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

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

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

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

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 companie’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 huntintin

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.

> “This first trial will have the goal of establishing that Htt-Rx delivery to the human brain and spinal cord is safe”

11:16 - Sangamo has partnered with Shire Pharmaceutials 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

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...

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.