Video feature: Huntington's disease research... in space!

The sky's no longer the limit for HD research: HDBuzz interviews Gwen Owens, who's sending the HD protein into space!

By Professor Ed Wild | September 27, 2013 | Edited by Dr Jeff Carroll

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The huntingtin protein, which in its mutant form causes Huntington's disease, is difficult to study because it forms clumps rather than neat crystals. Now, young HD researcher Gwen Owens of California Institute of Technology is reaching VERY high to try to crack the problem. In a special video interview screened at the recent HD World Congress, HDBuzz spoke to Gwen about her 'out-of-this-world' plans...

ED: Why is it important to study huntingtin, for people who want to come up with treatments for Huntington's disease?

GWEN: It's incredibly important to the disease... that we know that it's the single protein that appears to cause the disease and unfortunately we don't have any idea what it looks like.

ED: Which seems quite important. If you're going to try and fight something, you want to know what it looks like.

GWEN: Yes, indeed.

ED: We have really accurate understandings of the structure of some proteins, likeinsulin, or haemoglobin, or some of the more famous proteins, so why don't we... It's 2013; we've had 20 years since the gene was discovered. What have you guys been doing? Why don't we have an idea of what huntingtin looks like?

GWEN: Huntingtin has two properties that make it really difficult to study the structure. One is that it's huge, that it's one of the biggest proteins in your body. It's more than six times larger than most proteins. That makes it difficult to work with. The second is that it aggregates. That we know, that part of the problem with Huntington's disease is that this protein, huntingtin, aggregates in neurons and that also makes it very difficult to study.

ED: When you say 'aggregates', you mean it sticks together to form clumps?

GWEN: Exactly, yes.

ED: Why does the protein sticking together make it difficult to study?

GWEN: Well, our lab uses a technique called X-ray crystallography to figure out exactly where every carbon, every nitrogen, every oxygen is in a protein. For that, we need individual proteins, they can't be clumped together, in order to make a crystal of proteins.

ED: Okay, so you look at a crystal and from that you can figure out the structure of the protein?

GWEN: Yes. When a crystal is formed you can actually shoot a laser through it, and based on the pattern of how light hits off of the crystal, you can actually reconstruct where everything is.

ED: From the experiment that I know you're planning, it sounds like you've kind of got to the limits of what we can do in 2013, on Earth, to get crystals of this protein, right?

GWEN: As far as we can tell, yes. We've set up more than a 100,000 different individual experiments on Earth, and we can't get anything to crystallise such that we can get a structure.

ED: I would say that does sound like you've done your background work pretty well. Okay, well let's spill the beans then. What are you planning to do to try and get crystals of huntingtin to grow, so that you can study the structure?

GWEN: We're planning on sending some of these experiments up to the International Space Station.

ED: Huntingtin in space!

GWEN: Yes, exactly. Our lab received a grant from CASIS, The Center for the Advancement of Science in Space, which is a subsidiary of NASA. They were looking for crystallisation experiments to be done on the International Space Station, and I think we made a pretty good case for why huntingtin is a really interesting protein to try to crystallise on the ISS. They realised that some of the physics in how crystals grow is really different when you don’t have gravity. They found that for some of these proteins that we know crystallise well, that the crystals get much, much bigger and they form much, much better. They’ll be another 10 to 20 times bigger in some cases and they actually diffract, so when you shoot a laser through it, it actually does a much better job of giving you a structure.

ED: Much bigger and much purer, it sounds like.

GWEN: In many cases. Definitely not in all cases and in some cases it did actually make it worse, as well. Huntingtin we thought would be very, very interesting to try in this situation. Because while we can get tiny, tiny little crystals, we can’t get crystals that are big enough really to do our studies on Earth.

ED: How far above the Earth is the International Space Station?

GWEN: It’s about 250 miles.

ED: But we can see it, sometimes. It flies overhead and you can see it like a little light in the sky, right?

GWEN: Yes, almost every night, actually. You can look it up online exactly when the ISS will be passing overhead in your location.

ED: That’s cool. So, is it a zero gravity environment up there?

GWEN: No, it’s technically microgravity. There is some small pull from the Earth still, even though it is very high up.

ED: Let’s ask a basic question here. What happens when a crystal forms?

GWEN: So, to make a crystal you have a very high concentration of protein. Such that it starts essentially nucleating, so it forms a central core. Then it starts building more and more proteins on the outside of it, until you get something that you can see with your own eye as a crystal.

ED: So, in a solution you’ve got all these protein molecules, and they’re all just flying around and they’re spaced quite far apart from each other?

GWEN: Essentially, yes.

ED: Then when you grow a crystal, one by one the proteins stick to each other, but in an organised way. Is that right?

GWEN: Yes, indeed.

ED: It’s the organisation that makes it a crystal, rather than a blob?

GWEN: Yes.

ED: How does the lack of gravity help the crystals to grow? What is it about the lack of gravity that makes the crystals grow bigger?

GWEN: So, when a crystal is growing, as I said there is this really high concentration of protein that is slowly forming this crystal. You end up with really high protein concentration, in the general solution. Right next to where the crystal is growing you have really low concentration because it's just been sucked up into the crystal, it forms a lattice. So, you have really high and really low concentration right next to each other. In the oceans, we know that if you have really high salt and really low salt, it starts mixing. Its starts having what's called convective flow. The same thing happens with crystals, is you get this flow along the surface. Apparently this flow impedes the growth of the crystal and so when this flow occurs the crystal essentially stops growing.

ED: Right, but if you take away the gravity..?

GWEN: It gets rid of most of the flow. There is some amount of flow that is good for the crystal, but having the amount of flow that is on the surface, in some crystals that are growing rapidly on Earth, clearly it impedes the growth of the crystal.

ED: What's the biggest difference that's been seen with a crystal by growing it in micro gravity?

GWEN: For lysozyme, which is one of the very standard crystals that we actually use to test out some of our beam lines, there has been experiments that it's been 20 times the size. For our crystals, 20 times the size would be enough to start doing some interesting work on them.

ED: Oh, wow. So then you could shoot the laser beams through it and cool things would happen?

GWEN: Hopefully, yes.

ED: So, how do you get huntingtin into space? Do you FedEx it up there and there is a daily delivery? What happens?

GWEN: We're sending our samples up on SpaceX 3, which is scheduled to send a whole load of stuff up to the ISS in January of next year (2014).

ED: So, have you made the huntingtin already in your lab, or are you busy making it? Or will you do it the day before?

GWEN: We continuously make huntingtin proteins in our lab.

ED: How do you do that?

GWEN: We grow it in E. coli, which is a bacteria and we have this E. coli make the protein, the huntingtin, of different lengths. Sometimes we only use part of it, because it's such a big protein and E. coli has a lot of trouble making the whole protein.

ED: You inject extra DNA into the E. coli to turn it into a huntingtin factory?

GWEN: Exactly, yes. After we get it really, really pure then we can set up these crystallisation experiments.

ED: We know that there's a mutant protein, which is the one that does damage to cells, and there's a so-called 'wild type' or healthy protein which doesn't do damage to cells. Are you just sending up the wild type, or are you sending up any mutant protein?

GWEN: We're planning on sending up some mutant protein as well. The mutant protein aggregates more than the wild type protein, which is part of the cause of Huntington's disease. So, it's a lot harder for it to crystallise. We expect better results from the wild type but we think getting a structure of some of the mutant protein would be really interesting too, so we'll send some up as well.

ED: So, the very, very best result would be big crystals, of normal or wild type protein and big crystals of the mutant protein. You shine your laser, and we get to look at the differences?

GWEN: Absolutely, yes.

ED: Maybe even some clues as to where we could stick a drug, or what we might be able to do to turn the mutant crystal into something that looks a bit more like the wild type crystal?

GWEN: We would hope so, yes.

ED: How delicate is this specimen of huntingtin protein and how is it packaged?

GWEN: It's packaged in… Actually, I have it here. We have these little devices. This is six different little experiments. So, the trip up is … they should be fairly stable, because the experiment doesn't start until they get into micro gravity. The astronauts actually have to flip a couple of levers for us to start the experiment going. Otherwise, the huntingtin protein is not crystallising, before it's in micro gravity.

ED: So, they take out these little containers up there; flip the levers and then the whole experiment runs itself?

GWEN: Yes, exactly.

ED: Wow. That sounds good, because astronauts … they're not exactly rocket scientists, let's be honest.

GWEN: (Laughter) Yes.

ED: How long do the crystals grow then, once they flip the switches?

GWEN: It will be somewhere around four months, but it also depends on when the different SpaceX vehicles can come up and down.

ED: When does the SpaceX 3 rocket go up?

GWEN: January 15th.

ED: January 15th? Roughly when will the huntingtin come back down to Earth?

GWEN: Roughly, April. We're hoping.

ED: It's growing the whole time?

GWEN: Yes. Well, the astronauts flip a switch before it comes back down, so the experiment finishes before it reaches gravity again. If, say, it crystallised but then when it came down you have to deal with re-entry, and that can be a bit of a bumpy ride. That's probably the most difficult part, because we're worried about the crystals potentially breaking up.

ED: When something comes back down to Earth, doesn't it just fall into the sea?

GWEN: Yes. (Laughter) Delicately!

ED: How do you feel about that?

GWEN: The containers that the crystallisation experiments are in are very well isolated from vibration and from temperature changes. The protein should be coming down not too far away from where our lab is in Pasadena. So, we should be able to drive and be there almost when it splashes down. Get the protein and drive it as soon as we can back to our lab. Then shoot an x-ray laser through it.

ED: How quickly will you know after it arrives in the lab whether the crystals are big enough to be of any use to you?

GWEN: Within a couple of hours.

ED: So, that's going to be pretty exciting.

GWEN: Yes, yes. Absolutely.

ED: Can you give me some idea of the sorts of things that knowing the crystal structure of proteins has led to in the past?

GWEN: One example is when HIV was first discovered. Some of the HIV proteins, like the HIV protease, which is important in the function of the protein, its crystal structure was solved. Then using that, organic chemists and synthetic chemists were able to use that structure to make something that inhibited what they expected the function was. They kind of locked on to the structure and were able to make a new drug against HIV based on the crystal structure.

ED: Finally, do you have a message for the folks here in Rio and watching online?

GWEN: Sure, if you ever want to see when the ISS is passing overhead, you can always just go to the website spotthestation.nasa.gov and know that between January and April this year, huntingtin will be passing overhead.

ED: Well Gwen, this is absolutely amazing. I mean, it's so exciting that this is happening. I really appreciate you taking time to talk to me. I know that everyone here in Rio is going to be absolutely over the moon that this is happening. I guess, even if it doesn't work at all, it's totally worth trying and its really cool stuff, so thank you very much for taking the time to talk to us.

GWEN: Well, thank you very much for having me.

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.
aggregate Lumps of protein that form inside cells in Huntington's disease and some other degenerative diseases
neuron Brain cells that store and transmit information
insulin A hormone that regulates the body's use of sugar and fats, and many other aspects of metabolism