

Mendelspod podcast. <https://mendelspod.com/podcasts/last-major-disease-ignored-research-ron-davis-stanford-thinks-so/>

\* \* \*

Ron Davis is here. He's a professor of biochemistry and genetics, and director of the Stanford Genome Technology Center. Ron collaborated in developing the first DNA micro array, he helped develop the method for constructing the genetic linkage map that helped lead to the Human Genome Project.

In 2013 Atlantic Magazine said this: "A substantial number of major genetic advances of the past 20 years can be traced back to Davis in some way."

Most recently Ron is leading the End ME/CFS (or Chronic Fatigue Syndrome) Project. I'm very pleased to have him back on Mendelspod.

[Ad]

**Mendelspod:** Welcome back to the program.

**Ron Davis:** Thank you very much.

**M:** So, when we talked last, you had just won the Gruber price, and you announced on our program that you'd be using the money to invest in finding a cure for chronic fatigue syndrome.

**RD:** Yes.

**M:** Your son has the disease, and you just decided to take this on. That was about five years ago. And since then I've seen you really turn into an activist.

**RD:** I realized that that had to be done. And in fact, it was my daughter who said, you know, that this disease is so unknown to everybody that we're just gonna have to do this differently than, you know, like doing research on cancer or heart disease or some common disease. Nobody really knows about it, and yet it's a fairly common disease. And it's a horrible disease. And, so, we're gonna have to be a lot outspoken about it.

And that was when my son was still able to talk. And, she convinced him also that he had to be the, sort of, "poster child", as you might call it. He's not a child, but that's the concept. Because no one else is doing it. And he was pretty bad off, and he's gotten worse since then.

And, you have to make it real. You have to show somebody that is actually in very bad shape.

**M:** I've seen you out on the street with a bull horn.

**RD:** Yes! Correct. And that's not my normal method of [??] [laughter].

**M:** Right! And what about also this picture on the internet of you in a heroic cape?

**RD:** Yes. Well, I'll do anything. We have to do something that draws attention.

**M:** So, how would you summarize your work in the disease so far?

**RD:** Medically, we probably know a fair amount of this disease in terms of symptoms. But it doesn't tell you anything molecularly. And you have to have some molecular understanding of a disease, if you're going to use, there's sort of current methodologies we have in biology and medicine. It's very hard to use symptoms. And, so, from the point of view molecularly, we don't know anything. And, so...

**M:** Is that because it just hasn't been studied?

**RD:** Yes. Well, it's two reasons. It hasn't been studied, and the reason it hasn't been studied is because there's no money. And the reason there's no money is because there's no demonstrations of the fact that it's so prevalent. It's a vicious circle going on in terms of, it's *very very* frustrating.

**M:** Yeah, I personally ran into some of the stigma around it, because I went on a diagnostic odyssey myself for about four years. And, you know, some people started telling me it was chronic fatigue. And, so then I realized some doctors weren't comfortable giving a prescription for that.

But I remember a friend sent me a link to a New York Times article one time. I remember exactly where I was when I read it, and the time of day. Because it was talking about a Stanford study, and they were using an herpes antiviral, and it was working with some patients. And this article gave me so much hope. So I have some personal connection here.

There is this stigma about it. Why?

**RD:** I think it comes down to the fact that the patients don't really *look* very sick. My son does now, but that's because he's had such a hard time. But most of the patients, if you

met them on the street, if they were able to walk, you wouldn't notice that they're sick. If someone has a cold, you can really look into their face, you can see in their eyes, they're sick. And if they get very sick, like you have flu, it's pretty clear. This disease, you can be much sicker than having the flu, and you look normal. So, that's one problem.

Second problem is, doctors have a standard set of tests they like to run. You know, look at your cholesterol levels and a number of other things that they will measure. Maybe 30-40 things different things they will measure in a very, what you call an extensive medical exam. They're all normal. So, if you run the same tests on my son, who's bedbound, who can't talk, who can't eat, who can't swallow, has to be fed through a tube into his intestine externally, has to drink via a line that goes into his heart to put in fluid, cannot look at anybody, he lies there all day and he can't listen to music or read anything, because he can't read. His tests all come out normal.

And it's very systemic, but they're not measuring the right thing! They are measuring things that have shown up in disease in the past. And just because these tests don't show anything doesn't mean there's nothing wrong with you.

So, if you go a lot deeper and measure a lot of other things, then it's very clear. There's *a lot of things wrong* with these patients. It just doesn't show up.

**M:** So, you are seeing some molecular signatures?

**RD:** Yes, absolutely. There's clearly a lot of [inflammation, information???] going on in these patients. There's a lot of effects on the small molecules called metabolites. We don't know what's centrally controlling everything. That's what we're trying to establish, track it all back to what's primary effect, what's primary effect that's wrong. So yeah, you see a lot.

So, for my son's case, when we do something called metabolomics, which means measuring all the small molecules. We can't quite measure them all yet, we're up to about 1 200, and there's probably about 4 000 that we should probably look at. But, when we look at...

**M:** You're doing this longitudinally? With your son?

**RD:** Yes.

**M:** Sort of like what Mike Snyder is doing with the iPOP study?

**RD:** Oh, absolutely. Yes. His office is right next to mine here.

**M:** Aha. So it's these measurements on an ongoing basis?

**RD:** Exactly.

**M:** So, has a sort of lead candidate stuck out to you, as far as causal? Metabolite?

**RD:** No. So, my son is more than two standard deviations away from healthy controls in 193 metabolites.

**M:** Wow.

**RD:** That's a lot. And that's, and one of the metabolites is 16 standard deviations away. If you look at all these cytokines, they're all abnormal. And we're now looking at 63 cytokine type molecules, and they're all abnormal. So, there's a lot going on with these patients. So, you just have to look in the right place.

**M:** So, then it becomes a pathway kind of thing, or..? Looking at systems?

**RD:** I think it's a metabolic problem. Or some kind of systemic problem. There's *a lot* involved. The immune system is clearly involved. It's *conceivable* that this is an autoimmune disease. We don't know that yet. And it could involve either B cells, making antibodies, or it could involve T cells, or it could involve both. And that's an active area that we're working. We're working with Mark Davis, who is a superb immunologist at Stanford.

**M:** Yeah, I mean, you're totally connected to the right community. But you're usually on the technology side, giving them gadgets.

**RD:** Well, we try to do that too. So, we have a gadget we haven't published yet, because we don't totally understand what's going on. It's called a nano needle. It's nano fabricated. It measures electrical impedance of a solution, or we can do it with blood. And we have developed it as trying to do a fast test for sensitivity of cells to outside things. So, it could be bacteria and what antibiotic will kill them. Or it could be tumour cells and what anti-tumour agent will kill them. And that's easy to tell if a cell is completely dead.

[00:09:43] Or, what we can do in this is, we can tell that it's really responding to [leading towards death?], and that occurs by an increase in the electrical impedance.

We've looked at the white cell population from CFS patients. We started with my son, and comparing it to healthy control, and they look the same. But if we stress the cell, and we distress it by adding some salt. And this is now, we're getting into what are we actually

doing. I'm calling it stress, because we don't know exactly what we're doing. But under that kind of stress, there's a major increase in impedance, just like what we see in a tumour cell when we add an anti-tumour agent.

In other words, here's that it cannot handle that kind of osmotic stress. And healthy cells are fine, they don't change impedance at all. And we've done six CFS patients, ranging from severe to very mild. And they all show, all six of them show that. And we've compared that to eleven healthy controls, and none of them show it.

So, that is about the most... definitive test yet developed for this disease. I would have to [??] that's not enough, so it's not published yet. It won't get published until we do more. But we are encouraged by that, because you just said we develop devices. Yeah, we develop devices.

This is pretty inexpensive. It's battery powered. We could probably run it off of an iPhone for the computer, and we could probably develop a little electronic box for doing that impedance measuring. It's nano fabricated, it's small, it uses one drop of blood. So, this could be a diagnostic, it could be run at a doctor's office. It could probably be build with a finger stick.

**M:** Wow. Wow, very cool! So, I mean, you're wearing several hats here. You know, you were working on the technology side, but now you're deep into a specific disease, and one that's not very well known.

**RD:** Well, that's right. And I've had the position for, I don't know, ten to twenty years, that we really should make a big investment in technology.

**M:** You mean nationally?

**RD:** Nationally, and focus on healthcare. And this is a [??] of a device. But always focus on cost. Not just 'oh, we could measure something good'. How do you gonna do it cheaper? And that part of the equation is generally *never* thought about. It's thought about sometimes as an afterthought. And, the beautiful comparison there is in the genome project.

When we started to do the genome project, it was gonna cost us 3 billion dollars to do a genome of one person. It's now down below 1 000. It's now a few hundred dollars.

**M:** As a result of the big funding and the focus on that?

**RD:** All of it a result of technology, and focusing on cost. Once you get that mindset going, it's wonderful what these people do. They keep coming up with new ideas of how to make it even cheaper. Because the mindset is there, 'we have to make it cheaper, we have to make it cheaper'.

And now it has gotten so inexpensive that it's becoming sort of routine. And it's probably, people are in general, I mean, there's a lot of tests you do are as costly as sequencing your whole genome. What we need now is the next step, and that is interpretation. And that's a big bioinformatics type, you know, computer type software program.

I think we should consider this in all sorts of areas. You know, look at the cost structures. So, we have a collaboration with Intermountain West Healthcare System, which is in the West here, but not in California. And the concept is that, if they give us medical problems that are very costly, and we have no clue, we are a bunch of [scientist geeks?], I don't know what things cost. So, they have to pick out the very costly things that are in their practice. And then we look at them and say 'oh! I have an idea of how we can make this much cheaper'. And they have to pay for the development of that technology. The hypothesis here and there, their [???] is gonna work. The amount of money they have to spend on developing the technology to make it cheaper, they will actually make money by doing that.

**M:** The healthcare provider?

**RD:** Yes.

**M:** So, if the genome project, this was sort of like a big science, this was discovery.

**RD:** Yes.

**M:** This was basic science. And you're saying go to the other direction, go to the end with the patient, where the patient's treated, and say 'what's costing so much?'. And then go backwards from there.

**RD:** Yes. Well, I look at that and say 'how can we do something a lot better?'. For example, there are cases where if you can really accurately detect the presence of some protein molecule, you might get an earlier, much earlier on occasion, that there's something wrong. Like, for example, a heart attack. And, of course, obviously, early detection of cancer. So, we need to be, have more sensitive tools. Oh, now it get's focused! How do we make more sensitive tools? And that's one of the things that we're doing.

So, there's, you know, protein tests that people do for HIV or for other viruses, influenza and so forth. We have now at least a thousand times more in sensitivity. And, we've greatly increase the accuracy. And so, that's exactly what the genome project was about. Make it cheaper, but make it also better. So, a lot of medical tests, when you actually analyze what's called positive false negatives, they run around 10%.

**M:** Yeah. It's still very bad.

**RD:** People are shocked by that.

**M:** Yeah.

**RD:** But that's true. And so, if you get a test saying you have something. You don't necessarily have to believe it. You should get retested. And some are worse than 10%. So, people are being treated, and they don't even have the disease, because of a bogus test.

**M:** I saw that you'd come out, recently had a press release about this lab on a chip that was now down to just a penny cost. And, I mean, so it looks like it'll all go point of care and just super cheap for all these diagnostic tests.

**RD:** That's right. And we also want to enable people. You know, I don't want to have the big manufacturing plant building the devices. So, that's our nano fabrication is... it's, you know, how you make a computer chip. There's a pretty, you can do it pretty cheap because you can do it in high-throughput. But it's still pretty complicated. And it requires, mostly it requires pretty expensive equipment to make them.

So, this device uses an inkjet printer. Which is a pretty sophisticated devices, but because it's mass produced it's very inexpensive. So, all you need is the program that designs the circuitry. And the other thing you need is, we use an ink that has silver nano particles in it. So you just, you have to replace one of the ink cartridges.

**M:** Going back to CFS. How did you, how do you convince the world this is a real disease?

**RD:** I think that molecular data will do that, and I think we're close enough. When there's enough other publications, you know, not just one. Basically hitting the doctors over the head over and over again. And you explain this, if you think it's a psychosomatic disease, that sort of thing. And of course if we could actually cure it, that'll even be better [laughter]. [???], because now they can actually cure it. A teenager gets chronic fatigue syndrome, there's a good chance they're gonna have it for life. And that's a lot of money,

you have to take care of them. So, either the government spending a lot of money, or somebody spending a lot of money, taking care of them.

We also have to make clear to the scientific community, that this is not a bad thing to work on. In fact, it's a tremendous opportunity. And that's what I try to sell to my colleagues, because here's a major disease, estimated to be 2 million people in the US, probably more because so many of them are severely ill and bedridden and nobody ever sees them. So, you have a major disease that at the molecular level you don't know anything about it. This has gotta be the last disease like this.

And it is because of the way it was treated by the medical profession. It was ignored. And so, there are other diseases that we [???] know a lot about, but they are not ignored and people have worked on the for a long time. Yeah, I see it as a tremendous opportunity, and you're gonna be, there's not that many people working on it, and I know, NIH hasn't spent a lot of money on it, but they probably will. And they'd better, because that's their responsibility. And they're way off now. An AIDS patient gets a thousand times more money per patient than an ME/CFS patient gets. And ME/CFS is a worse disease. They've [got to put it into ???] some balance. Yes, it's infectious and you wanna contain the infection. But we're a long way towards that with all the drugs that have already been developed. And there's a lot of industrial activity around HIV.

**M:** What role has the NIH played? Are they funding this?

**RD:** Not yet. I have no NIH funds.

**M:** No fund for the CFS?

**RD:** No. They haven't been funded. And I think it's largely because the NIH doesn't really know how to start something new. The perfect example of that was the genome project was new. But that was fraught with an awful lot of arguments against it as well.

**M:** Yes. I've read about all the politics.

**RD:** And I credit Jim Watson for really getting it started on the right foot.

**M:** It took someone just saying 'we're gonna do this', and someone with a vision.

**RD:** Yeah, had vision and also understood how you solve problems. And you don't solve problems by saying 'Hey, we have billions of dollars for you. Just apply'. Well, the people who apply are the ones that desperately need money, and they are probably not the best scientists. And the best scientists are already busy. So, what Jim did, as opposed to saying

'we have all these billions', he went around and picked the people he wanted to work on the project. And then he asked them to come out to dinner with him. He ran round the country doing this. He had dinner with me, and after some nice pleasantries, I like him a lot, we talked, and then he said 'well, you're gonna work on the genome project'. And I said, 'I have no money to work on it'. And he said, 'don't worry about it, you will. We're gonna put a grant in. But you're gonna work on it'. What do you say to Jim Watson? You say 'OK!' [laughter]

**M:** One of the giants in science.

**RD:** And he did it over and over again, with lots of really good people. So, day one, when we, you know, we tried to get started on this, there were a lot of really really good people. And one thing about a bunch of good people, it attracts other good people.

**M:** How did you decide just personally you were going to take this on, at this level?

**RD:** Which one?

**M:** The CFS. Because it looks to me like, you know, basically, your philosophy is 'hey, it takes someone to stand up, someone who has the credibility you have, and the experience. And to say, we're doing this!'.

**RD:** Right. Well, it also has to do with, you sort of say I have a lot of credibility, as though kind of like it's money. And what am I gonna spend my credibility on? [soft laughter] There's no better cause than this as a cause. To risk all of my credibility on. So, it's something, I have to do it. It was no... Having my son being sick was obviously a motivation. But it also, I had absolutely no doubt that it was a disease.

And when you look at it from a distance, 'yeah maybe they're right, maybe it's not a disease'. Because you don't know anybody. And I know him, in terms of faking it or doing anything else, he was a real go-getter. And, passion about doing things, and passionate, he was a photographer, the passion about his photography. There's *no way* he would be confined to bed.

When he got a little bit better, because he had a fever, a very high fever. And, for some reason people get better, but not necessarily permanently. And, so, it lasted a couple of months that he was quite a bit better. He wanted his camera to sleep with. [soft laughter] And at one point, he said that he was getting worse again, and then he handed his camera back. He still wasn't taking pictures, but he just wanted the camera there.

**M:** And you saw that there were no answers for him?

**RD:** No, there were...

**M:** And that's when you said 'I have to do something'. It's like, we've talked to other parents of children with rare diseases, right? I mean, there they don't even know of a community at all. It's really in the dark. But they feel this compulsion to stand up for their child and say, you know, 'I'm gonna to do something, if nobody else is'.

**RD:** Well, it depends on what your skill sets are. And you should look at what your skill sets are, and try to make use of those to do something. In my case I'm sort of an inventor, I handle lots of problems, I'm very diverse in what I can do. So, that's sort of what I have to do.

**M:** Well, your also a hero. I mean, the cape looked right on you! [laughter]

**RD:** [laughter] Well, I'm not very comfortable with that. That's not me. I'm the person sitting in the background, doing these tools and handing them out to people. That's me. I'm a, kind of a, behind the scenes kind of individual. So, going out there and wearing a cape is just pushing myself, as much as I possibly can push myself.

But I would recommend that for anybody else doing something like this. Figure out what you're good at, and take it on as your part. And then, you can't do it all. And nor can I. I'm not gonna, I can't solve *everything*. But I can do my part. They've had so little hope for decades. There's nothing happening! And the prospects of something happening were just close to zero. The only thing good happening was an accident, and that's when Fluge and Mella in Norway were treating a lymphoma patient and noticed, and they get *a lot* of credit for this.

**M:** Yeah. They branched out a little.

**RD:** Yeah. And they noticed that, I'm not sure if the lymphoma patient survived, I don't remember that. They noticed that their chronic fatigue syndrome symptoms improved. And they didn't say, 'Oh, well, I'm an oncologist, you know, that's probably not a disease, ignore it'. The reason I say that is because lymphoma treatment with Rituximab is pretty common. And this disease is pretty common. So, there's got to be quite a large number of doctors that should have witnessed Rituximab treatment improving chronic fatigue syndrome, and ignored it.

**M:** And maybe they will come out a little bit more, with your encouragement?

**RD:** Right. And that's what doctors should be doing. Paying attention to their patients. But you'd sure hate so use that as a strategy, hoping for an accident! [laughter] So, we're gonna try to experiment, coming August, we're gonna get a lot of really good molecular people together. Some of them working on this disease, some in other fields. And have a lot of discussion about what we know and what we don't know and what we should be doing, and so forth. A lot of minds are better than one.

**M:** Okay, well, I look forward to that, and seeing the outcome. Ron Davis, he's the director of the Stanford Genome Technology Center. Thank you for taking some time.

**RD:** Oh sure, you're welcome. Thank you for doing what you're doing.