EuroBuzz News: Day 2

EuroBuzz news: Day 2. Ed and Jeff reporting from the European Huntington’s Disease Network 2012 meeting in Stockholm

By Dr Ed Wild September 15, 2012 Edited by Dr Jeff Carroll

Our second daily report from the European Huntington’s Disease Network 2012 Meeting in Stockholm. Video of both EuroBuzz evening sessions will be available to watch on HDBuzz.net next week.

Saturday, September 15, 2012

9:27 - Good morning from Stockholm and welcome to day 2 of HDBuzz reporting from the European Huntington’s Disease Network meeting

Elena Cattaneo reminds us that animals have had an HD gene for 800 million years.
Image credit: Claudio Catalli

9:27 - **Jeff:** Whoa! Elena Cattaneo, from the University of Milan, reminds us that animals have had an HD gene for 800 million years. Even sea urchins have a very similar gene. Why? What does this gene do that's so important. To try and understand why the HD gene is so important, Prof Cattaneo studies mouse cells that don't have the gene. These cells have trouble sticking together to form larger structures. Cattaneo is doing really cool experiments - her team is replacing the mouse HD gene with HD genes from diverse other species. This approach helps them understand the evolutionary history of this mysterious gene. If we had a better understanding of what the HD gene normally does, we might be able to come up with better ideas for therapies.

9:32 - **Ed:** Elena Cattaneo (Milan, Italy) tells us the Huntingtin protein is ancient and found in many species but the CAG bit is relatively new. Cattaneo studies the role of Huntingtin in the development of embryos. Very early brain structures can't form without huntingtin.

10:20 - **Jeff:** Fred Saudou is building tiny chambers that let him isolate different parts of brain cells from mice. This is a big help for trying to understand what aspects of these cells function is altered by the mutation that causes HD.

10:22 - **Ed:** Saudou: Important chemicals are transported in cells in bubbles called vesicles. An enzyme called GAPDH provides fuel for vesicles - huntingtin protein links the energy supply to the vesicle. A new and crucial explanation for what huntingtin does. So huntingtin links energy supply and transport of essential chemicals. This could explain one way the HD mutation harms cells.

10:28 - **Ed:** Lisa Ellerby (Novato, USA) is presenting important bearkthroughs in stem cell research for Huntington's disease. Induced pluripotent stem cells (IPS cells) are stem cells made from samples of patient skin & can be turned into other cell types. "In a decade or so" we may be able to use IPS cells to treat HD patients but right now they are useful for studying HD. Once stem cells have been made from patient skin samples, the HD mutation can be corrected in the lab. Once the HD mutation has been corrected in patient-derived stem cells, they are still able to be turned into neurons. Ellerby is part of a multi-centre collaborative effort to develop and study IP stem cells to understand and possibly treat HD.

10:51 - **Ed:** Leslie Thompson (California, USA): the early results of the stem cell consortium show that the cells look and behave like real neurons. IPS stem cells can be used to reveal things about HD in human neurons that we cannot study any other way. IPS stem cells can also be used to identify new drug targets for Huntington's disease, and test drugs in human cells.

11:41 - **Ed:** Bev Davidson (Iowa, USA) gives an update on huntingtin lowering or 'gene silencing' therapies - the most promising approach to treating HD. Gene silencing aims to 'switch off' the abnormal HD gene so that cells don't make the harmful huntingtin protein. Huntingtin lowering drugs can be made of DNA or a related 'message' molecule, RNA. Both are being developed and tested. It's been a long road to get from the idea of huntingtin lowering to where we are now. Tests in cells, mice, monkeys… HD mice given huntingtin lowering drugs live longer and have better neurological function & less damage to neurons. We've seen successes in Huntington's disease mice with both RNA and DNA based huntingtin lowering treatments. Davidson prefers 'huntingtin lowering' over 'gene silencing' because we don't want to get rid of all huntingtin. As we heard earlier, huntingtin is important in cells so we don't want to lose it completely. One option is to switch off just the mutant gene. Davidson has treated 'normal' rhesus monkeys with RNA-based huntingtin lowering drug injected into the brain. The RNA treatment was safe and didn't cause damage to brain cells, which it could have. The RNA treatment reduced huntingtin levels by about half. That could make a real difference if achieved in HD patients. DNA-based huntingtin lowering called 'ASO' treatment spreads further throughout the brain.

12:02 - **Ed:** Davidson says one concern, however, is whether the ASO treatment can get to the 'basal ganglia' - the deep bit affected early in HD. Silencing just the mutant copy of the gene is much more difficult but is being worked on. We could target the CAG repeat to try to silence the mutant gene only, but many genes have CAG repeats so that might cause problems. 'Micro RNAs' are good at silencing just the mutant gene while reducing the risk of unwanted effects on other genes. Recent breakthrough is 'single-stranded RNA' gene silencing which could combine the best of both approaches - DNA & RNA. We have 'many tools in the toolbox' when it comes to huntingtin lowering therapies.

12:17 - **Jeff:** Beverly Davidson, from the University of Iowa, is describing her labs work on silencing the HD gene in mouse models. Bev's lab has shown that they can use viruses to deliver silencing drugs to the brain, which has beneficial effects. Davidson's lab is now working on delivering silencing drugs to the brains of monkeys. This is much harder to do, as monkey brains are much bigger than mouse brains, and closer to the challenges posed by human brains. New work in Davidson's lab is also focused on working out how to deliver silencing drugs only to cells that need it. If we could deliver these drugs to only sick or stressed cells, we could potentially reduce side effects.

13:00 - **Jeff:** Great morning session! Stay tuned for more exciting science later today.

14:00 - **Ed:** And we're back from lunch to report on the afternoon sessions from the European Huntington's Disease Network meeting in Stockholm.

14:00 - **Ed:** Eminent HD researcher Gill Bates (London, UK) is reporting on work looking at the fragments that huntingtin breaks up into in cells. Huntingtin is cut up into different fragments, each with different useful or harmful properties. Proteins like huntingtin can also be manufactured in different forms, like arranging Lego blocks in different orders. Bates finds that in animals with the HD mutation, there are odd huntingtin forms where blocks 1 and 2 of the protein are not joined together (these blocks are called 'exons')

14:26 - **Ed:** Ellen Nollen (Groningen, Netherlands) works in Parkinson's disease, where abnormal blobs of protein cause the death of brain cells. Build up of abnormal protein blobs is called aggregation and is seen in many diseases including Huntington's disease. In Parkinson's the blobs are made of a protein called alpha synuclein. (In HD, they're made of huntingtin protein). Nollen says helping cells to handle abnormal protein buildup could be useful across degenerative brain diseases like Parkinson's and HD. Nollen studies alpha synuclein buildup in a worm called 'C. elegans' - a popular worm with scientists because it reproduces fast! By switching off genes one by one, they found several that prevented alpha synuclein buildup. Switching off one gene called TDO prevented protein buildup and improved the movement of the worms. Interestingly, TDO is related to the enzyme KMO which is already a potential target in Huntington's disease. Switching off the TDO gene in worms with a mutant HD gene protected them against some of its harmful effects. TDO is a new lead for Huntington's disease treatment research - always great to have a new target enter the pipeline.

14:49 - **Jeff:** Erich Wanker, from the Max Delbruck Center in Berlin, suggests that there are connections between the different 'neurodegenerative' diseases - including HD, Parkinson's Disease and Alzheimer's Disease. Erich has spent a lot of effort to map out which other proteins the HD protein bumps into as it goes about its business in the cell. This helps make a 'map' of what the HD protein might be doing. Similar questions have been asked by other researchers, including William Yang at UCLA whose work was covered recently by HDBuzz. Instead of focusing only on the HD protein, Wanker's group is systematically mapping all the interactions between proteins that cause a number of brain diseases. All his data is being shared openly, encouraging other researchers to look for their own favorite proteins partners.

14:51 - **Ed:** Erich Wanker (Berlin, Germany - the W is pronounced as a V) is mapping what other proteins the huntingtin bumps into in the cell. Erich is making a 'neuronet' - a 'map' of these interactions.

15:00 - **Ed:** Nicholas Perentos (Cambridge, UK) is talking about the recently developed sheep model of Huntington's disease. Sheep have big brains, are smart (despite stereotypes) & easy to look after - all very useful in testing treatments like gene silencing. It's early days for the HD sheep but they are shaping up nicely and are being studied very closely.

> **"**Huntingtin lowering drugs can be made of DNA or a related 'message' molecule, RNA. Both are being developed and tested. ″

15:08 - **Jeff:** We spend a lot of time talking about HD mice, but Nicholas Perentos is discussing recently-developed HD sheep! Why do we need sheep? Why on earth do we want a sheep model? Largely because they have large brains, which are anatomically more like human brains than mouse brains are. This makes them handy for testing therapies that require some kind of special brain delivery, like an injection.

15:17 - **Jeff:** Robert Pacifici, chief scientific officer at CHDI, lays out the case for excitement. CHDI and other groups are working hard on new drugs that are developed specifically for HD. Hopefully these will be more successful than drugs that have been tested so far in HD.

15:18 - **Ed:** Robert Pacifici (CHDI Foundation, USA) is presenting CHDI's extensive Huntington's disease drug development efforts. Pacifici surprises the audience, mimicking Clint Eastwood by talking to an empty chair about HD drug development.

15:22 - **Jeff:** Who are CHDI? They're a non-profit company drug development company. They're funded by a private foundation, which means they don't need to spend time fundraising. They're focused exclusively on HD. They work as a "virtual" company - 60 full time employees direct the research of hundreds of people at academic and commercial labs around the world. Being a non-profit entity is important, according to Pacifici - "because we don't have competitors, if someone else is already working on something, we can just reach out and help them". Observational trials, like PREDICT-HD and TRACK-HD are critical, according to Pacifici. As he says - "there is nothing more important to a drug hunter than an observation made in the population you want to treat".

15:30 - **Ed:** CHDI's Doug Macdonald gives an overview of CHDI's huntingtin lowering work. Lots going on and moving rapidly towards clinical trials. Successes and good safety data from several approaches - DNA-based drug injected into spinal fluid and RNA drug into brain. Huntingtin lowering techniques that selectively suppress the mutant copy of the HD gene are among CHDI's approaches.

15:37 - **Jeff:** The scientist who leads CHDI's efforts to lower HD gene is Doug MacDonald. He's leading projects to develop not 1 but 7 different technologies to try and reduce the levels of the HD protein that causes the disease.

15:45 - **Ed:** Andrea Caricasole (Siena Biotech, Italy) is talking about Siena's drug selisistat, which is being tested

across Europe - PADDINGTON study. Selisistat reduces activity of the enzyme sirtuin-1 and is aimed at helping cells get rid of the mutant huntington protein. Mutant huntingtin gets 'acetyl' tags added to it, which tell the cell to get rid of it. The enzyme sirtuin-1 acts to reduce this useful acetylation. So inhibiting sirtuin-1 ought to be helpful for HD. Safety study of selisistat will be completed in the next few weeks.

15:58 - **Ed:** Chris Schmidt (Pfizer) talks about PDE inhibition - which aims to improve signalling between cells in HD. PDE10 is an enzyme that removes signalling molecules from neurons after they receive a signal from another neuron, so, inhibiting PDE10 should increase the activity of these connection (called synapses) - which is less efficient in HD. Pfizer has developed an inhibitor of PDE-10A which performs well in the lab. The PDE10A inhibitor goes by the catchy name of PF-2,545,920. Pfizer and CHDI are collaborating to test the PDE10A inhibitor in several different models of Huntington's disease. PDE10A treatment in Huntington's disease neurons improves their electrical behavior. Pfizer: encouraging early results for the PDE10A inhibitor drug in an HD mouse model, too. Next, Pfizer is going to do a brain imaging study to measure PDE10 levels in HD subjects, in preparation for a trial.

16:10 - **Ed:** Two things are especially exciting here: (1) big drug companies investing in HD drug development and 2) how quickly PDE has developed as a target.

16:12 - **Ed:** Next up, Frank Gray from another drug giant, GSK, talking about another PDE inhibitor program for HD. GSK is focusing on PDE4, which is also involved in signalling at synapses, the connection between neurons. GSK's drug inhibits PDE4 and is called GSK356278. Snappy! GSK's drug shows benefits when tested on neurons growing in a dish - improvements in functions important for learning. GSK is initially developing their drug as a possible treatment for cognition (thinking) problems in Huntington's disease. PDE4 inhibitor drug has already been tested in human volunteers. Next GSK will aim for a trial in human HD patients. With any brain drug, side effects are a possible concern. Need to make sure the drug is safe and makes things better, not worse.

16:24 - **Ed:** Josef Priller (Berlin, Germany): apathy is a massive problem in HD - e.g. refusal to leave the house, get out of bed or socialise but there are no treatments that help with apathy in Huntington's disease. A drug called buproprion ("Wellbutrin") - which is mostly prescribed to help people quit smoking - is being tested as an HD apathy treatment. The trial is called Action-HD. It'll use clinical and functional MRI measures to judge success.

16:37 - **Ed:** Julie Stout: Reach2HD is the name for a trial of PBT2, a copper-reducing drug from Prana Biotech - Reach2HD is now enrolling in USA and Australia.

16:39 - **Jeff:** Prana Biotechnology is testing a drug called PBT2 in a trial in conjunction with the Huntington Study Group - this trial is recruiting now!

16:40 - **Ed:** What a packed therapeutics session! We've also heard about the Prequel study (coenzyme Q - no results yet) and a review of studies into Huntexil / Pridopidine.

17:55 - **Ed:** Matt Ellison reports on the success of HDYO, the Huntington's Disease Youth Organisation - young people taking a stand.

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

Learn more

EHDN 2012 program at the EHDN web site Elena Cattaneo's lab Frédéric Saudou's lab Erich Wanker's lab About Neuronet CHDI Foundation HDYO - Huntington's Disease Youth Organisation HDBuzz on Twitter (@HDBuzzFeed)

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- Glossary
- **induced pluripotent stem cells** Stem cells that have been grown from adult cells.
- **Parkinson's Disease** A neurodegenerative disease that, like HD, involves motor coordination problems
- **huntingtin protein** The protein produced by the HD gene.
- **neurodegenerative** A disease caused by progressive malfunctioning and death of brain cells (neurons)
- **gene silencing** An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein
- **observational** A study in which measurements are made in human volunteers but no experimental drug or treatment is given
- **therapeutics** treatments
- **CAG repeat** The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD
- **stem cells** Cells that can divide into cells of different types
- **neuron** Brain cells that store and transmit information
- **embryo** the earliest stage during the development of a baby, when it consists of just a few cells
- **vesicle** a tiny 'bubble' produced by a cell that can deliver chemicals to other cells
- **acetyl** a chemical tag that can be added to proteins or removed from them
- **PDE10** a brain protein that may be a good drug target and biomarker in Huntington's disease. PDE10 is found almost exclusively in parts of the brain where brain cells die in HD.
- **Exons** The small fraction of our DNA that is directly used to instruct cells how to make proteins
- **magnetic resonance** A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals
- **ASOs** A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene
- **KMO** kynurenine mono-oxygenase, an enzyme that controls the balance of harmful and protective chemicals resulting from the breakdown of proteins
- **RNA** the chemical, similar to DNA, that makes up the 'message' molecules that cells use as working copies of genes, when manufacturing proteins.
- Read more definitions in the glossary

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