

## 2015 Huntington's Disease Therapeutics Conference: Day 2



Day 2 of updates from the annual HD Therapeutics Conference in Palm Springs

By Dr Jeff Carroll on February 26, 2015

Edited by Dr Ed Wild

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*Our second update from the Annual Huntington's Disease Therapeutics Conference.*

### Wednesday: huntingtin-lowering drugs

09:03 - This morning's session is focused on what many scientists consider the most promising approach to HD therapy, "Huntingtin silencing" or huntingtin lowering

09:06 - The idea with Huntingtin silencing is to reduce the creation of the mutant huntingtin protein in cells, using a variety of techniques.

09:06 - For much more on this topic, see:

<http://en.hdbuzz.net/topic/29>

09:07 - Basically, every HD patient has a mutant HD gene. That gene is copied by the cell into a messenger RNA molecule, a working copy of the gene

09:08 - The RNA molecules are used by the cell as templates to create proteins. So: Mutant HD gene -> mutant HD messenger RNA -> mutant HD protein

09:09 - In theory, we could interfere with this chain at any point and have the same effect - reducing the levels of the mutant HD protein.

09:11 - George McAllister, of BioFocus, is leading a project that's looking for chemicals that reduce levels of mutant huntingtin protein

09:12 - His company is screening a massive number of chemicals: applying them to cells and seeing whether they reduce mutant huntingtin levels

09:15 - New technologies developed over the last few years let BioFocus use real human cells and measure infinitesimal levels of mutant huntingtin

09:32 - BioFocus is screening thousands of molecules, looking for one that reduces mutant huntingtin protein levels without making cells sick

09:35 - This is an interesting approach, they're looking for chemicals that reduce mutant huntingtin without necessarily knowing how they're working



This is what a room full of scientists trying to figure out how to develop Huntington's disease treatments looks like

09:41 - It's a cool way to look for drugs that work in ways you might not predict, which is a good way to learn about new approaches to the problem

09:46 - Dean Stamos, of Vertex Pharmaceuticals, addresses the conference on his company's efforts to come up with drugs to reduce mutant huntingtin

09:47 - Vertex discovered chemicals that block the activity of a protein called "Hsp90" had the result of reducing mutant huntingtin levels

09:50 - These chemicals turned out to not be good drugs, but could still teach us about how cells get rid of tricky proteins like mutant huntingtin

09:55 - Cells have very sophisticated ways of dealing with proteins, like mutant huntingtin, that don't fold up correctly.

09:57 - A number of tiny machines called "heat shock proteins" help cells keep all their proteins folded up in the correct shape, even after stress

10:00 - Hsp90 is "heat shock protein 90", Vertex developed specific molecules to block it, leading to long-term reduction of mutant huntingtin

10:01 - For reasons they haven't specified, Vertex doesn't feel like these drugs would be good for long-term use

10:06 - Lisa Stanek, Genzyme, is using primates to develop techniques for silencing mutant huntingtin using viral delivery of something called siRNA

10:09 - siRNA's are 'small interfering RNA'; short pieces of RNA (a cousin of DNA) that likes to pair up with specific RNA molecules in the cell

10:10 - Once in the cell, siRNA molecules find and destroy the huntingtin messenger RNA molecules, in turn reducing huntingtin protein levels

10:12 - They're using tiny, harmless, viruses that are good at getting siRNA into brain cells. These viruses are called "adeno-associated viruses"

10:17 - Stanek reminds the audience that treating mouse brains is pretty easy, but human brains are more than 1,000 times larger!

10:18 - To study this, we need to work in animals that have larger brains. Stanek's team has been working in primates to see how these viruses work

10:21 - Genzyme is conducting careful study of the safety of their viruses in monkeys - if there are any problems we want to catch them now.

10:26 - Trial injections of the viruses Genzyme wants to use for human trials give really impressive spread of the virus throughout the brain!

10:29 - This is exciting, one of the hurdles for this approach in the past was the relatively limited spread of injected virus within the brain

10:31 - Careful observation of injected monkeys revealed no health concerns for a month after they received their brain injections of test virus

11:06 - Next Geoff Nichol from Sangamo Biosciences is giving an update on 'Zinc Finger' drugs to reduce production of the mutant huntingtin protein

11:07 - More on zinc finger drugs here <http://en.hdbuzz.net/103>

11:10 - Zinc finger drugs aim to switch off production of the mutant protein at its source. They stick to the DNA of the gene inside cells

11:10 - After sticking, the mutant protein gene is switched off.

11:11 - What's more, the zinc finger drugs can switch off the mutant copy of the gene, while leaving the healthy copy alone

11:12 - Leaving the healthy huntingtin gene alone is very appealing because switching it off might cause unwanted side effects - but we don't know.

11:16 - Sangamo has partnered with Shire Pharmaceuticals to develop their zinc finger drugs

11:16 - The zinc finger drug is injected into the brain as a 'recipe' carried by a harmless virus.

11:17 - The virus takes up residence in brain cells and the cells themselves become a factory for making the zinc finger drug

11:18 - This means that in theory at least the zinc finger drugs could be a one-shot solution to prevent or slow HD.

11:18 - The flipside of that is that if there are unwanted effects, those will be longlasting too - so it's important to test these drugs carefully

11:19 - So far, the zinc finger drugs have been tested in several different mouse models of mice and look to be safe and effective.

11:19 - Figuring out how to deliver the drugs safely to the brain is the next big challenge for Sangamo and Shire.

11:21 - A clinical trial of zinc finger drugs is currently in the early planning stages, probably in patients with early symptoms

11:41 - Frank Bennett, of Isis Pharmaceuticals, addresses the conference on his companies efforts with drugs called "antisense oligonucleotides"

11:43 - These "ASO" molecules are another way to destroy specific RNA molecules, helping reduce the levels of a protein we want to get rid of

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11:44 - Isis has been working to develop ASO molecules that destroy the huntingtin RNA, and therefore reduce huntingtin protein levels

11:47 - Isis has proven in a large number of animal studies that reducing huntingtin in the brain using ASOs improves HD-like symptoms in mice

11:48 - Isis has experience with these types of molecules - they've treated more than 6,000 human patients in 100 clinical studies for other diseases

11:49 - Like many other drugs discussed today, ASOs can't get into the brain from the blood, so they need to be injected into it somehow

11:51 - To get into the brain, injections can be made at the base of the spine into the spinal fluid, which carries drugs to the brain

11:51 - This approach has been used in multiple human studies conducted by Isis for other diseases, and so far seems safe and effective.

11:52 - In mice treated with ASOs targeting huntingtin, the effect of the drug lasts for months without needing to be re-dosed.

11:56 - Like the other companies here today, Isis has already conducted detailed safety studies in primates

12:02 - As an extra check of their plan for delivery, Isis has done spinal delivery in pigs, who apparently have pretty long spinal cords!

12:05 - Will ASOs work in people? Isis has a program in a disease called Spinal Muscular Atrophy where the drug is being delivered similarly

12:07 - Brain and spinal cord tissue from Spinal Muscular Atrophy patients show that ASOs effectively get into the brain after spinal fluid delivery

12:09 - Though the numbers of patients are small, kids with spinal muscular atrophy treated with Isis' drugs seem to be showing disease improvement

12:11 - Isis is launching a human HD study, starting sometime in the first half of 2015! The drug is called "HTT-Rx", and the study is focused on safety.

12:13 - This first trial will have the goal of establishing that Htt-Rx delivery to the human brain and spinal cord is safe.

12:15 - What a morning! All these silencing approaches look like very exciting approaches for treating HD, and the technology has really advanced!

12:22 - Doug Macdonald, CHDI, is leading the foundations efforts to look for "biomarkers" for the huntingtin silencing studies. What's a biomarker?

12:23 - If we silence the huntingtin protein in the brain, how we will know the drugs worked? We can't very well take brain tissue samples to check

12:24 - So Macdonald is leading efforts to look for other ways to see the effect of silencing drugs in human brains.

12:25 - One way is to measure levels of the huntingtin protein in fluids we can get to, like the spinal fluid. Sampling this is pretty easy.

12:27 - Using rats, CHDI and Isis are testing whether levels of the huntingtin protein in the spinal fluid change after delivery of silencing drugs

12:30 - Data hot off the presses suggests it's possible that levels of the huntingtin protein in the spinal fluid somewhat mirror brain levels

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*Dr Wild and Dr Carroll have received research support from the Conference organizer, CHDI Foundation. For more information about our disclosure policy see our FAQ...*

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## Glossary

**ASOs** A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

**huntingtin protein** The protein produced by the HD gene.

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

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

**therapeutics** treatments

**biomarker** a test of any kind - including blood tests, thinking tests and brain scans - that can measure or predict the progression of a disease like HD. Biomarkers may make clinical trials of new drugs quicker and more reliable.

**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

**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.

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