Huntington's disease therapeutics conference 2018 - day 1

Our daily roundup of the science presented at the 2018 HD Therapeutics Conference in Palm Springs

By Professor Ed Wild | February 28, 2018 | Edited by Dr Jeff Carroll

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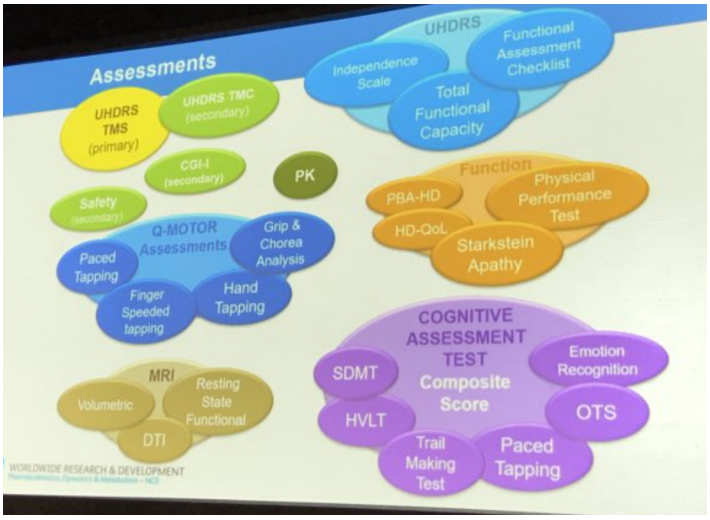
Jeff and Ed report from the Huntington's Disease Therapeutics Conference - the biggest annual gathering of HD researchers. This year's conference is bigger and more exciting than ever.

Tuesday morning - brain connections

Good morning from the first day of the 2018 HD Therapeutics Conference in sunny Palm Springs!



Slide showing all the assessments patients underwent in the Amaryllis study

Rui Costa, Columbia University, opens the session with a discussion about the brain circuits that dysfunction early in HD - called the "basal ganglia". These regions help the brain choose which movements to execute

Phillip Star, UCSF, is a neurosurgeon interested in HD. He reviews the history of the use of therapeutic brain surgery in HD, which has been pretty limited. Starr introduces the audience to newly developed devices that let researchers record brain activity from human volunteers for months or even years. Really cool! Starr is one of the few researchers who

have recorded the activity of brain cells in HD patients. In Parkinson's Disease patients, Starr's team records from two different sites in the circuits that control movement. They've identified patterns of brain activity that occur when patients experience specific symptoms. Starr proposes that similar recordings in HD patients may help us understand both the movement and non-movement symptoms of HD.

Henry Yin, Duke, also studies the brain circuits that control movement, using mice. He's able to wirelessly record brain activity and compare it to video recordings of the animal's behaviour. Yin's lab has built a very detailed map of the brain circuits that control the direction and velocity of movements. Because movement problems are such a big part of HD, Yin has begun investigating HD mouse models. Yin finds that HD mice have much more variable movements then normal mice - and they have a hard time accurately reaching targets.

Baljit Khakh, UCLA, studies a type of brain cell called an "astrocyte". These cells comprise almost half the brain, but they're poorly understood. Khakh's lab is focused on understanding astrocytes, and how they dysfunction in brain disease. Khakh's lab has developed a new tool that allows them to isolate astrocytes from intact brains and study changes that happen in HD mouse models during aging.

Next Marielle Delnomdedieu is updating us on Pfizer's 5.5-year program looking at a brain signalling substance called PDE10A to try to treat HD. The PDE10A program culminated in a study called Amaryllis. The trial was negative - the drug didn't improve HD symptoms overall - but as we said at the time, it was a good idea, carefully tested and we learned a lot. 270 HD patients in 6 countries tested Pfizer's PDE10A blocking drug, PF-02545920 (catchy!). Recruitment for the trial was fast and efficient - great job, HD community! Unfortunately the drug failed to improve movement or cognitive function but Pfizer have now analysed the mountain of data from the whole study. Many aspects of HD were measured in the trial. The drug was pretty safe and well tolerated. In some people the involuntray movements got worse and some people felt sleepy but the side effects seemed to settle over time. Patients in the amaryllis study were all invited to continue taking the drug in an "open label" extension study - open label means the patients knew they were getting the drug for sure. There was no change in the functional measures used in the study - assessments of how much a person can do in their everyday life. Looking in detail at the cognitive data, there was a suggestion that performance improved for a few weeks but then went back to how it was before. But we have to be careful not to over interpret - it is an interesting observation that could help us understand the drug & the brain. On a couple of computerised measurements of movement function (called q-motor tests), again a suggestion of short-lived improvement that faded away. To us this suggests the drug might be tickling the right part of the brain but HD is a really tough nut to crack.

Tuesday afternoon - stem cells

This afternoon's science sessions are on stem cells and regenerative medicine.

> **“Recruitment for the Amaryllis trial was fast and efficient - great job, HD community! ”**

Clive Svendsen from Cedars Sinai introduces the work of the HD iPSC Consortium - a group of scientists working on turning skin cells into brain cells. IPSC stands for induced pluripotent stem cells. That means cells from the body that can be tricked into thinking they are in an embryo, and can develop into any organ like muscle or brain cells. Svendsen uses “brain on a chip” methods to use these iPSCs to study HD. Little clumps of neurons growing on tiny spaces on a microchip that can control their growth and measure their responses. Techniques like this allow more complex experiments that model real brains more accurately than if you just dump stem cells into a Petri dish. Svendsen’s chip-brains have multiple cell types and blood vessels like the real brain. You can also see how the HD brains-on-a-chip respond to drugs. So that’s stem cells to model Huntington’s disease. What about treating HD using stem cells? Replacing lost neurons with new healthy ones? A few patients received transplantation of stem cells many years ago and there was brief improvement but eventually the transplanted cells died. The focus now is on getting better at growing the cells and turning them into the right kind of brain cell before starting new trials in patients. Neurons - the brain cells that use electricity to do thinking stuff - are really hard to turn into a treatment. It might be easier and more productive to use a different brain cell type called astrocytes. Astrocytes are a kind of brain cell that supports and connects neurons. They can be made easier than neurons and you can reprogram them to make chemicals that support neurons. We call those chemicals ‘growth factors’ and they have names like GDNF and BDNF. Svendsen is now running a clinical trial using stem cells injected into the spine, to treat ALS (motor neuron disease).

Next Bruno Chilian from Evotec presents work using stem cells specially engineered to study the CAG genetic expansion that causes HD. Instead of making stem cells from lots of different HD patients, Chilian took ‘normal’ cells and used genetic engineering to give them abnormally long CAG repeats in the Huntington gene, with several different lengths. This means that the cells are identical in every way EXCEPT the CAG repeat length and any differences are due to that. Using those methods, you can study thousands of cells with different CAG repeat lengths and use computers to figure out the differences. Cool quote that says a lot about how science works: “we repeated the experiment and luckily something else went wrong”. Chilian’s team uses software that’s rather like an email spam filter to figure out how HD cells differ from regular cells. Early days for these methods but they could reveal new and fundamental things about how the HD mutation makes things go wrong in the brain.

Josep Canals, Univ. Barcelona, studies the process by which stem cells turn into neurons, the type of brain cells that malfunction and die in HD. Understanding this process enables Canals’ lab to grow a huge number of neurons in dishes in the lab - useful both for basic research and also as a source of healthy cells for experimenting with cell transplantation.

Leslie Thompson, UCI, is using stem cells in a slightly different way than the previous speakers. Her lab is transplanting stem cells into the brains of HD mice in hopes of improving their symptoms. For these experiments, 100,000 cells are injected into each half of the brains of HD mice, followed by testing of their HD-like behaviors. This treatment significantly improved the movement symptoms of the mice. Some of the injected cells grow into mature neurons and form connections with other neurons in the brain, suggesting the injected cells are functional. Thompson's team is interested in moving towards human clinical trials in the near future.

Jane Lebkowski, Asterias Biotherapeutics, is also interested in using stem cells as a treatment, in her case for spinal cord injury. She ends the session on stem cells by describing the path to using stem cells in clinical trials. Using cells as treatments is powerful, but comes with a number of complications that must be worked out carefully before human studies are conducted. Asterias has delivered stem cells to patients with spinal cord injury in several trials, so their experience will be a huge assist to researchers interested in similar studies for HD.

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

GLOSSARY

induced pluripotent stem cells Stem cells that have been grown from adult cells.

motor neuron disease A progressive neurological disease in which motor (movement) neurons die. Also known as ALS or Lou Gehrig's disease.

genetic engineering A technique used by scientists to alter the genes (DNA) of an animal or other organism, so that its cells produce different proteins and behave differently

Parkinson's Disease A neurodegenerative disease that, like HD, involves motor coordination problems

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

therapeutics treatments

open label A trial in which the patient and doctor know what drug is being used. Open label trials are susceptible to bias through placebo effects.

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

GDNF glial cell-derived neurotrophic factor: a growth factor that protects neurons in Parkinson's Disease, and maybe HD

BDNF brain-derived neurotrophic factor: a growth factor that may be able to protect neurons in HD

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