ron Davis: Well, we're looking at very different things. He's been characterising the metabolomics that occurs in a person who has this disease - that's extremely valuable, to understand all the complexities of that; and in fact has found a unique signature. We're trying to go back to look at what is the primary effects that cause the illness – and that's a bit different. So there's nothing we're doing that is inconsistent with what Robert Naviaux is doing – in fact, it fits very well together, with what he is doing.

14:38 – Janet Dafoe reads a question: How much more money do you need, to keep this research going rapidly?

14:44 – Ron Davis: In my experience, in the Human Genome Project, in trying to develop technologies for that, I need about 5 million dollars to keep it going at a good clip – and I need that commitment for 5 million, for each year, and I need commitment for multiple years. If we were going to recruit a very skilled post-doctorate fellow, or other scientist - they want to know they have a job for several years. Even if we can make great advances, faster than that, we won't get the right people unless we can make a long term commitment to people.

So that's why I've said we need about 5 million dollars. We could probably use more, but that is a level that I know I could setup a very good team. This is a complex problem, it's a systemic disease; we need experts in a lot of different fields, working together. Some of that can be achieved by co-ordinating with other laboratories, which of course we are doing; but it's also truly useful to have everybody working together on a daily basis.

Thank you very much.