Oz Buzz Video: Day 2

The final day of Oz Buzz: the nightly news, interviews and features presentation from the HD World Congress 2011

By Dr Jeff Carroll | September 16, 2011 | Edited by Professor Ed Wild

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Charles Sabine, Jeff Carroll and Ed Wild present Oz Buzz 2: a summary of the daily news headlines, in-depth interviews with top HD researchers, and entertaining features from the Huntington's disease World Congress 2011 in Melbourne. This is a draft copy that will be updated with better quality video soon.

CHARLES: G'Day! A very good evening and welcome to the second, and I must say, unfortunately the last Oz Buzz. Welcome not just our audience here, but also to those all around the world watching this via the internet. As veterans of our first presentation will know we aim to report the news from this world congress in beautiful Melbourne, Australia to the global HD community in the spirit of what we believe is the dawning of a new age of communication between all members of the Huntington's disease community around the world. As Adlai Stevenson said: "On this shrunken globe, men can no longer live as strangers." And two men who should no longer be strangers to you are my co-presenters. Some say that when he was a soldier in Kosovo he was so handsome that wives of the fighters on both sides persuaded their husbands to lay down their arms and just look at him. [laughter] But to us, he's the pin-up in the white coat, from Boston, USA, Dr Jeff Carroll. [applause] Some say he's so intelligent that computers have been seen to melt in the presence of his gaze. But we know him as the man every woman loves for his intellect, charm and humour. What a waste. [laughter] Dr Ed Wild [applause] Right, gentlemen, let's get racing into the headlines of today's congress. Jeff, what did you learn today?

JEFF: We learned how to operate clickers [laughter] In the science sessions today we learned we should question our assumptions, at least that was the take home for me watching. Paul Muchowski gave a drug to mice that doesn't even get into the brain and yet had a major beneficial effect for HD-like symptoms. Maria Björkqvist suggested that the mutant huntingtin protein might have broad effects, not just in the brain, where we're always looking, but in every tissue in the body. And Steve Finkbeiner showed that evidence that clumps of protein found in the brains of people who've died of all neurodegenerative diseases might not be bad but might be a coping mechanism. In short I think we need to keep our minds open and listen to evidence we get even if it's surprising and challenges our assumptions.

CHARLES: Excellent, brief - that's what I like. Ed, what did it for you?

ED: Well Charles here's my headline: Clinical trials for Huntington's disease - bring them on. A big focus of today's talks, particularly this morning was how are we going to run the clinical trials that will test the new treatments. Trials that will make the most of the drugs that are in development and the efforts of the patients and researchers involved. Things have clearly come on hugely over the past few years. All of today's presenters pretty much agreed that thanks to the trial designs and measurement methods that we've been working on we're now ready for clinical trials in early Huntington's disease. The next hurdle will be testing new treatments in people with the HD mutation that don't have symptoms yet. We've not quite there yet but there's a lot of optimism today that we will be ready when we need to be. For example we heard that combining thinking tests with functional MRI scanning, which enables us to see changes in brain activity, could be a powerful way to detect drug effects in people who haven't had an onset of obvious symptoms. And so Charles before we head across to the sensuous realm of chat-landia, formerly known as the republic of chat-alonia and the fabled lost city of chat-lantis, it's back to you.

CHARLES: And so as my considerably smarter, younger and slimmer friends adjourn to chat-landia I will quickly remind everyone of the rules. Any technical nonsense, and the guest will hear the bell [bell] Get through without it and win a 'no-bell' prize, which is what every researcher covets more than anything in the world, an HDBuzz post-it pad. So to our first guest tonight. Rachael Scahill is a Senior Research Fellow at one of the great research institutes of my home town, University College London. She's at the Institute of Neurology there working with Professor Sarah Tabrizi on TRACK-HD study. Specifically Rachael works on advanced MRI imaging techniques, all of which means she's had the scary experience of looking inside my head. While she was at school Rachael apparently knitted a working model of the human digestive tract which is still on display at the school - so, you didn't get out much? [laughter] Ladies and gentlemen, Rachael Scahill [applause]

ED: Rachael, welcome

RACHAEL: Thank you very much

ED: We're talking about MRI scanning and I think it's best if I explain what anMRI scan is. As I understand it, having some experience in the area, an MRI scanner is a giant magnet which extracts a person's soul and uses it to construct images of their brain, hence the phrase magnetic personality.

RACHAEL: Something like that, it's along those lines

ED: Now with my hand hovering over the 'no-bell' bell broadly speaking how does an MRI scanner construct an image of someone's brain?

RACHAEL: Well it picks up signals from the tissue within the brain and measures different properties of the different water molecules in the brain. So different tissues within the brain: grey, quite conveniently, appears grey, and white, quite conveniently, appears white. They give off different signals that the magnet can pick up and we reconstruct that 3D image.

ED: And as time has gone on the scanners have got better and more accurate?

RACHAEL: Absolutely, as time has gone on we can get better, clearer pictures. And the 3 Tesla scans [bell] Sorry! The latest, high-field strength magnets, big strong magnets give us much bigger, better pictures.

ED: So here's the thing: we have a genetic test for Huntington's disease and when someone has symptoms we can see how bad their symptoms are, so why do we need to scan their brain?

RACHAEL: Very good question, lots of people don't like going in the scanner but we really get such valuable information from these lovely 3D pictures of the brain. We know that there are changes in the brain associated with the disease but people who have a positive genetic test, who aren't showing any symptoms of the disease at all, if we scan them many years before the expected onset we can pick up subtle brain changes. That gives us very valuable information, we can learn to understand the disease process and how that changes over time.

ED: The next step when you want to test a drug would be to use the scan, the changes in the scan, to help us figure out if the drug is working?

RACHAEL: Absolutely, once we get a clear picture of the natural course of the disease we can then see if a treatment has any effect. Whether, ideally it slows down the rate of brains loss, and then we can have some idea that the treatment is having a positive effect.

ED: So are we ready?

RACHAEL: Yes we are [applause]

CHARLES: So to our second guest: Steve Finkbeiner, Director of the Taube-Koret Center for Huntington's disease research in San Francisco. He works on molecular mechanisms of neurodegeneration. That's, to you and me, how cells look after proteins. Steve says that he gets so involved in problems that he can be very absent minded and after a calculus final, he went to the pool for a swim to blow off steam but became so obsessed with a math problem buzzing around his head that he forgot to put his swimsuit on before he left the locker room. [laughter] He said the expression of the people in the pool sobered him up very quickly. So, cold that day was it Steve? [laughter] Ladies and Gentlemen, Steve Finkbeiner. [applause]

JEFF: Hi Steve, thanks for coming. So I saw your talk today and you had a beautiful video. You built a robot microscope. Every other investigator in this room has slave students they use to do that. Why would you go to all the effort to build a robot microscope?

STEVE: There are a number of reasons, one is that even if you have slave students, it's faster than they are. Another issue is that when you do science it's by people, for people and there are some things about being a person doing science that has some limitations

and that's one of the reasons we have those carefully designed clinical trials: to keep our own biases out of the results that we get so we can be sure that whatever we get out is pretty much the accurate truth. The way this robot works is that we ask it to make the calls for us, we look over its shoulder but it tells us the result.

JEFF: You use that technology to be more objective?

STEVE: Absolutely

JEFF: And do you think you learned by using these more objective, blinded kind of techniques, things that perhaps you might have been biased against believing if it hasn't been such an objective way of looking at it?

STEVE: Yeah, there are some events actually that don't occur often enough. So if you're one slave student looking through a microscope you may dismiss it as a one-time event that's of no consequence, but this can look at a million cells and find out that fifty-thousand exhibit that phenotype. [bell] [laughter]

STEVE: Rats! Yes, so that exhibit a particular appearance or difference

JEFF: And so with this microscope you are tracking the actual movement of the huntingtin protein, which I think by now we've all learnt is what causes the disease in the cell. Do you think that these things that you are learning will actually help inform therapeutics for patients?

STEVE: I hope so! [laughter]

STEVE: Yeah! [laughter]

STEVE: Sure, I think our hope is that this is going to be a really powerful tool both for making really important observations but also for really working through some ideas. We're really hoping that this thing will give us an idea, a clear idea, of how the whole process works. So we can, in a really thoughtful way, go in and hit the things that will make the biggest difference.

JEFF: That sounds great, thank you very much [applause]

CHARLES: Now a video question from your native California

ED: Bursting through on the screen

CHARLES: Please play it

KEN: Hello again everyone in Melbourne, this is Gene Vertias aka Ken Serbin, the gene positive Huntington's Disease blogger in San Diego, California. Dr Finkbeiner you have found that the level of stress in the cell, is a better predictor than the dose of mutant

Huntingtin. Does this mean that in Huntington's disease each human being, or maybe even each neuron, responds uniquely in combating the disease? Thank you, Dr Finkbeiner, and everybody for your efforts, and have a successful congress.

STEVE: Ok well that's a good question. One of the things we discovered with this technology is that we can measure the dose that each cell gets of huntingtin but we can also measure how well this cell deals with the Huntingtin. It turns out that how well each cell can handle these proteins is a better predictor of how long it's going to live and how well it's going to do, than the dose it gets. We think that the cells have really powerful adaptive coping responses that they can elicit to try to deal with Huntingtin and the better they do at that the longer they live. There does seem to be from our work, evidence that, difference neurons do have different capacities for responding to mutant Huntingtin and dealing with it. That was a real surprise to us because in years past we tried to answer question using biochemistry to grind everything up, and then try to get the answer out. But with these approaches we can look at individual cells and see differences you would miss the other way.

ED: Thank you, Steve [applause]

CHARLES: Paul Muchowski is a professor at the Gladstone Institute of Neurological Disease in California and works on drug development to protect neurons. Paul also has a new line of research of particular interest to me which he will probably touch on. I happen to know he's a very good golfer, because he beat me. Well actually on consideration that's not a very high bar. He once toured though Europe playing timpani with a symphony. Interesting how many of these researchers are musicians. But most recently Paul recently co-stared in a rap video about scientific gangsters called "Today was a good day" and, yes, we can bring it to you. [song] [applause] Ladies and gentlemen, here he is, Ice-P Muchowski [laughter and applause]

ED: Maybe we should take a vote on whether people want to talk about the drugs for Huntington's disease, or the other thing. You gave a talk today in which, if I didn't misunderstand massively

JEFF: Which you never do

ED: That would never happen. You presented two completely different drugs that you have been working on which both make Huntington's disease mice live longer and improve their symptoms. That's a pretty impressive achievement. Let's talk about your drug JM6. Which is an inhibitor of an enzyme, so it reduces the activity of a molecular machine called KMO.

PAUL: Yes, we developed this drug together with my dad who is a chemist who who had worked for many, many years in drug development and helped us on this project. There has been a lot of research out there that suggesting that blocking this enzyme might be protective for Huntington's disease. No one had ever done it and I was quite surprised that no one had done it. We worked together on this drug in mice and saw some interesting

beneficial effects. One particularly interesting thing about it is that KMO seems to be important not just for Huntington's disease. We tested JM6 also in a mouse model of Alzheimer's and it also improved some of the symptoms those mice get. In the long run the more that we can find potential therapies that are also associated with more common diseases then this can be a good thing for Huntington's disease and bring in a lot more research and effort.

ED: Tell us about your other drug. That's the KMO drug. The other drug targets cannabinoid receptors, which are - if I'm not mistaken, the receptors, the molecular signaling proteins which are also activated when people smoke cannabis.

PAUL: Yes, the second project that I was talking about is a drug that mimics cannabis. It actually acts on a target that's only in immune cells and not in neurons. People have studied the effects of cannabis for many, many years and cannabis mediates the euphoric effects by hitting the receptors on neurons called the CB1 receptor and the drug that we're studying, it's the CB2 receptor that's only on immune cells. We believe that this receptor, this protein, regulates a lot of important functions of immune cells that create cross-talk with the brain and might be very regulate some of the degeneration that goes on in the brain.

ED: What was really interesting to me, Paul, was that both of these drugs are hitting targets outside the brain but the symptoms that are improving are certainly symptoms that are caused by problems within the brain. This seems to be opening up a new door where getting the drug into the brain, which has always been a huge problem, may not be the be all and end all. So effecting things in the blood or outside the brain can have effects within the brain because of changes that take place after the drug acts in the body. Is that correct?

PAUL: Yes, that's correct. To me personally this is one of the more interesting things we've found. The immune system has long been suspected by a lot of researchers as potentially influencing degeneration in the brain, for example in Alzheimer's. We sort of forgot, as researchers, that there's always a cross talk, communication, going on between the brain and the periphery. In my talk I gave the example of a fever you get, a bacterial infection, and right away your immune cells sense the bacterial, they send a signal up to the brain, and then the brain talks back to the immune cells to help resolve the infection. What we're thinking of is hijacking your body's natural communication lines to basically send signals up to the brain to be protective. I think we're going to have broad applicability of this, we just looked at a couple of examples but I suspect that more and more people are going to see that there's a lot of important cross talk between the brain and periphery that we might be able to take advantage of for drug development.

ED: Sounds great. We look forward to hearing about the next step which will be trials of these drugs or drugs like them in humans.

PAUL: Yes, I hope so.

ED: Thank you, Paul. Back to Charles. [applause]

CHARLES: I think tonight that it's only Paul who gets the coveted 'no-bell' prize [applause] Thank you to all of you in Chat-landia. Of course our guests and we must bid farewell to our wonderful 'doctors in da house'. They can be read every day of the year on HDBuzz.net. Ed Wild and the wonderful Jeff Carroll. [applause] Now someone who gave a talk here, not about a specific kind of research, today, but about a whole range of efforts to find treatments for HD was Robert Pacifici. Robert is the Chief Scientific Officer of CHDI. CHDI, the US based not-for-profit organization. But he hasn't always looked like a corporate lawyer, Robert used to follow the Grateful Dead. [Grateful Dead music plays] And at more than one hundred of their concerts, he went to, he experimented in other kinds of chemistry to those that he works in now. I would like to say come on down, Robert CHDI, the biggest funder and driver of HD research in the world. Just how many people... Before I start this you will get a chance to win your own prize Robert, if you answer all of these questions in less than a minute. Biggest funder of drug research, how many treatments are there in the pipeline, at CHDI, and when are they going to begin?

ROBERT: Treatments is a strong word. Obviously CHDI does its best to cover soup to nuts within drug discovery. There are efforts that are very early stage, blue sky, discovery type of work. Obviously some of the support of the observational trials that you heard about. And all the stuff that fits in between the two with the translational work. If you want a specific number, there are about twelve or so translational programs that are ongoing. These are all collaborative with our partners. In some cases this is with some of the presenters that you've seen at the conference, Isis Pharmaceuticals and others, and then there are certain programs we're running internally with contract research organisations. Then, lastly, there are things we've been able to do with large pharmaceutical companies where we've enticed them to take some of the compounds that they have developed, perhaps for other indications, and see whether we can test them within the HD context. So on any given day we've got about twelve shots on goal that we're doing our best to support and shepherd.

CHARLES: Very good

CHARLES: HDBuzz reader Laura Hudson, from the UK, wants to ask you: How long does it normally take for drugs to go through clinical trials?

ROBERT: Well this is probably not the answer you will want to hear but it's incredibly variable. It really depends on the nature of the drug, where did it start and how long is the clinical trial arm going to take. There are some industry benchmarks, the thing people point to is on average about fifteen years for development all the way through research including the clinical part of it; and somewhere around a billion dollars. But obviously sometimes you can get lucky for example as is the case with some our interactions with the pharmaceutical companies. For example they had compounds that had already been through phase one trials. They had really demonstrated the fact they were safe and well tolerated but had

never been tested with HD as an indication. They jump start by entering into the pipeline at phase two or even phase three. In general we do our best to minimize those timelines, more importantly we try and maximize our chances for success. There's a lot of things we can do, as I tried to highlight in my talk, before you get to the clinic. So that the warts and pimples of these compounds are worked out before you get to human testing.

CHARLES: Louise Stuart of Australia asks you: Are there any trials that people with the HD gene and with no symptoms can participate in to help future generations?

ROBERT: Absolutely, community involvement and engagement has certainly been a big theme here at the congress. For those of who have the opportunity to hear about Enroll-HD, I think that's the quintessential example. What we're looking to do is have a comprehensive catalogue of all of the folks that we may need to tap into in the future. Not only for some of the additional spin out trials but some for some of the larger registration trials. I think Enroll-HD is a great example of how everybody can get involved, whether they're symptomatic, whether they've been tested or even if they're a family member that's interested in helping.

CHARLES: Lastly Dawn Buie from Toronto wants to know: How important are collaborations in this field of drug discovery?

ROBERT: Simply put there's no way to discover a drug without collaboration. It's such a massive interdisciplinary effort where we need scientists from all different walks of life: medicinal chemistry, pharmacokinetics, biologists, clinicians. It's critical, not only within the science and medical domain but even to tap in to the patients and their caregivers. One of the things from my talk this morning is that nothing is more precious than an observation made in an affected individual. That observation may be something a patient reports, it may be something a caregiver reports, it may be something that comes out of a clinical trial. The collaboration and the ability for all the different folks to bring to bear their very diverse set of skills, insights and capabilities is absolutely essential to discovering a drug, and it's one of the beautiful things about the Huntington's community.

CHARLES: Thank you very much Robert

ROBERT: Thanks very much [applause]

CHARLES: Now to tell us about things from Melbourne. More Australian than Skippy the bush kangaroo. If she was any more Australian she'd fall off the end of the world: Mel Brinsmead. [applause]

CHARLES: From the convention centre, this place seems a quiet and peaceful place?

MEL: Not at all Charles, not at all. Throughout the 90s and the 2000s Melbourne was the scene of a gruesome gangland war. Thirty six knocked each other off. Pop down to the big market and get yourself an illegal copy, probably only stick to series one… I do have a bit more here… [laughter] For the last few days I've hearing all about this exercise and

stimulation business. However the most recent underbelly bloke was knocked off by an exercise bike to the back of the head: can you believe it? Think they took cognitive stimulation a little too literally.

CHARLES: Ok, there must be a more pleasant and wholesome side to Melbourne

MEL: Well, yes. In 1956 we hosted the Olympic games, that's how we ended up with the MCG, it was hosted there, or the G as we call it Melbourne.

CHARLES: Ok [laughter]

MEL: Oh yeah, sorry I forget another bit… The Olympics, next year, Australia's going to kick butt, sorry guys

CHARLES: Now you call it the G, I thought it was the MCG. Do you shorten everything? We need a lesson tonight in how to speak Australian?

MEL: Oh we sure do shorten everything, chuck [laughter]

CHARLES: Oh we sure do shorten everything, everything has a nickname. I'll give you a couple of examples: Biccies - Biscuit Chewey - Chewing gum Chocies - Chocolate Coldie - Cold drink, usually a beer in Melbourne or Australia Doozie - Something very significant or very large Pressie - Present So Charles, chocies make a doozie of a pressie [laughter]

CHARLES: Tell me about some famous Australian exports

MEL: Well perhaps the most famous of them all comes from the suburbs of Moonee Ponds: Dame Edna Everage possums. This one's for the Brit's out there. The entire cast of Neighbours. While you're in town make sure you get your tour of Ramsey Street. One more: Kath and Kim. These two classy shelias are from burbs of Fountain Lakes. Look at me, Charles, look at me. Cracker, check them out on YouTube. [laughter]

CHARLES: What else is on in Melbourne tonight?

MEL: Well for those of who aren't lucky enough to have a ticket tonight, head to Chinatown for some yum cha. Perhaps check out a movie, a good Aussie one at the moment is Red Dog. Apparently it's really Aussie. If music is more your scene, and good food, head North for Fitzroy. If you're into arts, street art, head to Hosier Lane. That's where you can find all the really cool graffiti.

CHARLES: But it's not all the rough stuff, there's a refined side to Melbourne?

MEL: There is, Romeo and Juliet is showing at the art's centre. I have heard the Australian ballet are now searching for this year's soldier for the Nutcracker. So, chuck, if you're in town a little longer come on down and audition. [laughter]

CHARLES: Moving on, what are we going to wear tonight?

MEL: Well it's blowing a gale out there so girls, hold on to your dresses. It's a little warmer than last night, it's 11. I'd probably still skip the linen suit and pop the ugg boots on. Ladies and gentlemen, don't forget your brolly. Melbourne has switched on the rain for tomorrow.

CHARLES: If we're headed for the dinner tonight what should we do?

MEL: Well if you're going to the fancy dinner tonight, it starts at 7 so I won't keep you too long. You can get there by cab, or taxi as you call them here. The taxi rank is over the road… that way. Or I've been told it's a 20 minute walk, we don't do that here! [laughter] If you're in heals I suggest you get a cab.

CHARLES: I look forward to seeing you there. Thank you so much for all of your work, I feel more Australian than I could ever have expected.

MEL: Thanks [applause]

CHARLES: Thank you, Mel. As Mel can tell you one thing about Australians is that they never do anything in excess. [song - INXS - Need You Tonight] [applause]

CHARLES: The music's working then. [laughter] Now, before we close I want to read you just a little bit of a poem which was written to this conference, just this week, by a lady from Melbourne who simply calls herself "A Huntington's Widow". She was so inspired by what she saw here that she wrote these words: We don't always know the terms the scientists may say but we treasure every word from them and praise the breakthroughs they bring our way so continue your wonderful programs as you help to spread the word again a great big thank you, the loudest you've ever heard. And so time's boomerang has circled the Yarra river and returned, crashing through the walls of the Melbourne Conference Centre, to tell us that we must end our reporting on the world congress here in Melbourne. So all that is left for me is to thank my co-presenters, doctors Ed Wild, Jeff Carroll and Melanie Brinsmead; the outstanding Oz Buzz production team of Lee Young, Jeff McDonald, Chris Pourchot, Ben Ryan, Alex Censor and Julie Stout. And of course everyone at the Melbourne Convention Centre. But most of all, the audience, here in Melbourne and around the world. I hope that we have succeeded in some way, of our quest to move the world of communication between all the parts of the HD community into a global chapter. Because Huntington's disease does not recognize borders or territories, so nor should we. On that note I would like to leave you with the words of the astronaut John-David Bartoe: "As I looked down, I saw a large river meandering slowly along for miles, passing from one country to another without stopping. I also saw huge forests, extending along several borders. And I watched the extent of one ocean touch the shores of separate continents. Two words leaped to mind as I looked down on all this: commonality and interdependence. We are all one world." Goodnight.

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

GLOSSARY

huntingtin protein The protein produced by the HD gene.

neurodegenerative A disease caused by progressive malfunctioning and death of brain cells (neurons)

clinical trial Very carefully planned experiments designed to answer specific questions about how a drug affects human beings

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

therapeutics treatments

Receptor a molecule on the surface of a cell that signalling chemicals attach to

neuron Brain cells that store and transmit information

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

KMO kynurenine mono-oxygenase, an enzyme that controls the balance of harmful and protective chemicals resulting from the breakdown of proteins

JM6 an experimental drug that is converted by the body into Ro-61, which inhibits the enzyme KMO
