Buzzilia Video: Day 3

Video from day 3 of Buzzilia: nightly news, interviews and features from the HD World Congress 2013 in Brazil

By Dr Jeff Carroll on October 28, 2013
Edited by Dr Ed Wild

In our final video feature from the 2013 World Congress on Huntington's disease in Rio de Janeiro, we interview we interview Jim Gusella of Harvard Medical School about genetic modifiers of HD, and Neil Aronin of University of Massachusetts Medical School about gene silencing and sheep.

You can see the unedited video including the 'Generation Game' feature (41 minutes) on Youtube

[Samba music]

ED: Thank you very much, and welcome, for the third and final time to Buzzilia, our live round up of the day's exciting events, and exciting events yet to come. Here, from the World Congress on Huntington's disease in Rio de Janeiro. We just want to take a moment to thank some very important people, some volunteers who help us translate HD Buzz, which is available in 12 languages.

JEFF: We hear today that there are 600m people living in Latin America, so there is bound to be a large number of Huntington's disease patients in this community. So we're excited that content on HD Buzz is available in both Spanish and Portuguese to hopefully assist these families as they try to learn about their condition.

ED: All of our translation is indeed done by volunteers, who give their time freely to translate into

languages, including Spanish and Portuguese. I think there are one or two, at least, HD Buzz translators in the audience. So if you translate for HD Buzz, please stand up. There we are. Please give them a warm round of applause. I know that people at home, a lot of translators, will be watching this video and they will be translating it, and they will appreciate that round of applause, so thank you for that.

JEFF: Finally, in our preliminary remarks, a brief shout out for the International Huntington Association. They've just elected a new board and are making a new start, with a big push to link together all the countries' agencies fighting Huntington's disease. So, if you're interested and you want to get involved, please email the International President, Ann Jones, her email is there. So, the highlights of the day; Ed, what stood out for you?

ED: We talked about biomarkers yesterday, for me, personally, today's highlight was a mention in a session with Tiago Mestre, who unfortunately we were hoping to interview, but he had to leave. He was talking about collection of cerebrospinal fluid or CSF. This is a clear fluid which bathes and surrounds the brain and spinal chord. You can collect it by sticking a fine needle into the base of the spine.

JEFF: Sounds pretty gruesome.

ED: Well, it sounds much worse than it is. When it's done in experienced hands, it's pretty well tolerated, and it's actually not that much different from a blood test. Although there's a bit more fuss before and after. Of course, we both know this because you had a lumbar puncture several years ago, at the hands of Dr Blair Leavitt, for HD research.

JEFF: I'm willing to do almost anything, obviously, for HD research.

ED: I had one a couple of weeks ago, in August, because we were collecting CSF and we needed control fluid, so I volunteered. Also, to see what it's like. I tweeted the experience. In fact, this is a video of me; you can see the fluid dripping out, there. That's me covered in antiseptic solution; I'm giving a thumbs up, there.

JEFF: You're curled up like a baby.

ED: Actually, in all honesty, I felt virtually nothing. This was me, that's my spinal fluid, this is a round of applause for anyone who gives CSF for Huntington's disease. If you want to read some of the tweets before, during and after, that's where you can find them. It tastes a bit like chicken. For the record, I did not drink my CSF.

JEFF: So, this sounds like something that's useful for families to do, if they want to contribute?

ED: I would say so. It's certainly not for everyone, it's not a typical, walk in the park kind of thing to do, but if you're inclined to be as helpful as possible for Huntington's research, and there happens to be a project running that you can sign up for, I would encourage it. There will certainly be more spinal fluid collections coming up, because measuring the levels of various molecules in the spinal fluid is certainly going to be an important way of, hopefully, running trials

in Huntington's disease. So one way that we can figure out if a drug is working is to see whether we see the expected changes in the spinal fluid. In order to do that, we need to be looking at the spinal fluid, now.

JEFF: Since this is our last live Buzzilia session, I wanted to glance ahead quickly to what's going to happen tomorrow. Which is a session on emerging new treatments and therapies, which is obviously of huge interest and really exciting for everyone here. Professor Bernard Landwehrmeyer is going to give an overview talk, of where we're at in terms of therapeutic development. So, I'm also particularly looking forward to updates on gene silencing approaches to Huntington's disease. So switching off the harmful Huntingtin gene.

ED: About which more in a moment, when we speak to Neil Aronin, but I think in general, it sounds like we are, like new treatments which have been developed specifically for HD, and several of them, are going to be entering clinical trials in the next year, or two.

JEFF: Yes, it's the fruition of decades of careful science that's happening. Really exciting new things happening, just in the next year.

ED: Our first lucky interviewee, actually we're very lucky to have him with us, is Jim Gusella, from Harvard Medical School. Now, Jim is a legend among Huntington's disease researchers. He was critical to the discovery of the gene, and all of the work that led to that. He has remained one of the most prominent researchers on the genetics of Huntington's disease. So, please welcome him to stage. Good evening, thank you for joining us. Have a seat on our opulent, yet minimalist couch. So, Jim, we're going to start with a really easy question. What is a gene?

JIM: That's a more complicated question than you'd think, but I'll try to give you the current definition, because it's actually a moving target. The DNA in an individual carries a code for making the various components of the cells of the individual. To do that, it has to have its message copied. It gets copied into a related molecule called RNA. Then that RNA is read by the machinery in the cell, in many cases to make a protein. So, the current definition of a gene, is that bit of DNA that makes an RNA that is functional. Because some RNAs, as it turns out, don't get made into proteins, but they still do things in the cell that are still being worked out as to exactly what they do. Is that clear enough, now?

ED: That's exceptionally clear. I think that does deserve a round of applause, and I did know this, that's actually an extraordinarily complicated question. A bit of a curve ball, right? That's the American thing to say? A bit of a curve ball?

JIM: Yes.

ED: A googly we would say, although I don't know anything about cricket, so I don't know where that word came from. So that's what a gene is. In my very, very simplistic way, if I were to say a gene was a recipe for a protein, would you be very cross with me?

JIM: That was, I think, probably the best accepted definition up until about five years ago.

ED: I'll take it.

JIM: Probably when you went to school, Ed.

ED: Of course, the gene that is closest to the hearts of everyone in this audience, and everyone watching at home, is the gene that causes Huntington's disease, which is the Huntingtin gene?

JIM: Yes, if you believe that nomenclature. It's actually the HTT gene.

ED: HTT gene.

JIM: Huntington is the product of that gene.

ED: Okay, every day is a school day. Since we know that that gene produces the protein that causes Huntington's disease, why do we need to think about any other genes?

JIM: It's like, if you think about a car, and you're driving the car, and all you have in your hands in a steering wheel. If all you had in your hands was a steering wheel, and there was nothing else there, you wouldn't get very far. The Huntington is a protein, it matters, it does things, but it does it in the context of a lot of other proteins and other components of the cell. So you can't consider it by itself. You've got to consider it as part of the machine that it works within. That's why we've got to worry about the others. Now, as it turns out, the others are not constant. The others vary just like Huntingtin varies. They don't vary in ways all the time that cause disease, sometimes they just vary in normal differences between individuals. So, one of the things to think about, when we think about Huntington's, not as a worry, but as an opportunity, is if we can figure out how Huntingtin works in different circumstances of people who have variations and find those where it doesn't cause as bad a disease - maybe a later onset or a less severe course - then we can use that information. So we don't have to just worry about it in terms of how does Huntingtin work, but maybe as taking an opportunity to make it a clue to a treatment.

ED: That's what a genetic modifier is, right? It's a gene which alters the… Well you tell me.

JIM: You see you've taken the 'tic' off of genetic.

ED: Sorry about that.

JIM: So a genetic modifier isn't necessarily a gene. It is a variation in the sequence of the DNA that when you find it, you don't immediately know how it works, necessarily. Its presence results in a difference in what you see in an individual. So if what you're looking at is the symptoms of Huntington's disease in an individual, and you find that those people who have a certain sequence in their DNA never show psychiatric symptoms, for example, that would be a genetic modifier. You would then have to go in and look at the DNA sequence and say, "How does this work? Does it work because it's part of a gene, or does it work some other way? Because it's regulating something?"

ED: So it's complex?

JIM: So it's complex, but tremendous opportunity, because looking at the genes is finite. There's only a limited amount of DNA in a person, about 3 billion bases. You can look at all of that at once. It's very different than looking at the universe of environmental factors that might be involved, because you can essentially look at a closed system and gradually eliminate all the differences as either not meaning anything, or being vey important.

ED: So you were instrumental in the discovery of the genetic marker 30 years ago, and the gene 20 years ago. We have a lot of genes; you can imprison them all in a lab, and study them until you have your answers. So, do we have genetic modifiers? Do we know what they are?

JIM: We do not have genetic modifiers that we know precisely what they are in humans, and precisely what their effects are. There are proof of principle genetic modifiers in knock-in mouse models, where specific genes have been found that modify the disease. There are candidate modifiers that have been found in humans that represent DNA sequences, that look like they're having an effect, but it's at a very early stage. In the sense that finding spurious results, when you're looking at millions and millions of possibilities all at the same time, is very frequent. So you have to go out of your way to prove that what you think is true, in fact, is not a spurious result. We're in the midst of that, right now, as part of a worldwide collaboration that's looking at thousands of Huntington's disease patients.

ED: People who follow HD Buzz, or follow the news from these sorts of meetings very closely, might be familiar with what has been happening the past couple of years. Which is that we thought we had found some genes that looked pretty good, and it looks like maybe a more careful relook at that has maybe taken those off the table. What happened there?

JIM: They way that you would look for modifiers has changed with improving technology. It used to be, probably up until six or seven years ago, that you could really only pick one gene and look at it, and say, "Does this vary between people?" You might, in fact, come to the point that it does vary, and then in a small sample of a few hundred people, it looks like the people have a certain form of the gene have, let's say, later onset disease. But you're studying that gene without taking into account the 25,000 other genes that you haven't looked at. So we now have the ability to look at them all simultaneously. It comes down to an analogy that I used earlier today in one of my talks, which is if you think about flipping a coin; if you flip a coin eight times and get heads eight times in a row, you're going to think that's a coin that is fixed. If you flip it 1,000, you're almost guaranteed, during that 1,000 times, to find eight heads in a row, at some point. It's like that with genetic modifiers; if you only look at a few and then home in on the ones that look positive, you've picked things that may not be true, but if you've looked at all of them, and then looked at only the ones that are positive, you're going to find things that are real. We now have the ability to look at all of them. So by taking that new technology and looking back at the old ones, we found that in fact, we were being optimistic about the old ones.

ED: So in a sense, it may sound like bad news that there are things that used to be modifiers, but may be not, but actually my way of looking at it would be to return to the idea that science is cumulative. Actually what's happened is that we now have better tools for distinguishing

between spurious results, and really solid results?

JIM: We have better tools, and the positive is also that in the past, when you identified a modifier that you thought was real, you then had to go and prove it biologically. You had to go into a biological system and study it. Doing that is a lot of work, a lot of expense, and a lot of time, and isn't always definitive. Whereas with the genetics now, because you can look at everything at once, you can come to a definitive result without ever going into the biological system, by pure statistics. Then, when you do go to that work of going into the biological system, you know you're working on something real. So you've also avoided work by now eliminating those things that enable you to go directly to the biological system when you don't need to. You've gone away from it; you can get the proof that something is real, and now just study it. It saves a lot of time, once you've got it.

ED: Fantastic. So the work goes on with huge sample sets, with thousands of patients who have donated their DNA, and you're optimistic?

JIM: I'm very optimistic. That said, it's just a starting point, because the way that these genetic modifier studies work, you don't look at a sample, and find something, and then it stops. The more samples you have, the more you're going to find, and the more samples you have that have different characteristics of the disease described in them, the more different kinds of things that you can find. So it's a cumulative process where the initial modifiers that you find give you something to work on that you know changes the disease. You also know that as you look at more samples, you're going to find more things that change the disease, and put together a better picture of exactly how to change it.

ED: Thank you very much, Jim, thanks for joining us. Best of luck with the ongoing work.

JIM: Thank you.

JEFF: Now, we're looking forward to a scientist who's speaking tomorrow, and who works on these hot new gene silencing drugs, Neil Aronin from the University of Massachusetts. So, gene silencing; as Ed and I talk to patients, this is definitely the thing we hear about the most, but a lot of people, of course, who will be watching at home, won't know it exists. So can you give me the quick definition of this approach for therapy?

NEIL: Well, I'm glad that Jim had organised the DNA and the RNA and the protein, because it makes my line of reasoning a lot easier. Gene silencing is actually a way to prevent the messenger RNA to make the protein.

JEFF: So we have this HTT gene that makes this intermediate molecule, and then that turns into the protein?

NEIL: That's correct, and the endogenous, or the natural RNAs that do this are those small, non-coding RNAs that Jim mentioned.

JEFF: They don't make proteins?

NEIL: They don't make proteins, but they do make small RNAs that can recognise messenger RNA and regulate them. So they regulate normally. They regulate how much of the messenger RNA is made, to then make protein.

JEFF: So the idea is to hijack this natural process that exists in cells, and instead tell it, "Hey, go and get rid of the bad Huntingtin"?

NEIL: That's correct. There are two natural processes. The first one that was discovered was actually in worms. These RNAs were made into two different strands that were connected. That's called an SI, or small interfering RNA. Now, we don't make those. We make what's called the micro RNA, which is about the same size as the SIRNA, but there's only one strand. We have probably close to 1,000 of them, and the majority, I'd say two thirds, are in the brain.

JEFF: So, on top of the complexity of these normal things that we make, there's also the complexity we hear from patients often that they hear about ASOs and RNAI. There are these different molecules that seem to be doing the same thing. So, could you just explain briefly the different approaches?

NEIL: Sure. The ASO is a synthetic molecule that's made mostly of DNA. So that's what genes are made of, too. They're single strand, they're about the same size as an SIRNA or the micro RNA, but they work in a very different way. The ASOs get into a cell, and then combined with an enzyme, or protein that cleaves other proteins, called RNAse-H. There are advantages to the ASOs, and there are advantages to the micro RNAs, or the SIRNAs. ASOs usually require a lot more to get into a cell, and it's more difficult, as you know, because you were a participant in some of these studies. It's more difficult to know ahead of time how it's going to work. The SIRNAs and the micro RNAs can actually be experimentally designed, and can work with much smaller concentrations.

JEFF: One thing, and I was going to bring this up, just interested in full disclosure, I work on a different technology than you work on. I think sometimes with patients and families, they think, "This is so stupid, they're competing in some sense against each other". I think, as a scientist I naturally think it's actually a really good thing. I wonder if you could speak to them, how you feel about that?

NEIL: How do I feel about the competition? I don't know.

JEFF: Is it good for science, or is it bad for science?

NEIL: They could be complimentary. As it turns out, in some early studies, the ASOs may get to certain areas of the brain better than small RNAs or RNAs that are embedded in a virus that we put in, and we'll talk about that tomorrow. So you can envisage that in the future, there could be treatment with an ASO, complimentary to those with the RNAI.

JEFF: In a way, we wouldn't have known this if different labs weren't working on different approaches, in the beginning?

NEIL: Correct.

JEFF: So, we've read your name a couple of times in connection with, of all things, sheep, and doing research in sheep. Could you explain just why on earth would you want to study sheep?

NEIL: I'll give you the explanation that I gave my mother, who said, "I thought you went to medical school?", and I'm working on sheep, and you could understand that. So, CHDI has organised a colony of sheep that have the mutant Huntington gene. It's a transgenic sheep. This is a worldwide effort. It was put together by a laboratory headed by Richard Faull and Russell Snell in Auckland, so in New Zealand. The sheep are grown and reared on an Australian sheep farm, which we actually visited. It looked like a sheep farm to me, but what would I know? We have organised treatment of these sheep, with an Adeno associated virus that has a micro RNA, or small RNA, that will target the mutant Huntingtin. The reason we're doing that is we want to establish safety, because you hear that all the time. We need to show that these AV, SIRNAs or micro RNAs are safe, and don't damage the brain. Also, some efficacy; how much knock down, or elimination of the gene we can expect.

JEFF: So how well do they work in the bigger brain?

NEIL: Yes. We plan to do this in late November, and we have about 120 sheep to our disposal.

ED: Brilliant, well, we'll leave it there. Gentleman, thank you both very much.

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

Glossary

CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

messenger RNA A message molecule, based on DNA, used by cells as the final set of instructions for making a protein.

transgenic an organism that has had an extra 'foreign' gene or genes inserted into its DNA.

efficacy A measure of whether a treatment works or not

knock-in an organism that has had one of its genes altered, for example by adding a long CAG repeat into the huntingtin gene.

siRNA A way of silencing genes using specially designed molecules of RNA – like DNA but made of only a single strand – that target the message molecules in cells and tell them not to make a certain protein

RNA interference A type of gene silencing treatment in which specially designed RNA molecules are used to switch off a gene

ASOs A type of gene silencing treatment in which specially designed DNA molecules are

used to switch off a gene

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
